

# Transdermal buprenorphine and fentanyl patches in cancer pain: a network systematic review

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**Abstract:** Treatment of cancer pain is generally based on the three-step World Health Organization (WHO) pain relief ladder, which utilizes a sequential approach with drugs of increasing potency. Goals of pain management include optimization of analgesia, optimization of activities of daily living, minimization of adverse effects, and avoidance of aberrant drug taking. In addition, it is recommended that analgesic regimens are individualized and simplified to help ensure patient compliance and should provide the least invasive, easiest, and safest route of opioid administration to ensure adequate analgesia. Buprenorphine and fentanyl are two opioids available for the relief of moderate-to-severe cancer pain. Available clinical data regarding the transdermal (TD) formulations of these opioids and the extent to which they fulfill the recommendations mentioned earlier are systematically reviewed, with the aim of providing additional information for oncologists and pain specialists regarding their comparative use. Due to lack of studies directly comparing TD buprenorphine with TD fentanyl, data comparing these with other step-3 opioids are also evaluated in a network fashion.

**Keywords:** analgesia, cancer pain management, chronic pain/drug therapy, drug evaluation, pain management, patch analgesics

→ Video abstract



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## Plain language summary

This review provides additional information for oncologists and pain specialists regarding the comparative efficacy and safety of buprenorphine and fentanyl 3–4-day patches in cancer pain management, especially in areas such as Asia where clinical experience with transdermal (TD) buprenorphine is low. Data regarding the buprenorphine 3–4-day patch and the fentanyl 3-day patch were systematically reviewed. Due to lack of studies directly comparing buprenorphine and fentanyl, data comparing these with other step-3 opioids (e.g., oral morphine, oxycodone, and methadone) were also examined. TD buprenorphine and TD fentanyl appear to have similar efficacy and tolerability. The buprenorphine 3–4-day patch may have a reduced risk of tolerance compared with the fentanyl 3-day patch and appears to be a useful option for patients with renal impairment, because it does not require any dose adjustment. In conclusion, the buprenorphine 3–4-day patch is safe and effective in patients with cancer pain. Due to its extended-release formulation, it is best used in patients with stable and predictable opioid requirements.

## Introduction

Pain is one of the most common symptoms among cancer patients,<sup>1</sup> estimated to be experienced by 59% of patients undergoing treatment and more prevalent among patients with advanced disease.<sup>2–4</sup> Cancer pain is most often caused by the cancer

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<http://dx.doi.org/10.2147/JPR.S140320>

Journal of Pain Research 2017:10 1963–1972

1963



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itself, but it may also be caused by the treatments received.<sup>2,4</sup> Prevalence of pain can also depend on the type of cancer, its stage, and patients' tolerance for pain.<sup>2,4,5</sup> To maximize patient outcomes, pain management with regular pain assessment is an essential part of oncologic management.<sup>1</sup> There is evidence that cancer survival is linked to symptom control, and that pain management contributes to improved quality of life (QoL).<sup>6</sup>

Treatment of cancer pain is generally based on the World Health Organization (WHO) pain relief ladder,<sup>3,7</sup> which proposes a three-step sequential approach corresponding to drugs with increasing efficacy.<sup>8</sup> However, more recently published guidelines by the European Association for Palliative Care (EAPC) and the European Society for Medical Oncology (ESMO) suggest giving low doses of strong opioids as an alternative to weak opioids to achieve better analgesia and tolerability.<sup>7,9</sup> Since the introduction of the three-step WHO ladder in 1986, the use of opioids has increased, although there are geographical variations in use.<sup>10</sup> Goals of pain management include<sup>1,11</sup> optimization of analgesia, optimization of activities of daily living, minimization of adverse effects (AEs), and avoidance of aberrant drug taking. For ongoing care, guidelines recommend oral or transdermal (TD) medications including extended-release or long-acting agents with rescue doses, and analgesic regimens are simplified for improved patient compliance.<sup>1</sup> The least invasive, easiest, and safest route of opioid administration should be provided to ensure adequate analgesia.<sup>1,3</sup> It is worth noting that when the WHO first published its Cancer Pain Relief Guidelines in 1986, there were no TD formulations available; thus, the intention was to shift the analgesic route of administration from parenteral to oral.

Adverse events are common with opioids,<sup>1,7</sup> and include constipation, nausea and vomiting, pruritus, delirium, respiratory depression, motor and cognitive impairment, and sedation.<sup>7,12</sup> Preemptive management of opioid-induced AEs, such as constipation, is important for patient compliance and QoL,<sup>13,14</sup> thus ensuring effective pain treatment.<sup>1,15</sup> Patients should be regularly reassessed and pain regimens modified to meet patient-specific goals for comfort, function, and safety.<sup>1,7</sup> Opioid switching should be considered if pain is inadequately controlled despite adequate dose titration, or in the presence of persistent AEs.<sup>1,9</sup> No single opioid is optimal for all patients.<sup>1</sup> In the presence of significant opioid-related AEs, switching to an equivalent dose of an alternative opioid may help improve the balance between analgesic efficacy and AEs.<sup>16,17</sup>

Buprenorphine and fentanyl are two strong opioids available for the relief of cancer pain. Buprenorphine is a semi-synthetic partial  $\mu$ -opioid receptor agonist as well as a  $\kappa$ - and  $\delta$ -opioid receptor antagonist. It binds to receptors with high affinity and has slow dissociation, contributing to a relatively long duration of analgesic action.<sup>11,18–21</sup> Fentanyl is a synthetic, highly lipid-soluble,  $\mu$ -opioid receptor agonist with a low molecular weight.<sup>11,18,22,23</sup> In contrast to buprenorphine, fentanyl has fast receptor association/dissociation kinetics.<sup>20</sup> Buprenorphine is available as parenteral, sublingual, and TD formulations, whereas fentanyl can be administered by the parenteral, spinal, TD, transmucosal, buccal, and intranasal routes.<sup>22,23</sup> With regard to the TD formulations, TD buprenorphine preparations vary across countries, with either 3–4- or 7-day dosing schedules, depending on preparation availability, while fentanyl has a 3-day dosing schedule.

TD opioid delivery avoids first-pass metabolism by the liver, increasing bioavailability and limiting variation in plasma concentration.<sup>11,24</sup> Increased drug bioavailability enables the use of lower drug doses, thus reducing the incidence of AEs.<sup>11</sup> TD delivery of opioids also allows consistent, long-term pain relief with continuous controlled release of opioid for 72–168 hours;<sup>24</sup> as such, they are best reserved for opioid-tolerant patients with stable opioid requirements.<sup>7,25</sup> Buprenorphine and fentanyl are particularly suited for TD administration since they combine the necessary characteristics (low molecular mass, high lipid solubility, and high potency) for good penetration of the skin.<sup>11,18,19,23</sup> While oral opioids are generally the first choice,<sup>1,26</sup> TD medications are recommended by guidelines for ongoing care of patients with cancer pain<sup>1</sup> and are preferred by many patients because they are noninvasive, easy to use, and their interference with daily activities is minimal.<sup>18,24,27</sup> TD buprenorphine and TD fentanyl are usually the treatment of choice for patients who are unable to swallow, patients with poor tolerance to morphine, and patients with poor compliance.<sup>1,7,9,11,18,26,27</sup>

The aim of this review was to provide additional data for oncologists and pain specialists regarding the use of TD buprenorphine and TD fentanyl in cancer pain management, particularly in areas such as Asia where clinical experience with the use of TD buprenorphine is low.<sup>28</sup> This review systematically examines the available data for the buprenorphine 3–4-day patch and the fentanyl 3-day patch. Due to lack of studies directly comparing TD buprenorphine and TD fentanyl, data comparing these with other step-3 opioids are also evaluated in a network fashion.

## Methods

### Search strategy

PubMed, EMBASE, and Cochrane library databases were used for the literature search, which was conducted on March 6, 2017. The search was performed using the following search string, searching all possible fields and MESH/Emtree terms, where available: (transdermal buprenorphine AND cancer pain) OR (transdermal fentanyl AND cancer pain) OR (transdermal buprenorphine AND transdermal fentanyl) OR (transdermal buprenorphine AND transdermal fentanyl AND cancer pain). The search was limited to studies in human beings and NOT “non-cancer pain.” Ad hoc searching was also performed, and the reference lists of all included articles were hand searched to identify additional articles.

### Study selection

Eligibility was initially assessed using titles and abstracts. Those that were not excluded were further screened using full-text articles. Articles included in the analysis were studies related to the use of TD buprenorphine and TD fentanyl for the relief of cancer pain and were either direct comparisons or indirect comparisons with other pain medications. Articles excluded from the analysis were study protocol/design, letters, commentaries/news, case reports, studies in non-cancer pain, patient surveys, studies with irrelevant treatments, and narrative reviews. Resulting studies were filtered to select

only those studies that examined the use of TD buprenorphine and/or TD fentanyl patches in cancer pain.

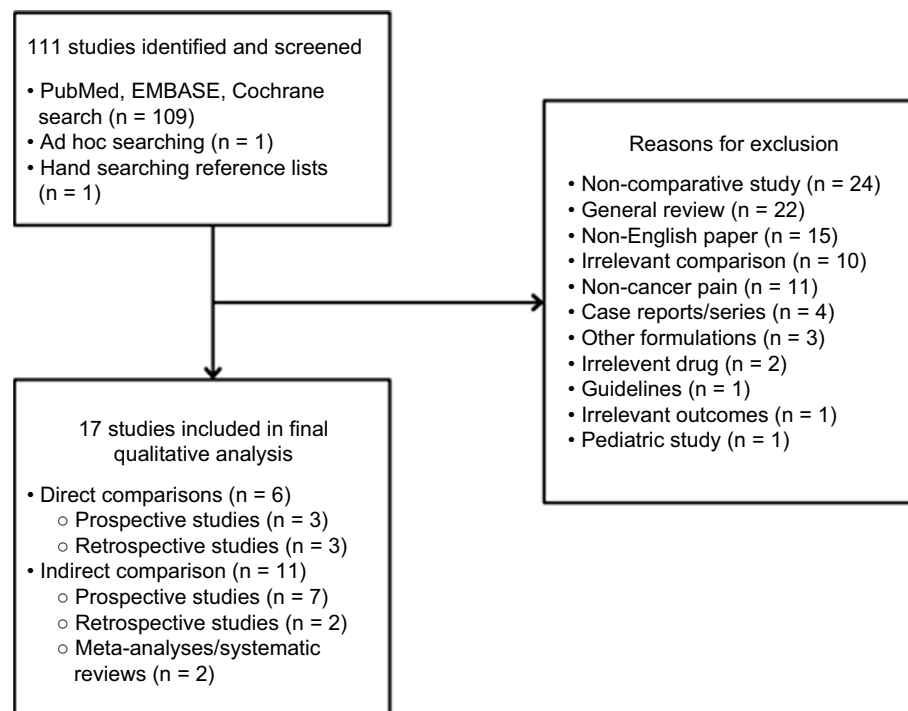
### Data extraction and assessment of study quality

Data collected from the articles included study design, patients, treatment characteristics, and results/endpoints. Outcomes examined included analgesic efficacy (pain scores, pain intensity difference [PID], proportion of responders), safety, switching outcomes (dosing, rescue medication), QoL, patient satisfaction/patient preference, and costs.

## Results

### Included studies

A PRISMA flow diagram showing the screening process and reasons for exclusion is shown in Figure 1. A total of 109 studies were identified from searching PubMed, EMBASE, and Cochrane library databases, one additional study was identified from hand searching the reference lists of identified articles,<sup>29</sup> and one study was identified by ad hoc searching.<sup>30</sup> The major reason for discarding articles was that they were non-comparative studies, or that they were general reviews or non-English language articles. In total, six studies that compared TD buprenorphine and TD fentanyl and 11 studies that compared TD buprenorphine and/or TD fentanyl with other pain medications were identified. Among studies



**Figure 1** PRISMA flow diagram of the study selection process.

comparing TD buprenorphine and TD fentanyl, three were prospective,<sup>24,31,32</sup> of which one was a direct comparison of TD buprenorphine and TD fentanyl,<sup>31</sup> and three studies were retrospective.<sup>33–35</sup> Among studies comparing TD buprenorphine and/or TD fentanyl with other pain medications, the majority (seven studies) were prospective,<sup>29,36–41</sup> two were retrospective,<sup>42,43</sup> and two were meta-analyses or systematic reviews.<sup>30,44</sup> Table 1 presents the design of included studies comparing TD buprenorphine with TD fentanyl, and Table 2 presents the design of included studies comparing TD buprenorphine and/or TD fentanyl with other pain medications.

## Utilization of TD buprenorphine and TD fentanyl

Two studies reported outcomes associated with utilization of TB buprenorphine or TD fentanyl in patients with cancer pain.<sup>33,37</sup> Of these one study directly compared TD buprenorphine with TD fentanyl<sup>33</sup> and one study compared TD buprenorphine and/or TD fentanyl with other pain medications.<sup>37</sup>

### Direct comparisons

A retrospective study examined mean prescribed doses of TD buprenorphine and TD fentanyl to compare calculated equipotent oral morphine doses.<sup>33</sup> Of 2544 patients in a German database who had received  $\geq 1$  prescription for TD buprenorphine or TD fentanyl for cancer pain, mean prescribed daily doses were lower with TD buprenorphine than with TD fentanyl.<sup>33</sup> Equipotent oral daily morphine doses,

calculated using current conversion ratios, were statistically significantly lower with TD buprenorphine than with TD fentanyl ( $P < 0.001$ ).<sup>33</sup>

### Indirect comparisons

Preliminary analysis of 330 patients enrolled in a multicenter, observational study in Italy showed that 56.7% of patients received a strong opioid.<sup>37</sup> Fentanyl and buprenorphine TD delivery systems were the most regularly prescribed (23.8% and 9.6% of patients, respectively). Morphine and oxycodone were prescribed in 11.3% and 10.8% of patients, respectively, while methadone was prescribed in only 1%.<sup>37</sup>

## Analgesic efficacy of TD buprenorphine and TD fentanyl

Eight prospective studies<sup>29,31,36–41</sup> and three retrospective studies<sup>34,35,42</sup> reported results regarding the efficacy of TD buprenorphine and TD fentanyl. Of these, three studies directly compared TD buprenorphine with TD fentanyl<sup>31,34,35</sup> and eight studies compared TD buprenorphine and/or TD fentanyl with other pain medications.<sup>29,36–42</sup>

The majority of studies evaluating the efficacy of TD buprenorphine and TD fentanyl were short-term studies ( $\leq 3$  months) except for two retrospective studies, which evaluated patterns of dosage changes for almost 1 year.<sup>34,35</sup>

### Direct comparisons

A prospective study comparing TD buprenorphine and TD fentanyl revealed that TD buprenorphine in patients with

**Table 1** Studies comparing TD buprenorphine with TD fentanyl

Reference	Study design	n	Patient characteristics	Treatment	Outcomes
Prospective					
Aurilio et al <sup>24</sup>	Prospective	32	Chronic cancer pain; insufficient analgesia	TD buprenorphine, TD fentanyl	Dosing Analgesic efficacy AEs Rescue medication
Melilli et al <sup>31</sup>	Observational, parallel-group, active-control	42	Outpatients with cancer; impaired renal function	TD buprenorphine vs TD fentanyl	Analgesic efficacy AEs Rescue medication
Mercadante et al <sup>32</sup>	Within-patient, two-way crossover	22	Optimally managed for cancer pain	TD buprenorphine $\rightarrow$ TD fentanyl vs TD fentanyl $\rightarrow$ TD buprenorphine	Analgesic efficacy AEs Rescue medication
Retrospective					
Sittl et al <sup>33</sup>		2544	Received $\geq 1$ prescription for cancer pain	TD buprenorphine, TD fentanyl	Dosing
Sittl et al <sup>34</sup>	Longitudinal	446	Cancer pain	TD buprenorphine, TD fentanyl	Dosing Rescue medication
Sittl et al <sup>35</sup>		605	Cancer pain	TD buprenorphine, TD fentanyl	Dosing

**Abbreviations:** AEs, adverse effects; TD, transdermal.

**Table 2** Studies comparing TD buprenorphine and/or TD fentanyl with other pain medications

Reference	Study design	n	Patient characteristics	Treatment	Outcomes
Prospective					
Ahmedzai et al <sup>36</sup>	Multicentre, randomized	202	Palliative care, receiving stable doses of morphine	TD fentanyl vs morphine	Analgesic efficacy AEs QoL Patient preference
van Seventer et al <sup>29</sup>	Multicentre, randomized, open-label	131	Moderate-to-severe cancer pain	TD fentanyl vs oral morphine	Analgesic efficacy AEs QoL
Apolone et al <sup>37</sup>	Multicentre, open-label, observational	330	Cancer	TD buprenorphine, TD fentanyl, morphine, oxycodone, methadone	Drug utilization
Kress et al <sup>38</sup>	Multicentre, randomized, open-label, parallel	220	Requiring WHO/step-3 opioids	TD fentanyl (Matrifen® 3-day patch) vs standard opioid treatment (TD fentanyl [Durogesic® patch] or oral opioids)	Analgesic efficacy AEs
Mercadante et al <sup>39</sup>	Multicentre, randomized	108	Advanced cancer; pain requiring strong opioids; previously received opioids for mild-to-moderate pain	TD fentanyl vs oral morphine or methadone	Analgesic efficacy AEs QoL Costs
Payne et al <sup>41</sup>	Multicentre, cross-sectional	504	Advanced cancer	TD fentanyl vs oral morphine	Analgesic efficacy AEs QoL Patient satisfaction
Wong et al <sup>40</sup>	Open, randomized	40	Terminal cancer pain	TD fentanyl vs oral morphine	Analgesic efficacy AEs Patient satisfaction
Retrospective					
Corli et al <sup>42</sup>	Exploratory analysis of a prospective, observational study	258	WHO/step-3 opioid naive	TD buprenorphine, TD fentanyl, morphine, oxycodone	Analgesic efficacy AEs Rescue medication
Mercadante et al <sup>43</sup>	Multicentre	201	Palliative care in a home setting	TD buprenorphine, TD fentanyl, morphine, oxycodone, hydromorphone	Analgesic efficacy AEs Switch rate Dosing Route of administration
Systematic reviews/meta-analyses					
Tassinari et al <sup>44</sup>	Meta-analysis (four studies)	425	Cancer pain	TD buprenorphine or TD fentanyl vs morphine	AEs Patient preference
Hadley et al <sup>30</sup>	Meta-analysis (four studies)	258	Outpatients with moderate-to-severe chronic cancer pain	TD fentanyl vs oral morphine	AEs

**Abbreviations:** AEs, adverse effects; QoL, quality of life; TD, transdermal; WHO, World Health Organization.

renal impairment was as effective at controlling moderate-to-severe cancer pain as TD fentanyl in patients without renal impairment.<sup>31</sup> Median Numerical Rating Scale (NRS) scores were 8.0 (95% CI 7.4, 8.4) at enrollment for both treatment groups. NRS pain score reductions were significant and constant over time, with no significant differences in pain scores between TD buprenorphine and TD fentanyl treatment groups.<sup>31</sup> The mean dose of TD buprenorphine increased by 48% and 26% at days 10–30 and days 30–90, respectively, whereas corresponding dose increases for TD fentanyl was 34% and 38%, respectively.<sup>31</sup> There were no statistically

significant differences in the use of rescue medication between the two treatment groups.<sup>31</sup>

Comparison of dosing in a retrospective study of 446 patients with cancer pain from a German database showed that, during treatment, increases in mean prescribed dosages were significantly greater with TD fentanyl than with TD buprenorphine (mean percentile change: 42.7% vs 21.7%;  $P < 0.05$ ).<sup>34</sup> Mean daily increases were 0.11% and 0.07% for TD fentanyl and TD buprenorphine, respectively ( $P < 0.05$ ).<sup>34</sup> No significant differences between treatment groups were reported for the use of rescue medication.<sup>34</sup> The authors

of the study suggested that tolerance development may be higher with TD fentanyl than with TD buprenorphine.<sup>34</sup> A similar German study in 605 patients with cancer pain confirmed these results.<sup>35</sup> A significantly greater proportion of TD buprenorphine recipients had stable dosages throughout treatment than patients receiving TD fentanyl (50.0% vs 26.2%;  $P < 0.05$ ).<sup>35</sup> Compared with TD buprenorphine, the proportion of patients with alternating dosage changes was significantly greater in patients receiving TD fentanyl (30.6% vs 11.8%;  $P < 0.05$ ).<sup>35</sup> In addition, over the entire treatment duration, mean percentage increases in dosage were significantly higher in the patients receiving TD fentanyl than those receiving TD buprenorphine (81.4% vs 34.5%;  $P < 0.05$ ).<sup>35</sup>

### Indirect comparisons

Retrospective exploratory analysis of data from a prospective study demonstrated that reductions in PID were similar between TD buprenorphine and TD fentanyl for average pain ( $-2.32$  vs  $-2.51$ ), but slightly better with TD buprenorphine for worst pain ( $-2.94$  vs  $-2.46$ ).<sup>42</sup> Full responders (defined as a PID  $\geq 30\%$ ) appeared to be slightly more frequent with TD buprenorphine than with TD fentanyl for both average pain (70.7% vs 68.2%) and worst pain (62.9% vs 54.5%). Switching opioids due to the lack of efficacy or AEs were less frequent with TD buprenorphine than with TD fentanyl (8.6% vs 20.0%). Recipients of TD fentanyl required greater dose increases than recipients of TD buprenorphine: increases in dose  $\geq 5\%$  a day were observed in 33.3% of patients receiving TD fentanyl compared with 15.5% of patients receiving TD buprenorphine ( $P < 0.05$ ).

Analysis of Index of Pain Management in an Italian Outcomes Research study in 330 patients suggested that, despite them receiving strong opioids, patients were undertreated.<sup>37</sup> While one study reported no significant differences in pain control with TD fentanyl vs oral morphine, significantly more rescue medication was used by patients treated with TD fentanyl (53.9% vs 41.5% of treatment days;  $P = 0.0005$ ).<sup>36</sup> Similar efficacy has been reported for comparisons of TD fentanyl with standard opioid treatment.<sup>29,38</sup>

No differences in pain intensity or non-opioid analgesic consumption were reported in a prospective, randomized study of TD fentanyl compared with oral morphine or methadone.<sup>39</sup> These results were confirmed in a study comparing TD fentanyl with oral morphine, with composite pain scores similar between treatment groups,<sup>41</sup> and in a study of 40 patients switched from immediate-release oral morphine to TD fentanyl or controlled-release oral morphine.<sup>40</sup>

## Safety of TD buprenorphine and TD fentanyl

Seven prospective studies,<sup>29,31,36,38–41</sup> one retrospective study,<sup>42</sup> and two meta-analyses<sup>30,44</sup> reported tolerability data for TD buprenorphine and TD fentanyl. Of these, one study directly compared TD buprenorphine with TD fentanyl<sup>31</sup> and nine studies compared TD buprenorphine and/or TD fentanyl with other pain medications.<sup>29,30,36,38–42,44</sup>

### Direct comparisons

A prospective study directly comparing TD buprenorphine with TD fentanyl revealed similar rates of AEs despite patients treated with TD buprenorphine having renal impairment vs no renal impairment in those receiving TD fentanyl.<sup>31</sup> The most common AEs were somnolence/confusion, nausea/vomiting, constipation and pruritus.<sup>31</sup> No patients required dose reduction or treatment interruption.<sup>31</sup>

### Indirect comparisons

Side effects appear to be less bothersome with TD fentanyl than with oral morphine.<sup>29,36,41</sup> Rates of constipation, in particular, appear to be lower with TD fentanyl than with oral morphine.<sup>29,36,40</sup> A meta-analysis comparing AEs of TD opioids and slow-release oral morphine reported a significant advantage of TD opioids for constipation (pooled odds ratio [OR] 0.38;  $P < 0.001$ ); however, no comparison of TD buprenorphine and TD fentanyl was performed.<sup>44</sup> Similarly, a Cochrane Database review of TD fentanyl demonstrated a reduction in opioid-related constipation compared with oral sustained-release morphine (28% vs 46%; risk ratio 0.61; 95% CI 0.47, 0.78).<sup>30</sup>

An exploratory analysis of data from a prospective observational noninterventive study examined the rate of AEs in 258 patients receiving TD buprenorphine, TD fentanyl, or oral morphine or oxycodone as standard care.<sup>42</sup> Univariate analysis of safety outcomes showed a greater proportion of TD fentanyl than TD buprenorphine recipients reported at least one AE symptom described as “much/very much” (71.1% of 32 patients vs 57.8% of 67 patients).<sup>42</sup> Overall, there was significant variability between all treatments ( $P > 0.05$ ).<sup>42</sup> Multivariate comparisons demonstrated ORs of 0.48 (95% CI 0.21, 1.13) for TD buprenorphine and 0.79 (95% CI 0.29, 2.16) for TD fentanyl compared with morphine.<sup>42</sup>

Finally, within-group analysis of data from a randomized study revealed significant increases in symptom intensity (nausea–vomiting, drowsiness, constipation, and confusion) during treatment with morphine and methadone but not with TD fentanyl.<sup>39</sup>

## Switching between TD opioids

One prospective study and two retrospective studies examined switching between TD opioids.<sup>24,32,43</sup> Of these, two studies directly compared TD buprenorphine with TD fentanyl<sup>24,32</sup> and one study compared TD buprenorphine and/or TD fentanyl with other pain medications.<sup>43</sup>

Switching between opioids resulted in improvements in pain scores, especially in patients whose pain was previously inadequately controlled.<sup>24,43</sup> In addition, there were generally no statistically significant differences in pain scores between patients who switched from TD fentanyl to TD buprenorphine and those who switched from TD buprenorphine to TD fentanyl.<sup>24,32</sup> It is of interest that in one study, a 50% dose reduction was made while switching between TD opioids,<sup>24</sup> which is greater than commonly used in practice. Retrospective analysis of data among patients switching opioids during home palliative care revealed that the most frequent reason for switching was convenience because they were no longer able to swallow, especially during the last days of life. A large number of patients switched from oral opioids, such as oral morphine and oxycodone to parenteral morphine ( $n = 79$ ), TD fentanyl ( $n = 28$ ), or TD buprenorphine ( $n = 2$ ).<sup>43</sup> The outcome of switching was good or partial in the majority of patients.

Similarly, use of rescue medication was reduced after switching in patients with previously inadequate analgesia,<sup>24</sup> but there were no differences between patients who switched from TD fentanyl to TD buprenorphine and those who switched from TD buprenorphine to TD fentanyl.<sup>24,32</sup> Switching between TD opioids also reduced the incidence of AEs,<sup>24</sup> with no between-group differences in symptom intensity.<sup>32</sup>

## QoL

Four prospective studies reported data regarding patient QoL with TD buprenorphine and/or TD fentanyl compared with other pain medications.<sup>29,36,39,41</sup> There were no significant differences in European Organization for Research and Treatment of Cancer (EORTC) QoL scores between TD fentanyl and oral morphine, but when the aggregated scale for emesis was separated into nausea and vomiting, the mean score for nausea was significantly lower for TD fentanyl ( $P = 0.04$ ).<sup>36</sup> Another comparison of TD fentanyl and oral morphine revealed significantly better functioning with TD fentanyl assessed using the Functional Assessment of Cancer Therapy-General (FACT-G) scale ( $P < 0.001$ ),<sup>41</sup> whereas evaluation of QoL using the Spitzer QoL Index showed no significant differences in QoL scores between TD fentanyl, oral morphine, and methadone.<sup>39</sup> A randomized open-label study revealed significantly less patient-reported interruption

of daily activities with TD fentanyl than with sustained-release oral morphine (12% vs 37%;  $P = 0.012$ ).<sup>29</sup>

## Patient satisfaction/patient preference with TD buprenorphine and TD fentanyl

Three prospective studies<sup>36,40,41</sup> and one meta-analysis<sup>44</sup> reported data regarding patient preference with TD buprenorphine and/or TD fentanyl compared with other pain medications. Two studies comparing TD fentanyl with oral morphine revealed that more patients preferred TD fentanyl over oral morphine.<sup>36,41</sup> Also, 17 of 20 patients switched from immediate-release oral morphine to TD fentanyl, and 19 of 20 patients switched from immediate-release oral morphine to controlled-release morphine, preferred TD fentanyl and controlled-release morphine, respectively, to immediate-release oral morphine.<sup>40</sup> Similarly, meta-analysis of data from three studies revealed a significant advantage of TD opiates compared with slow-release morphine;<sup>44</sup> however, patient preference with TD buprenorphine vs TD fentanyl was not compared.

## Costs

One prospective study reported data regarding treatment costs with TD fentanyl compared with other pain medications.<sup>39</sup> The costs of pharmacological cancer pain management, including opioids, symptomatic drugs (i.e., those used to control opioid-induced AEs), and non-opioid drugs, were examined. Among 108 patients receiving TD fentanyl, morphine, or methadone, no significant differences were observed in the cost of drugs used to manage opioid-induced adverse events and non-opioid analgesic drugs used, although methadone was significantly cheaper than TD fentanyl or morphine.<sup>39</sup> However, the authors noted that other relevant costs (i.e., hospital admissions, visits, contacts, transportation, educational materials, and domestic support) were not included in the analysis.

## Discussion

Findings from this network review have shown that TD buprenorphine and TD fentanyl have similar analgesic efficacy,<sup>31,42</sup> with TD buprenorphine appearing to be an appropriate choice in patients with renal impairment, showing similar analgesic efficacy and rates of AEs to TD fentanyl in patients without renal impairment.<sup>31</sup> Indeed, dose adjustments for renal dysfunction are not required for TD buprenorphine or TD fentanyl.<sup>27</sup> Accordingly, ESMO recommends the use of TD buprenorphine and TD fentanyl as the safest opioids of choice in patients with renal impairment.<sup>7</sup> The study by Melilli et al<sup>31</sup> confirms the usefulness of TD buprenorphine

in patients with renal impairment, and other studies help reinforce that, due to its pharmacokinetic profile, TD buprenorphine can be used in all stages of renal impairment without dose adjustment.<sup>45,46</sup>

In addition, results from our systematic review suggest that there is a potentially reduced risk of developing tolerance with TD buprenorphine than with TD fentanyl, as evidenced by a reduced need for dosage increases,<sup>34,47</sup> and tolerability may be slightly better with TD buprenorphine than with TD fentanyl, although it is important to note that the small patient population size in this study identified in our systematic review is a limitation.<sup>42</sup> In addition, there appears to be reduced constipation with TD opioids compared with oral morphine.<sup>36,40,44</sup> However, based on the available data, no meaningful comment can be made regarding the relative costs of TD opioids.

While the use of oral opioids is more common,<sup>1</sup> and preferentially recommended in some guidelines,<sup>26</sup> TD opioids could be considered first-line therapy for selected patients. National Comprehensive Cancer Network guidelines state that they can be used as indicated to maximize patient comfort,<sup>1</sup> while other guidelines (ESMO, EAPC, and UK National Health System) state that they are the preferred treatment in patients who are unable to swallow.<sup>7,9,26</sup> Other patient groups for whom TD opioids may be particularly useful include those unable to tolerate oral medications, those with poor compliance, and those with renal impairment.<sup>7,26</sup> However, it is important to note that TD opioids should be reserved for those patients whose opioid requirements are stable.<sup>7,26</sup>

With regard to the safety, TD opioids are relatively well tolerated, with reduced AEs vs oral opioids.<sup>27</sup> The most frequently reported AEs with TD buprenorphine are headache, dizziness, somnolence, constipation, dry mouth, nausea, vomiting, pruritus, erythema, and application site pruritus and reactions.<sup>19,48</sup> However, it is important to note that regulatory authorities in the USA and Canada have issued warnings regarding TD fentanyl overdoses and deaths.<sup>49–51</sup> Factors contributing to adverse drug events include: lack of appreciation that fentanyl is a strong opioid analgesic; inappropriate use in patients naive to strong opioids; lack of patient education regarding safe use, storage, and disposal; lack of awareness of the signs of an overdose; lack of awareness that the absorption rate of fentanyl may be increased if the skin under the patch becomes vasodilated, e.g., in febrile patients or by an external heat source; and lack of awareness of drug interactions increasing fentanyl levels.<sup>50–52</sup> Rates of constipation (16%–22%), nausea (2%–9%), and sedation (2%–11%) have been reported with TD opioids.<sup>27</sup> In particu-

lar, unlike TD fentanyl, TD buprenorphine has a ceiling effect on respiratory depression without an analgesic ceiling effect, which positively impacts its safety and abuse liability.<sup>53,54</sup>

TD buprenorphine also has a low abuse/physical dependency risk.<sup>55</sup> After long-term treatment with buprenorphine, withdrawal symptoms are usually mild in intensity with a delayed onset of more than 72 hours. They appear to be milder than those associated with morphine and fentanyl. Due to its slow dissociation from the  $\mu$ -receptor, the risk of drug dependence and analgesic tolerance appears to be lower with buprenorphine than with other  $\mu$ -opioids.<sup>55</sup>

An obvious limitation of the current review is the lack of studies directly comparing TD buprenorphine and TD fentanyl, or TD opioids with oral opioids. The previously mentioned Cochrane systematic review concluded that, given its widespread use in the palliative care setting, trial evidence for TD fentanyl is limited and of poor quality, with inadequate data for a meta-analysis.<sup>30</sup> In addition, studies comparing TD buprenorphine and TD fentanyl are of poor quality, being mostly retrospective, with few long-term data. In particular, more studies examining the relative costs of TD opioids would be useful.

## Conclusion

The aim of this review was to provide additional information for oncologists and pain specialists regarding the comparative use of TD buprenorphine and TD fentanyl in cancer pain management. The authors undertook a comprehensive review of the published literature. Data directly comparing these TD opioids were lacking; however, from the available data, it can be concluded that TD opioids are safe and effective in selected patients with cancer pain, especially those with stable and predictable opioid requirements; the TD delivery route will help to reduce tablet burden and may help compliance in selected patients. TD buprenorphine and TD fentanyl appear to have similar efficacy in patients with cancer pain. In addition, similar to TD fentanyl, TD buprenorphine appears to be particularly useful in patients with renal impairment, requiring no dose adjustment regardless of the stages of impairment. While comparative data suggest similar rates of AEs with TD buprenorphine and TD fentanyl, TD buprenorphine may have a reduced risk of tolerance compared with TD fentanyl, and additional studies show that TD buprenorphine has a ceiling effect on respiratory depression without a ceiling effect on analgesia, suggesting better overall tolerability of TD buprenorphine than TD fentanyl. Further studies directly comparing TD buprenorphine with TD fentanyl in cancer pain would be useful; long-term data, in particular, are lacking.



## Acknowledgment

Financial support for the writing of this review was provided by Mundipharma Pte Ltd.

## Disclosure

Dr Jin Seok Ahn reports personal fees from BMS, Eisai, Janssen, Roche, Menarini, and Boehringer Ingelheim outside the submitted work. Dr Setsuro Ogawa reports personal fees from Mundipharma K.K. outside the submitted work. Dr Tony O'Brien reports personal fees from Archimedes, AstraZeneca, Grunenthal, Janssen-Cilag, Mundipharma, and Teva outside the submitted work. Dr Andrea Bothwell reports personal fees from In Vivo Communications (Asia) Pte Ltd, the medical communications agency commissioned by Mundipharma Pte Ltd for this project, during the conduct of the study; personal fees from various pharmaceutical companies, outside the submitted work. Dr Hanlim Moon reports personal fees from Mundipharma Pte Ltd during the conduct of the study. Dr Yacine Hadjiat reports personal fees from Mundipharma Pte Ltd during the conduct of the study. Dr Abhijith Ganapathi reports personal fees from Mundipharma Pte Ltd during the conduct of the study. Dr Johnson Lin, Dr Chen Yuan, and Dr Brian HC Le report no conflicts of interest in this work.

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**Title:**

Transdermal buprenorphine and fentanyl patches in cancer pain: a network systematic review

**Date:**

2017-01-01

**Citation:**

Ahn, J. S., Lin, J., Ogawa, S., Yuan, C., O'Brien, T., Le, B. H. C., Bothwell, A. M., Moon, H., Hadjiat, Y. & Ganapathi, A. (2017). Transdermal buprenorphine and fentanyl patches in cancer pain: a network systematic review. JOURNAL OF PAIN RESEARCH, 10, pp.1963-1972. <https://doi.org/10.2147/JPR.S140320>.

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