

## MINI-REVIEW

# Cancer Pain Prevalence and its Management

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### Abstract

**Pain is a public health problem affecting more than half of cancer patients. Despite the success of the protocols currently used, pain cannot still be reduced satisfactorily in the large majority of patients. In order to improve pain management, all healthcare professionals involved with pain should have sufficient knowledge on pain assessment and treatment, and should inform patients to prevent patient-related barriers. In this compilation, the prevalence values and the treatment methods of cancer pain, and the barriers to pain management have been assessed.**

**Keywords:** Cancer - pain - management

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### Introduction

Pain is a common symptom among cancer patients, affecting the life style of the patient. 69% of cancer patients have reported that pain restricts their daily life activities (Breivik et al., 2009; Lee et al., 2014). The step-wise treatment, established by World Health Organization (WHO) in 1986, has been aimed to treat pain effectively. (Burton and Cleelan., 2001) This protocol reduces pain in 70 to 90% of patients when administered optimally. (Van den Beuken-van Everdingen et al., 2007) However, prevalence studies performed have demonstrated that cancer pain still affects 56 to 64% of patients. (Van den Beuken-van Everdingen et al., 2007; Breivik et al., 2009, Budkaew and Chumworathayi, 2013). Moreover, it has been reported that 43% of patients on therapy received insufficient treatment (Deandrea et al., 2008). Therefore, the healthcare providers should have sufficient knowledge on cancer pain.

According to the description of International Association for the Study of Pain (IASP), pain is an unpleasant, sensory, and emotional experience, originating from any site in body, manifesting potential tissue damage, and covering all past incidences of the person (Chapman et al., 1985). The prevalence and the severity of pain experienced by cancer patients depend upon several factors such as the stage, the site, and the region of metastasis related to the disease. In this respect, pain in cancer patients can be examined in three major groups, by cancer etiology, by anti-neoplastic treatment, and by cancer disease (Grond et al., 1996, Liang et al., 2013, Gong et al., 2013, Demir et al., 2013).

### Prevalence

In a study performed by directly contacting 5084 cancer patients, 56% of patients complain about pain experienced at least once monthly (Breivik et al., 2009). In a meta-analysis investigating the frequency of cancer pain in 1966-2005, the frequency of pain has been reported as 53%. Un the same study, the prevalence values by staging have been found as 33% in post-curative treatment patients, 59% in patients on anti-cancer treatment, and 64% in patients of advanced stage/metastatic/terminal period (Van den Beuken-van Everdingen et al., 2007). No difference has been observed between the patients at advanced stage or in terminal period and the patients on chemotherapy (CT).

Although no statistically significant difference is found among cancer types and frequency of pain, pain is observed the most frequently in head-neck cancers by a ratio of 70%. The ratios in other types are 59% for gastrointestinal, 55% for lung 55%, 54% for breast, 52% for urogenital, and 60% for gynecological (Van den Beuken-van Everdingen et al., 2007). And in hematological diseases, it has been indicated in previous literature that pain was observed at 5% for leukemia, and 38% for lymphoma, and that this ratio reached to 83% in final months of life, and that pain may also be experienced during the processes of diagnosis and active treatment (Foley., 1985; Costantini et al., 2009; Morselli et al., 2009).

Studies performed by PMI (Pain Medication Index), composed for comparing the pain severity stated by patients and the analgesic treatment received, and for assessing the related compliance in between, have been

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reviewed in a meta-analysis, and it has been demonstrated that 43% of patients did not receive the treatment they should have (Cleeland et al., 1994; Deandrea et al., 2008). In a prospective study performed by Apolone et al. (2009) at 110 sites (specific oncology, pain, palliative and care centers) in 1802 outpatients and in-patients with advanced stage and metastatic solid tumor, even though sufficient analgesic supplementation was provided to the patients, pain palliation has been ensured only in 25.3% of patients according to PMI (Apolone et al., 2009). It has reported that 11% of patients with moderate-severe intensity of pain received no treatment for pain (Breivik et al., 2009).

## Pain Management

The treatment of cancer pain requires close cooperation of oncology, algology, patient, and patient relative. Anticancer treatment, symptomatic pain control, rehabilitation, and psychiatric support are the essential elements of the treatment for the patient with cancer pain (Mahigir et al., 2012).

The primary element in early stage is the cause-oriented treatment (chemotherapy, radiotherapy, and antibiotic treatment in presence of infection). The probability of pain regression is 75% with anti-neoplastic treatment in early stage tumors (Bonica., 1990). Here the issue to be considered with caution is the performance of pharmacological pain control in parallel to maintaining the cause-related treatment in patient with pain.

And in advanced stage, since the quality of life is more in the forefront than the life span, the primary issue is the control of other symptoms (infection, vomiting, etc.), including pain.

## WHO Guideline for Steps and Pharmacological Treatment

World Health Organization (WHO) has published a treatment scheme, aiming to control cancer pain, and to use analgesics and adjuvant drugs, and non-opioids, weak and potent opioids in three steps by pain severity. In pain treatment of cancer patients, adjuvant drugs are drugs used to supplement and to reduce the analgesic

dose at every step of WHO Analgesic Ladder System. Anticonvulsant drugs may be used for throbbing and sharp pains. The selection of adjuvant drugs should be made by the nature of pain, and they can be added to non-opioid and opioid drugs at all treatment stages (Coyle and Layman-Goldstein, 2007; Mitra and Jones, 2012).

In this ladder treatment, it has been aimed that the step is selected by pain severity, oral route of administration is preferred firstly, the agents are used to ensure day-long pain control, the treatment is individualized, and that the details are regarded highly. Generally, non-opioid drugs such as paracetamol and non-steroid anti-inflammatory drugs (NSAID) are used alone or in combination at first step, and if pain cannot be controlled, patient progresses to second step. At the second step, a mild, weak-moderate effect opioid such as codeine is selected to supplement the first step. If pain persists, patient progresses to the third step, the weak-effect opioid is replaced by a potent opioid such as morphine, and it is titrated up to pain reducing dose (Ripamonti and Bandieri, 2011). Pharmacological analgesics used in the ladder system are shown in Table 1.

Non-opioid analgesics and adjuvant drugs may be used for mild pain (NRS=0-3) treatment. Paracetamol and Non-steroidal anti-inflammatory drugs (NSAIDs) may be used commonly at any stage of cancer pain as a part of the treatment according to WHO's analgesic ladder treatment. Non-opioid analgesics selected and their characteristics are included in Table 2 (Ripamonti and Bandieri., 2011).

In single dose studies, NSAIDs are superior to placebo in relief of cancer pain. No evidence is available to indicate the efficacy and the safety of any NSAID compared to another NSAID (McNicol et al., 2009). In a study performed, it has been reported that among NSAIDs, naproxen, diclofenac, and indomethacin reduce cancer pain by 70.9%, 67.3%, and 63.6% respectively (Ventafridda et al., 1990).

Randomized clinical studies have demonstrated that addition of paracetamol to potent opioids contributes to pain palliation in a very minor part of cancer patients with pain. However, these results have not been supported with another study (Stockler et al., 2004).

In another study, it has been reported that the efficacy of dipyrone (metamizole sodium) 2g administered every

**Table 1. Analgesic Drugs**

Non-Opioid Drugs	Opioid Drugs	Adjuvant Drugs	
Paracetamol	Weak Opioid	Potent opioid drugs	Antidepressants:
Acetylsalicylic acid	Dihydrocodeine	Drugs	Amitriptyline
Ibuprofen	Codeine	Morphine sulfate	Clomipramine
Ketoprofen	Tramadol	Morphine	Nortriptyline
Diclofenac	Propoxifen	Oxycodone	Fluoxetine
Mefenamic acid		Hydro-morphine	Duloxetine
Naproxen		Fentanyl TTS	Antiepileptic drugs:
		Buprenorphine	Carbamazepine
		Methadone	Gabapentin
		Nicomorphine	Pregabalin
			Neuroleptics:
			Haloperidol
			Chlorpromazine
			Corticosteroids:
			Dexamethasone
			Prednisolone

**Table 2. WHO Step**

Substance	Forms used commonly	Onset time (minutes)	Side effect	Maximal daily dose	
Acetaminophen (paracetamol)	500-1000mg Tablet, suppository	15-30	Hepatotoxicity	4x1000mg	
Acetylsalicylic acid	500-1000mg Tablet	15-30	GI toxicity, allergy, thrombocyte inhibition	3x1000mg	
Ibuprofen	200-400-600mg Tablet;	15-30; 120+	GI and renal toxicity	4x600mg;	
Ketoprofen	800mg slow release tablet, local gel	30+	GI and renal toxicity	3x800mg slow release tablet	
	25-75mg Tablet; 100-150-200mg slow release tablet			4x75mg;	
Diclofenac	25-50-75mg Tablet;	30-120	GI and renal toxicity	2x200mg	
	slow release tablet 100mg			4x50mg;	
Mefenamic acid	250-500mg Capsule	30+	GI and renal toxicity	2x100mg	
Naproxen	250-500mg Capsule	30+	GI and renal toxicity	4x500mg	
	250-375-500mg Tablet			2x500mg	
Comparison of weak opioids selected for WHO 2nd Step					
Dihydro-codeine	60-90-120mg slow release tablet	0.17	12	240	60-120mg
Codeine	15-30-60mg tablet		4-6	360mg	15-60mg
Tramadol	100mg/ml drop; 50mg capsule;	0.1-0.2	2-4	400mg	
	100-150-200mg slow release tablet			50-100mg	
Comparison of potent opioids selected for WHO 3rd Step					
Morphine sulfate	Oral	1	None	20-40mg	
Morphine	I.V.	3	None	5-10mg	
Oxycodone	Oral	5/1/02	None	20mg	
Hydro-morphine	Oral	4-7	None	8mg	
Transdermal Fentanyl	TTS	+4*	None	12 µg/h	
Buprenorphine	Oral	75	4mg	0.4mg	
Buprenorphine	I.V.	100	3mg	0.3-0.6mg	
Transdermal Buprenorphine	TTS	+4*	140 µg/h	17.5-35 µg/h	
Methadone	Oral	4-8-12**	None	10mg	
Nicomorphine	Oral	1	20mg	5mg	
Nicomorphine	I.V.	3	20mg	5mg	

\*It was calculated by conversion ofmg/day to µg/h; \*\*For 4 effects, daily morphine dose <90mg, for 8 effects, 90-300mg, and for 12 effects >300mg; GI; gastrointestinal toxicity

8 hours is comparable to the efficacy of morphine 10mg administered orally every 4 hours in relief of cancer pains (Rodríguez et al., 1994).

If sufficient effect cannot be ensured with non-opioid and adjuvant analgesics, included at first step, or if pain severity is NRS=4-6 in patient's initial assessment, a weak opioid should be added to this combination. Traditionally, in patients with mild-moderate severity, fast release weak opioids, namely codeine, dihydrocodeine, tramadol, or propoxifen are used. These analgesics have combined products, composed with acetaminophen, aspirin, or NSAID (WHO, 1996). Besides provision of efficient analgesia, codeine does not cause a significant tolerance and dependency even in chronic use. It is possible to adjust codeine at various doses by taking patient's pain severity into account, and it is very useful in step-wise treatment (WHO, 1996).

There are a few controversial issues regarding the drugs used at the second step of WHO Analgesic Ladder System. The first one is that as observed in a meta-analysis compiled from randomized clinical trials (RTC), the efficacy of weak opioids is not at a level sufficient enough to relieve pain completely. The second one is that no significant difference has been observed in RCTs between the efficacy of non-opioid analgesics and the efficacy of analgesia obtained as a result of combination with weak opioids. Furthermore, in light of the current studies, no clear difference could be demonstrated between the drugs used at 1<sup>st</sup> and 2<sup>nd</sup> steps in terms of efficacy. Additionally in non-controlled studies, it has been demonstrated that patient progressed to the third step in a short time such as 30-40 days due to basic reasons such as the effect duration of 2<sup>nd</sup> step, side effects, and insufficient analgesia. Another limitation in use of weak opioids is the observation of

“ceiling effect” (Ceiling effect is that the effect does not increase although the drug dose increases, and that only side effects are observed additionally) (Ripamonti and Bandieri., 2011).

Many authors have suggested that 2<sup>nd</sup> step of WHO Analgesic Ladder System is removed, and that the earlier use of low dose morphine would be more appropriate instead. Therefore, a RCT is required to be conducted for the role of 2<sup>nd</sup> step (Marinangeli et al., 2004; Maltoni et al., 2005; Mercadante et al., 2006).

If sufficient palliation cannot be ensured with weak opioids, NSAIDs, and adjuvant analgesics, included at second step, or if pain severity is NRS≥7 in patient's initial assessment, patient should progress to 3<sup>rd</sup> step of WHO Analgesic Ladder System, using potent opioids instead of weak ones.

Potent opioids have fast and slow release preparations. Morphine, hydromorphine, buprenorphine, methadone, fentanyl, and alfentanil are the most used potent opioids. (Ripamonti and Bandieri., 2009; Ripamonti and Bareggi., 2010). These can be administered by oral, parenteral, buccal, transdermal, transmucosal, and transnasal routes (Liang et al., 2013). Optimal pain control may be achieved by regular administration of analgesic doses.

Morphine is the single opioid analgesic in the drug list, recommended by WHO for children and adults with pain (WHO, 2007). Morphine may be used at required dose for the required duration by appropriate dose adjustment. The treatment may be initiated by administering the fast release form of 5mg orally used every 4 hours. Lower doses may be required in elderly patients and/or in patients with impaired renal functions. If pain is not relieved, the next dose may be administered by an increase of 30 to 50%. With decrease of pain severity or with side effects

(even though pain is relieved, tendency to sleep, absent-mindedness, fatigue, and decreased number of respirations, etc. are present) observed, indicating that the increased drug dose is excessive, the drug dose may be decreased by 50% of the last dose increased. When oral morphine dose is switched to parenteral, it should be roughly divided into three to obtain the equivalent analgesic effect. However, dose decrease and increase may be required. After patient's pain is controlled appropriately, and after a constant dose is determined to ensure a pain-free period of 48 hours, patient may be switched to the use of slow release forms of morphine. These forms may be used orally twice a day with a dosing interval of 12 hours (Quigley, 2005; Ripamonti and Bandieri, 2009).

Opioid is switched in practice to increase the toleration of the drug or the pain palliation. Even though no high quality study is available to support this practice, switch to an alternative opioid is an approach requiring to be considered in clinical practice. In this practice, the equivalent analgesic doses of different opioids should be well known. Equivalent analgesic doses are provided by routes of administration for each opioid (Mercadante and Bruera, 2006; Ripamonti and Bandieri, 2009).

For example, if the switch is from morphine to methadone, the dose of methadone should be reduced by 75-90% because of the accumulation risk due to long half-life (De Leon-Casasola, 2004).

## **Roles of Radiotherapy, Radioisotopes, and Bisphosphonates**

Radiotherapy (RT) has a critical effect and characteristic due to its relief of bone metastasis and pain. Moreover, it has an effect on cerebral metastasis and on tumor pressures upon nerve structure.

In a systematic compilation, it has been demonstrated that RT, used for bone pain palliation, was required in 42% of patients, improvement in pain levels is ensured in at least 50% of patients, and that full pain palliation is also ensured in 27% of patients at the end of the first month (McQuay et al., 2008).

Moreover, even though no apparent outcome is available in prostate cancer patients with bone metastasis resistant to hormonal treatment, at a few randomized controlled trials containing minor figures of radioisotope treatment, it has been demonstrated to relieve pain in breast and lung cancer patients with bone metastasis (Sciuto et al., 2001; Han et al., 2002; Leondi et al., 2004).

Bisphosphonates (BPP) are used in hypercalcemia developing due to para-neoplastic syndrome of cancers in order to reduce the risk of pathological fracture in cases of pain-free bone metastasis, and for palliation in cases of bone metastasis with pain. Sufficient evidence is available to indicate the efficacy of BPPs in patients with bone metastasis (Wog and Wiffen., 2002). However, BPPs should not be considered as alternatives to analgesic treatment, and should be initiated after the resolution of dental problems, if possible (Dimopoulos et al., 2009; Ripamonti et al., 2009).

## **Conclusions**

As the chemotherapy and surgery become aggressive, the time cancer patients spend with advanced stage disease increases, and this situation renders the treatment of cancer pain a chronic process, which requires the ensuring of success in the long term (Burton and Cleeland, 2001). Even though pain pharmacology is developed at a level to provide efficient pain management, the majority of patients, still complaining about pain, require the emphasis to be laid upon the other obstacles encountered in pain management. Pain treatment may be interrupted due to healthcare policies of the countries. However, when access to opioids, which is the main element of advanced stage pain treatment, is considered, the same pain prevalence values in Asian-African countries, where access to opioids is restricted, and in North American-European countries, where no problems are experienced regarding access, demonstrate that the real issue originates from individual reasons (Van den Beuken-van Everdingen et al., 2007).

The obstacles in pain management may be grouped into two briefly as patient-related reasons and as healthcare professional related reasons. Patients may prevent their own pain treatments with their inaccurate beliefs about analgesics and their side effects by not adhering to their treatment regimes. Studies performed have demonstrated that patient training alone may reduce pain to 30%. Patients, abstaining from reporting their pain, suffer from more pain, and PMI values of these patients appear to be lower than of the patients reporting their pain to their doctors (Oldenmenger et al., 2009). And another study has demonstrated that pain, described by patient relatives, is more severe than the pain described by the patient himself/herself (Miaskowski et al., 1997). Therefore, the best approach will be to discuss pain with the patient himself/herself.

Healthcare professional related reasons are the obstacles to pain management, which may be corrected the most easily. The problems encountered at this subject can be summarized as insufficient knowledge and experience of healthcare professionals in relation to pain assessment and treatment, and as their being indifferent to patient's pain (Van den Beuken-van Everdingen et al., 2007; Oldenmenger et al., 2009). It has been reported that 57 to 76% of medical oncologists do not inquire about patient's pain, and in another study it has been shown that 55% of patients try to retain his/her pain on the agenda by constantly reminding their doctors their pain (Von Roenn et al., 1993; Breivik et al., 2009).

In conclusion, in treatment approaches aiming optimal palliation, optimal reduction of pain and pain-free lives of cancer patients should be among the primary targets. Therefore, professionals such as medical oncologists, involved in pains of cancer patients, should have constantly up-to-date and sufficient knowledge on subjects such as the nature of cancer pain and the best possible treatment. Taking the pains of patients seriously and inquiring them at each visit are the most basic conditions for administering the available treatment protocols in the best way.

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