# EML OPIOIDS FOR CANCER PAIN: A COMPARATIVE OVERVIEW

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INTRODUCTION

Cancer pain is commonly treated effectively with opioids administered at regular intervals with rescue doses for the management of episodic pain.

Opioids are the cornerstone of cancer pain management and their use has been increasing in the last years all over the world. Today, opioid therapy represents the best choice to control pain for the majority of cancer patients.

Pain management must be individualized taking into account the available drugs, patient's clinical situation and intensity of pain so nowadays more analgesic drugs must be made available.

Morphine is the strong opioid of choice for the treatment of moderate to severe cancer pain according to the World Health Organization. This recommendation from the WHO was derived by virtue of availability, familiarity to clinicians, established effectiveness, and simplicity of administration with relative inexpensive cost. It was not based on proven therapeutic superiority over other options.

In clinical practice, patients treated with oral morphine sometimes present with the following clinical situations: (1) pain is controlled but the patient experiences some intolerable adverse effects; (2) pain is not adequately controlled and it is impossible to increase the morphine dose because of adverse effects; (3) pain is not adequately controlled by continuously increasing the dose of morphine but the morphine does not produce adverse effects. However, there is no single opioid of choice for all patients, but one opioid can be optimal for an individual patient.

Methadone is another attractive alternative mu-opioid analgesic because of its lack of neuroactive metabolites, clearance independent of renal function, good oral bioavailability, extremely low cost, long half-life with fewer doses needed per day, potential to control pain no longer responsive to other opioids, and other extra-opioid analgesic effects caused by its noncompetitive antagonist activity at the N-methyl-D-aspartate receptors. Moreover methadone presents low tolerance with the advantage to avoid a continuous increase of the dose.
In special situations, patient may experience several comorbidities such as malabsorption, vomiting or severe constipation resulting in not taking oral agents so alternative routes like the transdermal one are strongly recommended. The same route is indicated also in patients with poor compliance to medications and in patients who are already taking a large number of drugs.

In these cases, transdermal fentanyl may represent the best way to cancer pain management. Due to its pharmacokinetic characteristics, it also represents a mainstay of treatment for patients with renal failure for which the assumption of morphine, codeine, tramadol and all analgesic drugs which have active metabolites being excreted renally are not recommended.

As physicians cannot predict a patients’ treatment response, previous opioid exposure can be considered as a therapeutic trial that allows the determination of the individual response. After starting the prescribed initial opioid, clinical efficacy may decrease gradually in time or even abruptly, resulting in a need for dose increase. In some cases dose increases do not provide analgesia, and further dose increments are ineffective. Alternatively, adverse effects may occur that are difficult to control with symptomatic therapies.

If an opioid fails to provide adequate analgesia or causes unmanageable adverse effects, this agent has to be stopped and a different opioid should be offered.

For these reason, we strongly support the introduction of methadone, fentanyl and tramadol into the new World Health Organization list of essential medicines for the management of cancer pain.
CANCER PAIN

Definition

According to the International Association for the Study of Pain (IASP), Pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” (1,2). Pain is both a sensation (conscious awareness of a noxious stimulus) and an emotional experience (intense feelings of displeasure resulting in a set of reactive behavior). Pain is always a subjective sensation; it is what the patient says hurts (1,2) and may be affected by emotional (anxiety, depression, hopelessness), social and spiritual components (3) thus defined "Total pain".

The perception of the intensity of pain is not proportional to the type or to the extension of the tissue damage but depends on the interactions between nociceptive and non-nociceptive impulses in ascending pathways, in relation to the activation of descending pain-inhibitory systems.

Pain has been defined as the fifth vital sign by the American Pain Society and its routine assessment is emphasized by international guidelines.

A proper pain assessment is fundamental for an effective and individualized treatment. Poor pain assessment is the greatest barrier to effective cancer pain management (4). As pain is a subjective perception, objective measurement is not possible. A variety of instruments have been developed to measure the intensity of pain (5).
References


CANCER PAIN

Prevalence

Pain is a frequent and impacting symptom not only in advanced cancer but also in any phase of the disease. Pain occurs at diagnosis in 20% to 50% of patients with cancer (1). Pain prevalence ranges from 64% in patients with metastatic, advanced or terminal phase disease, 59% in patients on anticancer treatment and 33% in patients after curative treatment (2).

These data show that, although several guidelines for the treatment of oncological pain have been published (3-5), pain continues to be present in a high percentage of patients in any stage of the disease. Furthermore, no difference in pain prevalence was found between patients on anticancer active treatment and those with advanced or terminal disease. In the latter population, the most frequent causes of pain are painful peripheral neuropathy, radiation-induced brachial plexopathy, chronic pelvic pain secondary to radiation, and post-surgical pain (6). It is necessary to change the oncological clinical practice by implementing a routine pain evaluation, with an analysis of its causes and an appropriate use of analgesic drugs within a multimodal approach. Finally, we have to consider the population of survivors, who need an organized follow up (7,8).

In the 18 studies that reported the pain severity, one third of the patients rated their pain as moderate to severe (2); these patients require a therapy with opioid analgesics to be adequately treated. More precisely, they need a personalized therapy with the right drug at the right dose through the most appropriate route of administration. Opioid switching, the use of adjuvant drugs, and the change of the route of administration must go hand in hand throughout the entire patient’s history, and have to consider both the presence of side effects and the patient’s compliance.

The different pain prevalence according to the site of the primary tumour is well known and described; certain types of cancer are characterized by a high percentage of patients, that is more than 70%, that experience pain and these are head-and-neck, pancreatic, genitourinary, oesophagus, and prostate cancer (2, 9).
Moreover, nearly half of the cancer patients were under-treated with a high variability across study designs and clinical settings. Recent studies conducted both in Italy and in Europe (10,11) confirmed these data, showing that pain was present in all phases of cancer disease (early and metastatic) and was not adequately treated in a significant percentage of patients, ranging from 56% to 82.3%.

Age affects cancer pain (12): younger patients experience more pain and more pain flares than older patients (13); moreover elderly patients receive less opioids than younger patients (14).

In prospective study (15) the adequacy of analgesic care of cancer patients was assessed by means of Pain Management Index (PMI) in 1802 valid cases of in- and outpatients with advanced/metastatic solid tumor enrolled in specifically devoted to cancer and/or pain management (oncology/pain /palliative centers or hospices). The study showed that patients were still classified as potentially under-treated in 25.3% of the cases (range 9.8%–55.3%) (15).

Although in the last years the percentage of patients undertreated is reduced of 25% (43.4% vs. 31.8%) (16) more than 1/3 of the cancer patients with pain do not receive an adequate treatment.

Contrary to the percentage of incidence of pain reported in hematologic patients (5% with leukemia and 38% with lymphoma) in the past literature a significant proportion of patients with lymphoma and leukemia may suffer from pain not only in the last months of life (83%)(10,17) but also at the time of diagnosis and during active therapies (18).

According to the World Health Organization (WHO) the incidence of cancer was 12,667,470 new cases in 2008 and based on the projections it will be more than15 million in 2020 (19).

These statistics suggest that cancer-related pain may be a major issue of healthcare systems worldwide.
References


19. Frankish H. 15 million new cancer cases per year by 2020, says WHO. The Lancet 2003; 361: 1278
Pathophysiology

Pain can be caused by cancer itself or comorbidities; it may result following surgery, radiotherapy, chemotherapy, targeted therapy, supportive care treatments, and/or diagnostic procedures; or it may be unrelated to cancer (1).

Cancer pain may be acute, chronic or episodic. Episodic pain (breakthrough pain) may be unpredictable or predictable (incident pain).

From a pathophysiological point of view, pain can be classified as nociceptive (somatic and visceral), neuropathic (central, peripheral, sympathetic) idiopathic (2,3). However, in the clinical setting, pain is more frequently a mixed pain and may involve multiple mechanisms, explaining the utility of combinations of different classes of analgesic drugs.

About 80% of patients with cancer have ≥ 2 types of pain, and 33% have ≥ 4 types of pain. Pain can be either acute or chronic with acute exacerbations; nociceptive, neuropathic, or mixed; it can also be related to benign comorbidities (e.g. bedsores, osteoporosis, postoperative scar pain, diabetic neuropathy). Different and concomitant causes of pain need a multimodal approach as far as the evaluation of the causes, the intensity, and the treatment are concerned.

In cancer patients, pain is a direct result of the tumor in 75-80% of cases, is caused by anticancer treatments in 15-19% of patients and is unrelated to cancer and its treatments in 3-5% (4). This coincidental pain has a variety of causes, for example it may be related to debility, decubitus (nociceptive), or post-herpetic neuralgia (neuropathic-peripheral and central). Pain may also be a consequence of the diagnostic procedures used in cancer treatment (1). Numerous distinct acute and chronic cancer pain syndromes have been recognized and described (4,5).
References


Treatment of Cancer Pain

Despite published guidelines and educational programs on the assessment and treatment of cancer-related pain, in any stage of oncological disease, unrelieved pain continues to be a substantial worldwide public health concern either in patients with solid and hematological malignancies. The proper and regular self-reporting assessment of pain is the first step for an effective and individualized treatment. According to the W.H.O. guidelines, opioid analgesics are the mainstay of analgesic therapy and are classified according to their ability to control mild to moderate pain (weak opioids, second step of the W.H.O. analgesic ladder), and to control moderate to severe pain (strong opioids, third step of the W.H.O. analgesic ladder). Opioid analgesics may be associated with non-opioids drugs such as paracetamol or nonsteroidal anti-inflammatory drugs and to adjuvant drugs (for neuropathic pain and symptom control). At the moment WHO guidelines are under revision by experts.

In clinical practice the role and the utility of weak opioids (e.g. codeine, dihydrocodeine, tramadol) is a controversial point (1,2) and further research on this topic is needed. Morphine has been placed by WHO on its Essential Drug List since its inception in 1977.

Guidelines tend to consider morphine and morphine-like opioids comparable and interchangeable in the treatment of chronic cancer pain, but individual responses to these drugs can vary (3,4).

A study designed to compare the analgesic efficacy of four strong opioids, that are oral morphine, oral oxycodone, transdermal fentanyl, and transdermal buprenorphine, show that the four drugs are characterized by the same level of pain relief, but 8.9 to 14.4% of the patients are identified as not responders (the highest percentage referring to patients treated with buprenorphine) and 11 to 15.3% of the patients as poor responders. Furthermore, even those patients who experience a good analgesic response to these opioids need continuous dose adjustments (the highest increase being needed by those patients treated with fentanyl) and patients treated with morphine frequently need switches to other opioids. Patients treated with oxycodone more frequently need the use of adjuvant.
drugs. The side effects are similar, apart from those affecting the CNS, such as allucination and confusion, which are more frequent during a treatment with morphine (3).

These data confirm that there is no evidence to show superiority or inferiority of these drugs compared to morphine. The purpose of the overview is to highlight new data about the efficacy and tolerability of opioids that are different than oral morphine, which is now the essential drug according to WHO, [and alternatives limited to hydromorphone and oxycodone].

Among these new drugs we include methadone, transdermic fentanyl and tramadol.

Oral methadone is considered to be an useful and safe alternative to oral morphine. Because of its pharmacokinetics and pharmacodynamics methadone is to be used by experts in order to avoid overdose. Methadone has the potential to control pain which is difficulty controlled by other opioids. Although the oral administration is considered the first choice, intravenous, subcutaneous, rectal, transdermal, sublingual, intranasal, and spinal routes may be used in particular situations.

Transdermal opioids, such as fentanyl, are reserved to those patients whose opioid need is stable, when gastrointestinal symptoms preclude the oral administration, and when compliance to oral opioids (which need multiple daily administration) is poor.

Switching from one opioid to another can improve analgesia and tolerability (1).

Tramadol may be considered as an alternative to morphine in those countries where morphine is not available.
References


METHADONE

Introduction

Pharmacology of methadone

Chemical characteristics

Methadone is a synthetic opioid agonist with a chemical structure totally different from that of the classical opium alkaloids such as morphine and codeine.

Methadone is used as a racemic mixture of levorotatory (L-methadone) and dextrorotatory (D-methadone) isomers. For many years, the analgesic efficacy of methadone has been attributed almost entirely to the action of L-methadone, whereas D-methadone was considered to be an excipient. Recent findings indicate that D-methadone also contributes to the analgesic action of the racemic mixture by blocking N-methyl-D-aspartate (NMDA) receptors [1-3].

Methadone is a basic drug, available as a hydrochloride salt in an aqueous solution that can be administered by oral, parenteral, or rectal routes.

Pharmacodynamics

Several studies have demonstrated that the affinity of methadone to mu receptors is similar to that of morphine [4]. Delta and k opioid receptor activation also produces analgesia. The affinity of methadone for k receptors does not seem significantly different from that of morphine, but methadone has a greater affinity for δ receptors than morphine does [5].

Moreover, unlike morphine, both isomers of methadone are able to block NMDA receptors. Finally, the L-isomer of methadone inhibits the serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE) neuronal re-uptake [6]. Because both the blockage of NMDA receptors and the activation of serotoninergic and noradrenergic pathways descending from the brainstem inhibit nociceptive transmission [7,8], the analgesic action of methadone is probably mediated by synergistic mechanisms different from those of morphine.
Pharmacokinetics

Methadone is a lipophilic drug easily and rapidly absorbed by the gastrointestinal tract. Indeed, its oral bioavailability is 80% (range, 41–99%). The peak plasma level occurs 4 hours after oral administration [9,10]. Methadone has a large distribution volume with tissue binding higher than protein binding, and accumulation occurs with repeated dosing; consequently adverse effects related to methadone are delayed over the time because linked to methadone reabsorption from the tissue. The protein binding of methadone has been shown to range from 60% to 90%. Methadone is mainly bound to a1-acid glycoprotein (AAG). Because cancer is frequently associated with elevated levels of AAG, the free fraction of methadone may vary significantly among cancer patients [11,12]. Lower concentrations of AAG increase free plasma concentrations and the activity of methadone. The greater lipid solubility of methadone explains its enhanced protein binding and its considerable distribution and accumulation in tissues. The increased protein binding and tissue accumulation in turn contribute to the prolonged retention of methadone in plasma, as is particularly evident during repeated treatment. Methadone has been described as a drug with a rapid and extensive distribution phase followed by a slow elimination phase. The terminal elimination half-life varies from 13 to 58 hours (120 hours in some patients) [13]. In the liver, methadone undergoes an extensive oxidative biotransformation through N-demethylation. In humans, the hepatic extraction ratio indicates that less than 10% of methadone reaching the liver is extracted from the blood [14]. This value is similar to the value of free fraction of methadone in blood. Therefore, a considerable change in the binding of methadone could alter the hepatic clearance of methadone. The two major metabolites that result from hepatic biotransformation do not exert any pharmacological activity [9]. In addition to the hepatic extraction, methadone is partially metabolized in the intestinal wall by CYP3A4 enzyme [15]. The liver metabolism and fecal excretion is the primary route of methadone elimination in most persons. Indeed, a significant portion of the methadone that is filtered through the glomerulus is reabsorbed by the kidney, and approximately 60% of methadone is eliminated by non-renal routes. Although a decreased urinary
pH can significantly increase the renal clearance of methadone, the renal route is not a major route of elimination if urine pH is above 6 [16].

Several studies have shown large variations among individuals in methadone pharmacokinetics. As with the other opioids, no clear relationship between plasma concentrations and analgesic effects of methadone has been established [17]. The main pharmacokinetic differences between morphine and methadone are shown in Table 1. Of course, the dose adjustment is more difficult with methadone than with a drug with a shorter half-life, such as morphine. For this reason, a good knowledge of recently refined equianalgesic dose tables is important to achieve good pain management while establishing the optimum methadone dose, especially in patients previously treated with morphine.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Main pharmacokinetic differences between methadone and morphine</th>
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<tbody>
<tr>
<td>Characteristic</td>
<td>Methadone</td>
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<tr>
<td>Oral bioavailability</td>
<td>80%</td>
</tr>
<tr>
<td>Protein binding</td>
<td>60–90%</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>30 hours</td>
</tr>
<tr>
<td>Active metabolites</td>
<td>No</td>
</tr>
<tr>
<td>Influenced by renal disease</td>
<td>+</td>
</tr>
<tr>
<td>Influenced by liver disease</td>
<td>+++</td>
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</tbody>
</table>

+, slightly; +++ highly.

**Drug interactions**

In general, a drug interaction can be defined as one substance’s altering the effects of another drug being administered at the same time [18]. Drug interactions can involve drugs and chemicals, drugs and nutrients, or drug–drug interactions. Drug–drug interactions are the most significant and can be broadly categorized as pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions may produce changes in absorption, protein binding, distribution, biotransformation, and excretion.
Pharmacodynamic interactions involve the drug mechanisms of action and usually can be predicted and recognized more easily than pharmacokinetic interactions. As an example, the concomitant administration of two drugs with depressant effects on the central nervous system (e.g., methadone and a benzodiazepine) will increase the likelihood of negative effects caused by the inhibition of brain functions (e.g., respiratory depression and sedation).

There are several interactions of methadone with the drugs most commonly used to treat cancer patients, with particular reference to the interactions involving the cytochrome P-450 system in the liver. A characteristic of low-extraction drugs such as methadone is that changes in hepatic metabolism by induction or inhibition may significantly affect their clearance and elimination half-life. Therefore, the probability of drug interaction is higher with methadone administration than with morphine or other opioids. Unlike morphine, which is glucuronated, methadone is metabolized by the cytochrome P-450 group of enzymes and does not produce active metabolites. The main enzyme mediating N-demethylation of methadone in the liver is CYP3A4, with lesser involvement of CYP1A2 and CYP2D6 [4,19]. Therefore, the most important interactions between methadone and other drugs involve drugs that induce or inhibit CYP3A4 (Table 2). These drugs can reduce or

<table>
<thead>
<tr>
<th>Inhibitors</th>
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<tr>
<td>Ketoconazole</td>
<td>Carbamazepine</td>
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<td>Fluconazole</td>
<td>Phenytoin</td>
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<td>Nefazodone</td>
<td>Rifampicin</td>
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<td>Clarithromycin</td>
<td>Ritonavir</td>
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<td>Erythromycin</td>
<td>Glucocorticoids</td>
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<td>Ciprofloxacins</td>
<td>Fusidic acid</td>
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<tr>
<td>Norfloxacin</td>
<td>Cimetidine</td>
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</table>

* active metabolite of fluoxetine
increase methadone plasma concentrations. Because methadone strongly inhibits CYP2D6 [20], it can reduce the hepatic biotransformation of drugs metabolized by this enzyme, such as the neuroleptics haloperidol, domperidone, and risperidone and the tricyclic antidepressants. Table 3 shows the most important methadone drug interactions in clinical conditions. Although a drug–drug interaction is more often produced by a drug capable of inhibiting or increasing hepatic metabolism, an interaction can also be related to the concomitant administration of drugs that are metabolized by the same CYP450 enzyme (eg, methadone and risperidone).

Table 3
Main pharmacokinetic interactions of methadone

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect of the interaction</th>
</tr>
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<tbody>
<tr>
<td>Zidovudine</td>
<td>↑ plasma levels of zidovudine</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>↓ plasma levels of methadone</td>
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<tr>
<td>Nifedipine</td>
<td>↑ plasma levels of nifedipine</td>
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<td>Fluoxetine</td>
<td>↑ plasma levels of methadone</td>
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<td>Fluvoxamine</td>
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<td>Sertraline</td>
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<td>Tricyclic antidepressants</td>
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<td>Carbamazepine</td>
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<td>Phenytoin</td>
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<td>Phenobarbital</td>
<td>↓ plasma levels of methadone</td>
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<tr>
<td>Risperidone</td>
<td>↓ plasma levels of methadone</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>↓ plasma levels of methadone</td>
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References


Efficacy of Methadone in Clinical Studies

Total N. of Publication / Year of Publication

Number of Publications


Year of Publication
Figure 1. Consort – like report of Eligible Papers.

Identified Papers From Medline and Cross References*  
N= 90

Not Eligible Papers
Toxicities N=9  
Pharmacokinetics N= 6  
Epidemiological Studies N= 17  
Other N= 22  
Total Not Eligible N=54

Eligible Papers  
N= 36

Source: PUBMED  
Search: methadone AND (cancer pain)  
Date 8-11-2016
Summary of data for Efficacy (Table 1, Appendix 1).

Search Method
A literature review based on the guidance of the Centre for Reviews and Dissemination was conducted.

An iterative approach was used starting with an electronic search of the MEDLINE database (via PubMed – customized range date until November 8th, 2016. We considered all the eligible paper published in the last five years (Figure 1). The generic search terms “methadone” AND “cancer pain” were used. Citation tracking and search for all related eligible articles in PubMed were performed. We identified 36 eligible paper for efficacy analysis with N=3 Randomized Controlled Trials, N=8 Systematic Reviews, N=2 prospective open label studies, N=1 Observational Studies, N=6 retrospective Studies, N=9 Case report /Case series and N=7 letter to the editor. Major percentage of evidence came from systematic reviews, with about 22% of eligible papers.

Our report did not consider letters to the editor.

Levels of evidence analyzed may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size. For more details please refer to the Oxford Centre for Evidence-Based Medicine (http://www.cemb.net/index.aspx?o=5653).

Randomized Controlled Trials (Table 2, Appendix 1).
We identified N= 3 randomized controlled trials published between 2013 [1] and 2016 [2].

The first trial published by Poulain P et al. in 2016 (1) was a national, randomized, multicenter trial aimed to compare two methadone titration methods (stop-and-go vs. progressive) in patients with cancer-related pain who were inadequately relieved by or intolerant to Level 3 opioids where the primary end point was the rate of success or failure at Day 4, defined as pain relief (reduction of at
least two points on the visual scale and a pain score <5 for two consecutive days) and no overdose (Rudkin scale ≥3 and respiratory rate <8/minute). Pain relief was obtained in 80% and the rate of success/failure was approximately 40% at Day 4 in both groups, with overdoses in 13% of the patients throughout the study.

The second study published by Humann J et al. (2) was a randomised controlled trial versus fentanyl performed with 52 strong opioids naive patients with head-and-neck cancer with pain Numerical Rating Scale > 4 and a neuropathic pain component. The primary outcomes were reduction in average pain, clinical success (defined as 50% average pain decrease) and reduction in pain interference. Reduction in NRS was higher with the use of Methadone at 1, 3 and 5 weeks (pain change 2.9, 3.1 and 3.1) compared to Fentanyl (1.4, 1.7 and 2.0). This difference was significant at 1 (p = 0.011) and at 3 weeks (p = 0.03) and represented the first evidence of efficacy of Methadone versus Fentanyl in cancer patients with a neuropathic pain component. The last study was a RCT published by Lauretti GR et al. in 2013 in 722 cancer patients randomized to six groups and prospectively studied to examine analgesia and adverse effects for 3 weeks (3) (please see Table 2 for details). Epidural methadone plus lidocaine resulted in dose-dependent analgesia, further improved by epidural dexamethasone, which also improved fatigue.
Systematic Review (Table 3, Appendix 1).

We identified N= 8 Systematic Reviews published between 2012 [3], 2014 [2], 2015 [2] and 2016 [1].

The first paper published by Taveros et al. in 2016 (4) regards a specific setting of pain management i.e. the use of methadone for cancer pain in patients on treatment with methadone for chronic substance abuse. The authors searched PubMed, PsychINFO, EMBase, Clinical Key, the Cochrane Library and CINAHL resulting in 680 hits with only 7 met inclusion criteria for the study. Most of the studies favored the use of methadone either in scheduled divided doses every 4-8 hours or by continuous intravenous infusion. The conclusions were that treating MMT-maintained patients with methadone for analgesia may be preferable to using other opioid analgesics, but the overall strength of the evidence was poor, consisting mainly of case series. The second paper published in 2015 by MC Lean S et al. (5) was a systematic review on the methods of rotation to methadone from other opioids. Authors selected 25 of a total of 3214 identified potentially relevant studies. As already observed, the evidence identified was mainly from uncontrolled observational studies and studies were heterogeneous in methodology and outcome measures. One trial compared three-day switch (3DS) and rapid conversion (RC) methods; two, 3DS; 10, RC; nine, ad libitum (AL). Success rates were as follows: 3DS-93%, RC-71.7%, and AL-92.8%. The single clinical trial and retrospective studies demonstrated poorer analgesia and an excess of adverse events in the RC group (five dropouts because of AEs) compared with the 3DS group with no severe AEs). The three days switch probably represent the best and safety rotation method.

Good P et al (6) conducted an important systematic review published in 2014 where the authors analyzed the evidence for the use of methadone in cancer pain management. The authors conducted a systematic literature search for randomized controlled trials (RCTs) published post the 2007 Cochrane review of methadone in cancer pain.
The studies used different routes of administration, dosing, initiation, and titration of methadone and distinct pain scoring tools and did not address the issues raised by the Cochrane review. Methadone has an important role in the management of cancer pain, with many advantages including low cost, high oral bioavailability, rapid onset of action, once-daily dosing, and postulated benefits in difficult pain control scenarios. However, due to limited research in this area, methadone dosing remains a challenge, with vigilant dose initiation, adjustment, and monitoring required.

Taberna M et al. carried out another systematic review in 2014 (7) focusing on the role of methadone in pain management in elderly population. This was the first important review on this setting. Only seven articles were obtained none of them specific to methadone use in elderly patients with cancer. For these aspects, we can say that there are insufficient data on the use of methadone as an analgesic in the elderly with cancer.

On this way, especially for opioids switching to methadone, we report the systematic review from Mercadante S et al (8) were author conclusions were that existing data were not conclusive because this aspect did not receive particular attention in most studies and age has not been found to be independently associated with the dose ratio.

No more relevant adjunctive data about methadone were find by Koyyalagunta D et al (9) in their systematic review. Authors reported that the evidence for methadone was poor based on low quality studies with inconsistent results.

Due to the particular focus of the review and the poor level of evidence, we did not consider the paper of Afsharimani et al and Ripamonti CI (Table 3) for our report.
Retrospective Studies (Table 4, Appendix 1).

We identified N= 6 Retrospective Studies published between 2012 [1], 2013 [1], 2015 [1] and 2016 [3].
Primary endpoints for these analyses were safety and efficacy/effectiveness (for one paper only).
All identified papers were uncontrolled retrospective analyses with heterogeneous methodology and outcome measures.
The first study published in 2016 by Sugiyama Y et al. (10) regards the effectiveness on management of neuropathic pain in 22 non-opioid naïve cancer patients with the mean FPS (FACE Pain Scale) score reduction from 4.43 to 1.86, and methadone switching either reduced the number of prescriptions or stopped them entirely in 12 out of 17 (70.5%) patients who had used adjuvant analgesics before switching to methadone.
This was another evidence on neuropathic pain relief with methadone in cancer patients, as just reported by Haumann J et al. (2) (Table 1).
Courtemanche F et al. reported the efficacy and safety on the use of Methadone as co-analgesic in the management of cancer pain (11). A cohort of 146 patients was followed retrospectively for up to 60 days with 49% of them qualified as significant responders (≥30% reduction in pain intensity).
No clear data was available about cumulative dosing of methadone and, as reported by author, there was a substantial amount of missing data.
Similar data on the use of methadone as co-analgesic drug in the management of cancer pain came from the analysis of Salpeter et al. (12,13).
Author reports the use of low dose of methadone (median daily dose, 5 mg) in association with haloperidol for pain control patients underwent conversion from another opiate without dose escalation or opioid-induced hyperalgesia.
Finally, another important analysis came from the retrospective study of Peirano GP et al. (14) on the safety and efficacy of methadone in a developing country palliative care unit as first line
treatment as an helpful palliative strategy in low-resources countries given its long-acting effect at low cost.

**Prospective Open Label studies; Observational studies (Table 5, Appendix 1).**

We identified N= 2 Prospective Open-label Studies and N=1 Observational Study.

All identified papers were very heterogeneous for outcome measures evaluation tools.

Primary end-point for all these studies was the efficacy and safety of Opioid rotation to methadone for refractory cancer pain.

The most important study was published by Porta Sales J et al. in 2016 (15). This was a Prospective Open-label Studies of 145 patients whose treatment was rotated from other opioids to methadone. Main outcome measure was change in the variable "worst pain" at day 28 with Brief Pain Inventory.

Rotation to methadone was performed for the following reasons: poor pain control (77.9%), opioid side effects (2.1%), or both (20%). The mean daily oral morphine equivalent dose before rotation was 193.7 mg. The median worst and average pain scores decreased significantly (p < .0001) from baseline to day 28: The median worst pain score decreased from 9 (interquartile range [IQR]: 8-10) to 6 (IQR: 3-8), and the median average pain score decreased from 6 (IQR: 5-7) to 4 (IQR: 2-5). The proportions of patients with moderate to severe worst and average pain decreased by 30.3% and 47.5%, respectively, by day 28. No increase in opioid toxicity was observed during the study.

The results of this study, conducted prospectively under real clinical conditions, support the efficacy and safety of oral methadone as a second-line opioid in ambulatory patients with cancer. Data from the other reported trials (Table 5) are similar to the Porta Sales’ ones.
Case Report; Case Series (Table 6, Appendix 1).

We identified N= 10 Case Reports/Case Series published from 2012 [3], 2013 [5], 2014 [1] to 2015 [1].

Three of them regarded the safety and efficacy of the intra-venous administration of Methadone. One of them (Rasmussen VF et al – 16) reported two case report of high dose of IV methadone in pediatric cancer patients.

Similar to the analyzed data in our report, two studies reported the efficacy of Methadone as co-analgesic drug in the management of refractory cancer pain (17,18) and two other studies (19,20) analyzed the switching to methadone from other opioids.

Globally, presented data are in line with other reported results with high level of evidence.
References


Toxicities of Methadone in Clinical Studies

Figure 1. Search for Toxicity.

Identified Papers From Medline and Cross References*  
N= 90

Not Eligible Papers
- Efficacy N=36
- Pharmacokinetics N= 6
- Epidemiological Studies N= 17
- Other N= 22
Total Not Eligible N=81

Eligible Papers
N= 9

Source: PUBMED  
Search: methadone AND (cancer pain)  
Date 8-11-2016
Summary of data for Toxicity (Table 1, Appendix 2).

Search Method

A literature review based on the guidance of the Centre for Reviews and Dissemination was conducted.

An iterative approach was used starting with an electronic search of the MEDLINE database (via PubMed – customized range date until November 8th, 2016. We considered all the eligible paper published in the last five years (Figure 1). The generic search terms “methadone” AND “cancer pain” were used. Citation tracking and search for all related eligible articles in PubMed were performed. We identified 36 eligible paper for toxicity analysis with N=2 Reviews, N=1 Observational Studies, N=2 retrospective Studies, N=3 Case report /Case series Major percentage of evidence came from case reports.

Levels of evidence analyzed may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size. For more details please refer to the Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=5653).
Review (Table 2, Appendix 2).

We identified N=2 reviews published between 2013 [1] and 2016 [1].

The first paper published in 2014 by Dowson c et al. (1) focus on the development of developed bilateral peripheral edema from methadone in the in patient with ependymoma with low back and scrotal pain. In the associated review, authors explored the possible underlying mechanisms.

There have been cases published reporting the development of edema with methadone maintenance therapy but no cases on the association with methadone and peripheral edema in the palliative care setting.

Following cessation of methadone peripheral edema was resolved.

The second paper published by Dahan A et al. (2) analyzed the opioid-induced respiratory depression associated with the use of methadone.

This is a review from thirty-four reports describing 42 chronic pain patients experiencing opioid-induced respiratory depression. Cases published before the year 2000 (pre-2000) predominantly involved morphine in cancer patients, whereas cases since 2000 (post-2000) predominantly involved methadone or transdermal fentanyl in non-cancer pain patients. Specific factors that contributed to OIRD were elevated opioid plasma levels due to renal impairment and sensory deafferentiation in pre-2000 cases, and elevated plasma levels due to drug interactions on the cytochrome P450 in post-2000 cases. Due to the setting (chronic non cancer pain), we reported the data only for pharmacovigilance info on the use of methadone, but there are not reviews or systematic reviews particularly focused on cancer patients.
Retrospective Studies (Table 3, Appendix 2).

We identified N= 2 retrospective studies published between 2013 [1] and 2016 [1]. Cardiac toxicities from methadone are one of the most reported toxicities from this drug. Methadone prolongs cardiac conduction, from mild corrected QT (QTc) prolongation to torsades de pointes and ventricular fibrillation, in adults. However, methadone use for pain and its effects on cardiac conduction have not been investigated in pediatric populations.

Anghelescu DL et al. (3) published in 2016 a retrospective review of QTc intervals in patients receiving methadone in a 4-years observation period.

Of the 61 patients who received methadone, 37 met our inclusion criteria and underwent 137 electrocardiograms (ECGs). During methadone treatment, the mean QTc was longer than that at baseline (446.5 vs. 437.55 ms). The mean methadone dose was 27.0±24.3 mg/d (range, 5-125 mg/d; median, 20 mg/d) or 0.47±0.45 mg/kg per day (range, 0.05-2.25 mg/kg per day; median, 0.37 mg/kg per day), and the mean duration of therapy was 49 days. The authors identified a correlation between automated and manual ECG readings by two cardiologists (Pearson r=0.649; p<0.0001), but the authors found no correlations between methadone dose or duration and concurrent QTc-prolonging medications, sex, age, electrolyte abnormalities, or renal or hepatic dysfunction. Authors concluded that at a clinically effective analgesic dose, methadone dosage and duration were not correlated with QTc prolongation, even in the presence of other risk factors, suggesting that methadone use may be safe in pediatric populations.

Second study published by Moryl N et al. in 2013 (4) focused on metabolic toxicities from methadone, analyzing whether or not rapid methadone dose increase can be associated with onset of hypoglycemia by a retrospective chart review of 59 consecutive opioid-tolerant patients with cancer who received methadone for pain while inpatients in a tertiary cancer center. Eleven patients had hypoglycemia while receiving methadone, of them two patients had at least two episodes of hypoglycemia. In the 11 cases of documented hypoglycemia, mean methadone dose was nearly
doubled (92 percent increase) within 2 days before the onset of hypoglycemia. None of the other recorded factors correlated with glucose level in this group of patients. Authors concluded that a patient who develops unexplained sweating, palpitations, or lethargy during methadone titration may benefit from blood glucose monitoring.

**Observational Studies (Table 4, Appendix 2).**

We identified N= 2 observational studies published between 2013. As previously reported in our analysis, cardiac toxicities from methadone are one of the most reported toxicities.

All the identified observational studies analyzed focused on cardiac toxicity, particularly on prolonged QTc interval.

Most recent retrospective study (3) demonstrated that at a clinically effective analgesic dose, methadone dosage and duration were not correlated with QTc prolongation, even in the presence of other risk factors.

In their prospective study, van den Beuken-van Everdingen MH et al. (5) in a period of 3 years, while 130 patients used methadone as pain treatment at a stable dose for at least 1 week, 12-lead electrocardiograms (ECGs) were performed. Corrected QT times, demographic features, methadone dose, duration of therapy, and relevant co medication were documented. The study found that in our patients with pain, with relatively low doses of methadone, 5 percent had QTc times ≥500 ms and were thus at serious at risk for TdP. ECGs have to be made in all patients with methadone therapy 1 week after introducing methadone.

No additional data were found in the study of Mercadante et al. (6).

We can conclude that, about cardiac safety, evidences are poor and not clear and we think that more studies are required.
We identified 3 observational studies published between 2012 [2] and 2013 [1]. After full text paper analysis, we excluded 2/3 studies from our report because the setting was the chronic non-cancer pain management. We considered only the case reported by Amos LB et al. (7) about severe central sleep apnea in a child with leukemia as serious adverse effect from chronic methadone therapy. Due to the general conditions of the patient with chemotherapy-related cerebral atrophy and renal insufficiency, we think that impaired methadone clearance may have also contributed to the severity of his sleep-disordered breathing. Maintenance methadone treatment is not a common pediatric practice; therefore, the adverse effects of methadone therapy, are rarely reported in children and the use of this drug in the pediatric population need trained expertise on pain management.
References


**Clinical considerations on Methadone**

Methadone is an old drug (1) considered to be a useful alternative to oral morphine, hydromorphone and transdermal fentanyl in treating moderate to severe cancer–related pain and extensive reviews on the subject have been published in recent years (2-4).

Oral methadone provides the potential to control pain that does not respond to morphine or other opioids because methadone shows incomplete cross-tolerance with other \( \mu \)-opioid receptor agonist analgesics (5-11). Moreover, there is the possibility of using it instead of other opioids when accumulation of active metabolite is the cause of side effects such as myoclonus, sedation, confusion, nausea and vomiting (5-11). Although morphine and methadone demonstrate approximately the same analgesic potency after single dose administration, in switching from one opioid to methadone a reduction of the equianalgesic dose by one-fourth to one-twelfth is recommended (12,13). Methadone represents an effective alternative to oral morphine, but more caution is needed in its administration, compared with other opioids, because of marked inter-individual differences in its half-life in plasma. This is the main reason why attention is required when using this drug in treating chronic cancer pain.

The low cost of methadone paradoxically may contribute to the limited knowledge of its characteristics and to the restricted therapeutic use of this drug because of the little financial incentive for pharmaceutical companies to invest in research or to disseminate scientific information. The low cost of methadone, is of great importance for its ability in developing countries (14).

For the strength of evidences reported, we can conclude that in the last five years there was a lot of published paper on this setting. However, quality of these study remains poor, today methadone still represent a good and efficacious treatment on the management of cancer pain in specific conditions.
References


TRANSDERMAL FENTANYL SYSTEM (TTS)

Introduction

Pharmacokinetics and Pharmacodynamics

Substances with high lipid solubility and molecular weight below 800-1000 daltons (kDa) can pass through the skin. The absorption rate varies according to different factors such as the type of the vehicle, the skin characteristics (the thickness of stratum corneum), conditions, presence of cachexia, body surface (1).

In general drugs that are successfully administered transdermally are those in which the daily dose is very low (no more than a few milligrams). Patient compliance with this route of administration is excellent, and skin reactions are rarely observed. Among opioids, the potent synthetic drug fentanyl citrate is particularly suitable for transdermal administration, and its utility in pain therapy has been extensively evaluated. Pharmacokinetic studies demonstrated that the rate of absorption of fentanyl from the transdermal delivery is constant beginning 4-8 h after placement of the patches. Steady state is reached on the third day. However, a wide individual variability exists (2). There is a lag period after patch application before plasma concentrations approach therapeutic levels. This lag period is highly variable, with a mean value of about 13 h (3). Fentanyl is metabolized in the liver primarily (> 75%) by CYP3A4 to inactive norfentanyl (4). Fentanyl renal clearance accounts for less than 10% of the dose (5, 6). Fentanyl is ~ 80% bound in plasma to albumin and α1-acid glycoprotein (7). Intravenous and Transdermal fentanyl clearance is reduced by impaired liver function and co administration of CYP3A4 inhibitors and increase with co administration of CYP3A4 inducers (8,9). The transdermal fentanyl works till 72 hours. However, published data show that application intervals have to be shortened in about 25% of patients (10) at 48-60 hours because on the 3rd day of each patch period the need of rescue doses of short release oral morphine was major of 1st and 2nd day (10,11). In 11 to 43% of patients during long-term treatment, the patch had to be changed every 48 h (12).
The effectiveness of TTS fentanyl was first demonstrated in postoperative pain. Especially for the high incidence of respiratory depression, this use is now contraindicated. Conversely, in stable, chronic, cancer pain this formulation offers an interesting alternative to oral morphine. In comparison with oral morphine TTS fentanyl seem to cause fewer gastrointestinal side effects, with special reference to constipation (13,14). Of course, this formulation is contraindicated during the titration phase, or to control breakthrough pain.

The permeability coefficient for fentanyl is affected by temperature. A rise in body temperature to 40 ºC may increase the absorption rate by about one-third (13). Acute toxicity related to increased absorption secondary to high temperature has been reported (14). A recent study in volunteers demonstrated that the application of local heat to the transdermal patch significantly increase systemic delivery of fentanyl (15).

Four cases of death due to the intravenous injection of fentanyl extracted from transdermal patches have been reported (125).

To minimize the problem of the “dose-dumping” due to membrane damage, and the risk of illegal diversion, a transdermal matrix patch formulation of fentanyl has been developed (16).
References


Efficacy of Transdermal Fentanyl in clinical Studies.

Figure 1. Consort – like report of Eligible Papers for Efficacy.

A literature review based on the guidance of the Centre for Reviews and Dissemination was conducted.

An iterative approach was used starting with an electronic search of the MEDLINE database (via PubMed – customized range date until November 8th, 2016. We considered all the eligible paper published in the last five years (Figure 1). The generic search terms (“fentanyl” AND “cancer pain”) were used. Citation tracking and search for all related eligible articles in PubMed were performed. We identified 19 eligible paper for efficacy analysis with N=1 Randomized Controlled Trials, N=4 Reviews, N=7 prospective open label studies, N=7 Retrospective Studies. We did not
find case reports/case series. Major percentage of evidence came from prospective open-label studies and retrospective studies reviews, with about 74% of eligible papers. Our report did not consider letters to the editor.

Levels of evidence analyzed may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size. For more details please refer to the Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=5653)

**Randomized Trial (Table 2, Appendix 3).**

In the last five years literature search, only one randomized controlled trial was identified. The study was published by Raptis E et al. in 2014 (1) and was a randomized open – label trial on the use of pregabalin versus opioids for the treatment of neuropathic cancer pain. Patients were randomized into two groups and received increasing doses of either oral pregabalin or transdermal fentanyl for 28 days. VAS score, patient satisfaction, need for opioid rescue, and adverse events were recorded.

In the pregabalin group, a significantly higher proportion of patients achieved at least 30% reduction in VAS compared with the fentanyl group (73.3%, 95% CI: 60.3%-83.93 vs. 36.7%, 95% CI: 24.5%-50.1%, P < 0.0001, respectively), while the percentage mean change from baseline was also significantly different [46% (95% CI: 39.5%-52.8%) for pregabalin and 22% (95% CI: 14.9%-29.5%) for fentanyl (P < 0.0001)]. Patient-reported satisfaction was more frequent with pregabalin, while adverse events and treatment discontinuations were more frequent in the fentanyl group. We can say that a prompt use of a neuropathic pain-specific adjuvant, such as pregabalin may lead to better control of the neuropathic component, with opioid-sparing effects. However, trans-dermal fentanyl still remains the optimal choice for pain management.
**Retrospective Studies (Table 3, Appendix 3).**

We identified N= 7 Retrospective Studies published between 2011 [1], 2013 [1], 2015 [1] and 2016 [4].

Main intervention of these studies was the opioid switching to TDF in advanced cancer patients. The objective of these analyses was the opioids conversion ratio (for four paper) and the safety and efficacy of TDF formulations.

The most recent study published by Reddy A et al. in 2016 (2) reviewed 2471 consecutive patient visits (938 patients) to determine the opioid rotation ratio of TDF to strong opioids, as measured by morphine equivalent daily dose (MEEDD).

The same authors published in 2016 another important retrospective analysis on 6790 consecutive patients from 2010 to 2013 to identify those who underwent rotation from other opioids to TDF (3). In total, 129 patients underwent opioid rotation from other opioids to TDF. The mean patient age was 56 years, 59% were men, and 88% had advanced cancer. Uncontrolled pain (80%) was the most frequent reason for opioid rotation. In 101 patients who underwent opioid rotation and had no worsening of pain at follow-up, the median ORR from net MEDD to TDF (in mg per day) was 0.01 (range, -0.02 to 0.04), and the correlation coefficient of the TDF dose to the net MEDD was 0.77 (P < .0001). The ORR was not significantly impacted by body mass index or serum albumin. The ORR of 0.01 suggests that an MEDD of 100 mg is equivalent to 1 mg TDF daily or approximately 40 micrograms per hour of TDF (1000 micrograms/24 hours). On this way, another similar study was published in the same year by Matsumura C. et al. (4) about conversion ratio and adequate fentanyl dose in 122 patients with cancer pain in opioid switching from oral oxycodone.

We can say that we should carefully and rapidly control pain in opioid switching based on the adequate dose indicated in these studies.
Two papers analyzed safety and efficacy of once-a-day TDF formulations (5,6). Data supports the use of this formulation as a dominant strategy for patients receiving a 72-h transdermal fentanyl not lasting 72 h.

The last study considered in our report regards data published by Bilen A. et al in 2012 (7) about the use of TDF among geriatric population in 181 patients. Demographic data, cancer type, duration of pain, side effects, visual analog scale (VAS) score, treatment assessment scale (TAS) score, TDF dosage, and the number of patients in whom therapy has been terminated were recorded. After the usage of TDF, reduction in pain score was observed in both groups (p<0.001). The TAS score was similar between the groups at the end of the first month, but it was lower in Group G in the following months. Constipation, dry mouth, somnolence, and dyspnea were seen more frequently in Group G. Because of these side effects, the number of patients in whom therapy was terminated was higher in Group G. Authors concluded that the TDF patch is a good choice for cancer pain treatment for both adult and geriatric patients. Since it was observed that the incidence of side effects was higher in the geriatric patients, they should be treated more carefully.
Prospective Open-label Studies; Observational Studies (Table 4, Appendix 3).


The first prospective open-label studies analyzed (8) the use of Transdermal Fentanyl for pain management in Opioid-Naive Pediatric Cancer Patients where sixty-four male and female pediatric patients with moderate to severe chronic cancer pain, ages ranging 2-14 years, were included. Patients were observed for pain relief using the Visual Analog Scale and the Wong-Baker FACES Pain Rating Scale, play performance score, and for side effects. There was significant improvement of visual analog scale and FACES pain scores from the baseline to the second day of application (P < 0.001). By the 15th day, scores reached 1.18 ± 0.393 and 1.13 ± 0.35, respectively (P < 0.001).

Play performance scale improved from the third day of application of the patch when compared with the baseline (P < 0.001), reaching 55.02 ± 8.35 (P < 0.001) at the end of the study. The sedation score increased on the second day to 2 in 10 patients and to 3 in 54 patients. By the seventh day, 56 patients had a sedation score of 1. All patients returned to baseline by the 15th day. Itching was reported in 16 cases, and erythema occurred in 10 cases. No significant side effects were reported.

Kang JH described similar data in 2015 (9) on the efficacy of low-dose transdermal fentanyl in opioid-naive cancer patients with moderate-to-severe pain. Low-dose TDF was an effective treatment for patients with cancer pain of moderate-to-severe intensity.

Data reported from Zhu YL et al (10) on the use of new formulation of TDF among Chinese population did not discord with all reported ones, but not all the patients were opioid naïve.

The other analyzed papers regarded the opioid switching to TDF. We reported two observational studies and one prospective open-label study. The last one, published by Minami S in 2014 (11) was an open-label two-centered prospective study in patients with thoracic malignancy suffering persistent malignancy-related pain with numeric rating scale of pain intensity ≤ 3 which had been
controlled by oral oxycodone ≤ 20 mg/day. Eligible patients switched from oral oxycodone to 12.5 μg/h of transdermal fentanyl matrix patch. The dose was allowed to be titrated upwards every 3 day by 25-50%, except for the first increase from 12.5 μg/hr to 25 μg/hr, until achieving adequate pain control. The data on patients' global assessment scores measured on a five-step scale, an 11-point numeric rating scale of pain intensity, the severity of adverse effects using a four-point categorical rating scale, and the Epworth sleepiness scale questionnaire were collected for 15 days. Forty-nine eligible patients were analyzed. Overall patients' satisfaction score significantly improved from day 1 (2.7 ± 0.9) to day 15 (2.3 ± 0.9) (p < 0.05), and 90% and 78% of patients remained to receive the minimum dose of fentanyl patch on day 8 and 15 from the opioid switch. There was a significant difference in sleepiness throughout the study period, though no difference was detected in pain intensity and other adverse effects.

No significant data were reported from the other two observational studies (Table 4).

Systematic Reviews and Non-Systematic reviews (Table 5, Appendix 3).

We identified N= 2 Systematic Reviews and N=2 other non-systematic reviews published between 2012 [1], 2013 [1] and 2014 [2].

We did not find papers published in the last two years.

The most important evidence came from the Cochrane Systematic Review on the use of transdermal fentanyl for cancer pain published in 2013 (12) to determine the analgesic efficacy of transdermal fentanyl for relief of cancer pain and to assess the adverse events associated with the use of transdermal fentanyl for relief of cancer pain. There were 1244 participants randomised in classically designed RCTs, of whom 1197 had evaluable data, and 138 patients enrolled in an enriched enrolment, randomised withdrawal (EERW) trial. Overall, 600 participants were treated with transdermal fentanyl patches, 382 with various formulations of morphine, 36 with methadone, and 221 with paracetamol plus codeine. There were major sources of potential bias, including lack
of blinding, small size, high levels of attrition, and inconsistent reporting. There were insufficient comparable data for meta-analysis to be undertaken or to produce numbers needed to treat (NNT) for the analgesic effect. In seven studies with 461 participants reporting pain intensity results after about two weeks, the mean or median pain scores were on the borderline of mild and moderate pain. Most participants would have had no worse than mild pain on treatment. Another reported that 77% of participants using transdermal fentanyl had an undefined successful outcome. Fewer participants experienced constipation with transdermal fentanyl (28%) than with oral morphine (46%), giving a risk ratio of 0.61 (95% CI 0.47 to 0.78); the NNT to prevent constipation was 5.5 (95% CI 3.8 to 10).

The authors concluded that the randomized trial literature for effectiveness of transdermal fentanyl is limited, but it is an important medicine. Most studies recruited fewer than 100 participants and did not provide data appropriate for meta-analysis. Only a few reported how many patients had good pain relief but, where data were reported, a majority had no worse than mild pain within a reasonably short time period.

The evidence pointed to a useful and significant reduction in complaints about constipation for transdermal fentanyl compared with oral morphine.

Another important paper published in 2012 was a comprehensive review of the literature for randomized controlled trials (RCTs) of opioids for cancer pain (13). The literature search was done using PubMed, EMBASE, Cochrane library, clinical trials, national clearing house, Web of Science, previous narrative systematic reviews, and cross references. The studies were assessed using the modified Cochrane and Jadad criteria. Analysis of evidence was done utilizing the modified quality of evidence developed by United States Preventive Services Task Force (USPSTF). This systematic review of RCTs of opioids for cancer pain showed fair evidence for the efficacy of transdermal fentanyl and poor evidence for morphine, tramadol, oxycodone, methadone, and codeine. The evidence was fair based on only one randomized controlled trials.
References


Toxicity of Transdermal Fentanyl in Clinical Studies.

Figure 2. Consort – like report of Eligible Papers for Toxicity.

Source: PUBMED
Search: (“fentanyl”AND “cancer pain”)
Date 18-11-2016
Publication dates: 5 years
Summary of data for Toxicity (Table 1, Appendix 4).

A literature review based on the guidance of the Centre for Reviews and Dissemination was conducted.

An iterative approach was used starting with an electronic search of the MEDLINE database (via PubMed – customized range date until November 8th, 2016. We considered all the eligible paper published in the last five years (Figure 1). The generic search terms (“fentanyl” AND “cancer pain”) were used. Citation tracking and search for all related eligible articles in PubMed were performed. We identified 3 eligible paper for toxicity analysis with N=1 observational study and N=2 case reports/case series.

Levels of evidence analyzed may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size. For more details please refer to the Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=5653).

Observational Studies (Table 2, Appendix 4).

We identified only one observational study about the effects of using transdermal fentanyl (TDF) on cognitive functions in cancer pain (Table 7).

Analysis of the study was possible with the abstract reading because the paper was written in Turkish. Fifty patients with cancer pain who had no previous opioid treatments were included in the study. Pain was evaluated with Visual Analogue Scale (VAS) while, cognitive functions were assessed using by Addenbrooke's Cognitive Examination final revised version (ACE-R). In addition, performance was evaluated with Eastern Cooperative Oncology Group Performance Status (ECOG) and adverse reactions were noted. Patient algological evaluation was done in the first application and the normal cognitive functions were established using ACE-R. In most cases
the treatment began with 25 µg/h TDF and, at certain stages of the treatment, the dose was increased so that VAS ≤2. ACE-R was applied again on day 30 under sufficient analgesia. All patients were compared using ACE-R total scores and subgroups (attention-orientation, memory, fluency, language, visuospatial abilities) at before and after TDF treatment. At the end of the study, attention-orientation, memory, fluency, language, and ACER total scores showed a statistically significant improvement after TDF treatment than before. No significant change was obtained for the visuospatial abilities. No difference was detected in performance status. Author’s conclusion was that the use of TDF for the treatment of cancer pain is not associated with impairment in cognitive performance.

**Case Report; Case Series (Table 3, Appendix 4).**

Only two papers were indentified on this setting and type of publication (Table 7). Both of them were published in 2015.

The first paper published by Hemati K et al. (1) report three case reports of severe diarrhea without most common side effects associated with Fentanyl patches during first 72 h of patient's treatment. In the 12 h after TDF removal the authors describe the reducing of patient’s diarrhea frequency and the return of the patient's normal defecation habits. This in an important but not frequent adverse effect but clinicians must consider this toxicity within the differential diagnosis of diarrhea in cancer patients.

Second paper reports a case of fentanyl tolerance (2). Opioids are not generally deemed to have an analgesic ceiling effect on cancer pain. However, there have been occasional reports of tolerance to opioid development induced by multiple doses of fentanyl. The authors report a case of suspected tolerance to the analgesic effect of opioid, in which an increasing dose of fentanyl failed to relieve the patient's cancer pain symptoms, but opioid switching to oxycodone injections enabled a dose reduction to below the equivalent dose conversion ratio.
References


Clinical considerations on Transdermal Fentanyl

Among opioids, the potent synthetic drug fentanyl citrate is particularly suitable for transdermal administration, and its utility in pain therapy has been extensively evaluated.

Transdermal fentanyl systems (TTS) are available in five release programs of 12, 25, 50, 75, 100 µg/h depending on the patch size, and the drug is released continuously for a maximum of 72 hours (1). When a TTS is removed, fentanyl continues to be absorbed into the systemic circulation from the cutaneous depot. However, opioid withdrawal symptoms may occur after discontinuation of TTS administration, as well as after conversion from other opioids to TTS, (2-4).

In stable, chronic, cancer pain this formulation offers an interesting alternative to oral morphine (5-8). The transdermal route of fentanyl administration is indicated in patients with nausea, vomiting, problems with swallowing, severe constipation, and poor compliance.

Of course, this formulation is contraindicated during the titration phase, in opioid-naïve patients, or to control breakthrough pain.

It has become so popular that frequently physicians use transdermal fentanyl as first choice opioid administration for treating moderate to severe pain (9). In June 2005 an “Important drug warning” was published by Janssen (10,11). According to this warning “Duragesic ® should only be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to Duragesic ® 25 mcg/h. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid”.

It was recently emphasized that ensuring adequate opioid tolerance before prescribing a fentanyl patch is an important way to improve its safe use (12,13). Globally, we can conclude that transdermal fentanyl represents a good choice for cancer pain management due to the demonstrated
efficacy of pain relief and quality of life basing on acceptable level of evidences reported in literature and analyzed in our report.
References


TRAMADOL

Introduction

Tramadol is a synthetic drug with opioid and non-opioid properties. Tramadol consists of two enantiomers: 1. (+) tramadol and its metabolite (+)-O-desmethyl-tramadol that is agonist of the mu opioid receptor, and also inhibits serotonin reuptake; 2. (-)-tramadol inhibits norepinephrine reuptake. These complementary and synergic actions are responsible of tramadol analgesic properties (1).

Tramadol is rapidly and almost completely absorbed after oral administration but its absolute bioavailability is only 66%-77% due to first-pass metabolism. After repeated oral administration or after an intramuscular administration the bioavailability is about 90%-100%, the excretion is mostly via kidneys (90%) and in the stools (10%). Tramadol is extensively metabolized in the liver by demethylation, oxidation and conjugation (2-4). O-demethyl-tramadol (M1) is the main active metabolite, it is catalyzed by cytochrome P450 (CYP) 2D6 and is two to four times more potent than parent compound. The elimination time of this metabolite is double in patients with hepatic or renal impairment (3), thus dose adjustment is required in patients with hepatic or renal impairments. Conversely, poor metabolizers have 14-fold lower concentrations of the active metabolite and may have less analgesia than expected. Plasma protein binding is ~20% and is rapidly distributed in the body. Peak plasma tramadol levels after oral, rectal, and intramuscular intake are reached in 1-2 hours, 3 hours, and 45 minutes respectively. The drug has a terminal half-life of about 5-6 hours (5,6). This relatively short half-life results in a required dosage frequency of 4-6 times daily (6).

Extended-release preparations have a longer half-life (10-13.4 hours) and about half peak concentration after 4 to 6 hours.

With respect to morphine, the potency is considered to be about 1/10 when administrated via parenteral route and 1/5 when administered orally (10). Other authors found morphine tramadol ratios ranging from 1:3.8 to 1:5.3 (7-10).
Oral tramadol (up to 400 mg/day) is considered effective and safe in the treatment of cancer pain (7-9). Despite the absence of clear advantages to using tramadol compared to other opioids, it remains a very used opioid and it is often available in countries where morphine is not. For this reason it might be considered to be enlisted as an Essential drug by WHO.
References


Efficacy of Tramadol in Clinical Studies

Figure 1. Consort-Like diagram of selected papers for efficacy.

Identified Papers From Medline and Cross References*
N= 36 +1*

Not Eligible Papers
Toxicities N=2
Pharmacokinetics N= 7
Epidemiological Studies N= 6
BTcP N= 1
Non-Cancer Pain N= 8
Other N= 8
Total Not Eligible N=32

Eligible Papers
N= 5

Search: ("tramadol" AND "cancer pain")
Source: PubMed
Publication Dates: 5 years
Search Date: 24-11-2016
Summary of data for Efficacy (Table 1, Appendix 5).

A literature review based on the guidance of the Centre for Reviews and Dissemination was conducted.

An iterative approach was used starting with an electronic search of the MEDLINE database (via PubMed – customized range date until November 24th, 2016. We considered all the eligible paper published in the last five years (Figure 1). The generic search terms ("tramadol" AND "cancer pain") were used. Citation tracking and search for all related eligible articles in PubMed were performed. We identified only 4 eligible paper for efficacy analysis with N=3 Randomized Controlled Trials, N=1 Review, N=1 prospective open label studies. We did not find retrospective studies or case reports/case series. Major percentage of last 5 years evidences came from randomized trials. One trial was identified with cross-references analysis.

Levels of evidence analyzed may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size. For more details please refer to the Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=5653).
**Randomized Controlled Trials (Table 2, Appendix 5).**

In the last five years literature search, three randomized controlled trials were identified.

The most important study was published by Bandieri et al. on the Journal of Clinical Oncology (1) in 2016 and analyzed the efficacy of low dose morphine versus weak opioids such as tramadol alone or in combinations with paracetamol, or codeine in fixed combination with Paracetamol. The study was conducted among 240 Italian cancer patients randomly assigned to receive either low-dose oral morphine (M) or a weak opioid (WO) from randomization until day 28. The primary outcome occurred in 88.2% of the low-dose morphine and in 57.7% of the weak-opioid group (odds risk, 6.18; 95% CI, 3.12 to 12.24; P.001). The percentage of responder patients was higher in the low-dose morphine group, as early as at 1 week. This study does not support the use of tramadol versus low dose morphine but represents a simplified approach to increase patient access to strong (and low cost) opioids at an earlier stage in the disease trajectory, improving overall pain control.

The second one was published in 2016 by Kress HG et al. (2) but after full-text reading we cannot consider this paper for our report for two reasons: the study regards the opioid conversion rates from tramadol to tapentadol prolonged release and this is not the objective of our revision. Moreover, it is a post hoc subgroup analysis of a randomized-withdrawal, active- and placebo-controlled, double blind phase 3 study.

The last study was published by Bilen A et al in 2013 (3) analyzed the efficacy of tramadol as co-analgesic in cancer patients using trans-dermal fentanyl (TDF) in 50 cancer patients. Study was positive for the main objective and when TDF and tramadol are used together, TDF need is reduced and patients better tolerate the pain management protocol.
Systematic Review (Table 3, Appendix 5).

Only one systematic review was identified by our search. The study was published in 2012 (4) and it’s comprehensive review of the literature for randomized controlled trials (RCTs) of opioids for cancer pain. The literature search was done using PubMed, EMBASE, Cochrane library, clinical trials, national clearing house, Web of Science, previous narrative systematic reviews, and cross references. The studies were assessed using the modified Cochrane and Jadad criteria. Analysis of evidence was done utilizing the modified quality of evidence developed by United States Preventive Services Task Force (USPSTF). This systematic review of RCTs of opioids for cancer pain showed fair evidence for the efficacy of transdermal fentanyl and poor evidence for morphine, tramadol, oxycodone, methadone, and codeine. For tramadol, there were 3 trials evaluating tramadol. One trial evaluated the influence of tramadol on the dose escalation of transdermal fentanyl. One study evaluated tramadol to placebo for neuropathic cancer pain. The third study evaluated tramadol compared to morphine in 20 patients in each group. The evidence was poor based on 3 low quality studies (this study was analyzed also for transdermal fentanyl report).
Prospective Open Label Study (Table 4, Appendix 5).

Only one Prospective Open Label Study was identified by our search. The objective of the study published on 2015 (5) was to determine the efficacy of a fixed combination of tramadol and paracetamol (acetaminophen) in the treatment of pain in 353 advanced cancer patients.

The average duration of treatment with a fixed combination tramadol and acetaminophen was 57 days (13-330 days). Already after 24 hours of treatment the average pain score was significantly lower (p<0.0001) compared to the admission day [5.00 (4:00 to 8:00) during the first days versus 2.00 (1:00 to 7:00) during the second day of treatment]. The average dose of the fixed combination tramadol and acetaminophen tablets was 4.8 ± 1.8 (180 mg of tramadol and 1560 mg paracetamol).

Side effects, in the treatment of pain with a fixed combination tramadol and acetaminophen, were found in 29.18% of patients, with a predominance of nausea and vomiting.
References


A literature review based on the guidance of the Centre for Reviews and Dissemination was conducted.

An iterative approach was used starting with an electronic search of the MEDLINE database (via PubMed – customized range date until November 24th, 2016. We considered all the eligible paper published in the last five years (Figure 1). The generic search terms ("tramadol" AND "cancer pain") were used. Citation tracking and search for all related eligible articles in PubMed were performed. We identified only 2 eligible paper for toxicities analysis with N=2 case reports/case series.
Case Report; Case Series (Table 1, Appendix 6).

Only two papers were indentified on this setting and type of publication (Table 5). Both of them were published in 2015.

First paper was published by Kurten C et al. (1) and reports about a 79-year-old non-diabetic patient admitted to the emergency room with severe hypoglycemia after 50 mg of tramadol tablet for headache. As already in retrospective studies (Level of Evidence 3) reported for methadone (2) mechanisms and the risk factors for this potential side effect remain unclear. We consider this paper of adverse effect in non-cancer patients due to the potential class- metabolic toxicities of opioids and their management. Article was in German.

The second paper (3) considers another little known adverse effect from opioids (seizures) in a laryngeal cancer patient on treatment with tramadol. Some reports have found that tramadol triggers seizure activity at high doses, whereas a few preclinical studies have found that this seizure activity is not dose-related. After tramadol was stopped, patient symptoms quickly improved.

There are many reports of seizures following tramadol overdoses, including seizures associated with intravenous tramadol as premedication, seizures in drug abusers, and seizures in association with tramadol intoxication. In all of these cases, high blood tramadol concentrations likely induced the seizure activity. However, the relationship between the tramadol dose and seizure activity remain controversial.
References


Adverse effects of tramadol

Although tramadol is considered to be a drug at low risk of causing respiratory depression, two cases of severe respiratory depression after tramadol use have been described in children (1) and in one adult with cancer pain and renal insufficiency (2).

Case report of hyponatremia may occur during tramadol treatment (3-5). Natremia must be measured when neurological abnormality occurs with tramadol treatment.

Withdrawal syndrome may occasionally present during tramadol treatment (6,7).

Seizures have been reported with tramadol at normal doses (8), so the drug should be avoided in patients with epilepsy.

A severe serotonin syndrome may occur when tramadol is combined with drugs that increase serotonin activity such as monoamine oxidase inhibitors (MAOIs) (9).

Although tramadol is thought to have low abuse and dependence potentials worldwide, its abuse has become a serious problem in many countries, particularly in the Middle East, Africa, and West Asia (10).

There is evidence that the incidence rate for abuse of tramadol is 69/1,000 persons per year and the dependence rate is 6.9/1,000 persons per year (11).
References


9. Park SH, Wackernah RC, Stimmel GL. Serotonin Syndrome: is it a reason to avoid the use of tramadol with antidepressants?. J of Pharmacy Practice 2014; 27/1:71-78


Clinical Role of Tramadol

Tramadol is considered a “weak” opioid because of its ceiling effect for which more than a certain threshold of dose cannot increase the effectiveness of the drug but only influence the appearance of side effects. Unlike the role of “strong” opioids, which is universally recognized in the treatment of moderate to severe pain, there is no common agreement regarding the role of tramadol and others “weak” opioids for mild to moderate pain. Controversial points regarding the use of second step are that (1) there are insufficient data regarding the effectiveness and toxicities of the so called “weak” opioids; (2) both codeine and tramadol may be less analgesic in poor metabolizers; (3) the second-step drugs are often marketed in combination with a non-opioid such as paracetamol, aspirin, or NSAID and it is the latter component that limits the dose; and (4) these drugs are often expensive in respect to their potential benefits (cost–benefit ratio). Various authors have debated the role and the utility of the second step of the WHO analgesic ladder.

Several authors have suggested abolishing the second step and initiating earlier low-dose morphine therapy. In routine clinical practice, the question that arises is what really changes regarding the analgesia and tolerability of weak opioids, or low-dose strong opioids, if one or the other is used even for mild–moderate pain? Low dose oral morphine is a reliable treatment in opioid-naïve advanced cancer patients (1-3).

Basing on the quality of all analyzed studies and the strength of evidence, we can conclude that the evidence about the use of tramadol remains poor. However, this may be explained with the low number of studies in the last five years in this particular setting.

We have to consider that oral tramadol is present also in countries where oral morphine is not present or in countries where there are several restrictions in using morphine (oral or parenteral) so to prevent proper pain treatment.

In these situations tramadol may have a particular role if we consider the right dosage (up to 400 mg/day) and pay attention to the adverse effects in particular in patients with renal impairment (4).
References


