

## A Retrospective Study on Opioid Therapy to Manage Pain in Cancer in a Tertiary Care Hospital

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### Abstract

Cancer is one of the most leading causes of mortality in the general population. Most cancers are accompanied with pain. Pain management in cancer is just as important as treatment of cancer for better quality of life for the patient. The primary objective of the study includes the role of opioids in managing cancer pain and also check for dose titrations, ADRs of opioids and its management and the role of Co-Analgesics used in Cancer Pain Management. A retrospective, observational study of 5 years from 1<sup>st</sup> June 2016 to 31<sup>st</sup> May 2021. The study was conducted in the Oncology department of Lourde's hospital, Kochi which is a tertiary care teaching hospital. 98 patients admitted in the oncology department who were taking opioids for their cancer pain management and who were included based on the inclusion criteria. The patient's pain scores were obtained and statistical analysis was done, which showed  $p < 0.001$ , there is a significant difference existing between pain among cancer patients before and after taking opioids. This proves that there is a significant reduction in pain after taking opioids. All patients received adequate dose titration (100%) and the main ADR recorded was constipation [22.4%]. Also the use of co-analgesics significantly plays a role in mitigating the pain intensity in patients with cancer. The study found that the use of opioids as analgesic medication for cancer patients is the cornerstone for cancer pain management because of the effectiveness of opioids in mitigating pain.

**Keywords:** Oncology, cancer pain, opioids, Co-analgesics, Dose titration, ADR.

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### INTRODUCTION

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body [1]. Cancer is a genetic disease, it is caused by changes to genes that control the way our cell's function, especially how they grow and divide. Genetic changes that cause cancer can happen because of errors that occur as cells divide, of damage to DNA caused by harmful substances in the environment, such as the chemicals in tobacco smoke and ultraviolet rays from the sun. The body normally eliminates cells with damaged DNA before they turn cancerous. But the body's ability to do so goes down as we age. This is part of the reason why there is a higher risk of cancer later in life.

Cancer treatment is based on the stages of cancer. The aim of treatment for cancer may be cure, control and prolongation of life, or palliation of

symptoms. The goal is to stop the cancer from spreading further. Some treatments may be given to reduce side effects of other treatments. The selection of treatment and its progress depends on the type of cancer, its locality and stage of progression, traditional and most widely used treatment methods. Some of the modern modalities include hormone-based therapy, anti-angiogenic modalities, stem cell therapies, immunotherapy and dendritic cell-based immunotherapy [2].

According to WHO, cancer is a leading cause of death globally which resulted in an estimated 10 million deaths in 2020 alone based on GLOBOCAN 2020 report [3]. As there is a significant increase in number of cancer cases reported yearly, Cancer pain management (CPM) is vital to improve patient's quality of life. Pain keeps people from doing things they enjoy. It can prevent them from talking and spending time

with others. It can affect their mood and their ability to think. And pain can make it hard to eat and sleep, which can make other symptoms worse. Pain can also increase blood pressure and heart rate, and can negatively affect healing [4]. The importance of pain assessment and rational use of analgesics based on pain severity, the results indicate that assessment is often poor and suboptimal treatment. Many patients feel that their treating clinicians prioritise the treatment of cancer over the treatment of pain and that this is reflected in lack of assessment or time devoted to the issue in consultations. Consequently, many patients feeling disempowered, that their quality of life is not a consideration for their treating clinician, and that their clinicians do not understand their pain or know how to treat it [5]. So, it is the responsibility of the treating physician to ensure that their patients' pain is also adequately controlled.

Cancer pain management includes both pharmacological treatment (medications) and non pharmacological treatments (Restorative therapies, Interventional procedures, Behavioural health approaches, Complementary and Integrative health). The medications used in cancer pain management includes opioid analgesics and non opioid analgesics. The opioid analgesics can be divided into those used for mild to moderate pain and those used for moderate to severe pain. These drugs are associated with development of physical dependence and tolerance. In order to avoid withdrawal symptoms, the dose should be decreased gradually. A vast majority of patients with cancer will require opioids which remains the most effective means of relieving moderate to severe cancer pain [6]. Several factors must be considered if opioids are to be used effectively. There is no standard recommended dose. Start at the low dose and then gradually tapered as needed. Starting doses for children is based on body weight. Mainly used opioids include morphine, tramadol, hydromorphone, methadone, pethidine, oxycodone, buprenorphine. Non opioid analgesic includes drugs such as acetylsalicylic acid, paracetamol, ibuprofen, indomethacin etc [7]. The drug is selected based on local factors such as availability and cost. Mainly these drugs are used in the pain associated with bone cancer. These drugs display a ceiling effect i.e. drug dose escalation over a given level does not produce further pain relief. If the non-opioid no longer controls the pain, an opioid analgesic should be added.

Drug selection should be appropriate to the severity of the pain. It may be most appropriate with severe pain to begin with a strong opioid, When pain is controlled, the patient should be maintained on the dose that is effective. It is usually not necessary to step down unless the cause of pain is believed to have resolved (e.g., post-operatively, in remission from cancer). Along any step in pain management additional drugs – “adjuvants”- may be used. Adjuvants include: antidepressants (e.g., amitriptyline), anticonvulsants

(e.g., gabapentin), corticosteroids (e.g. dexamethasone), and anxiolytics (e.g., diazepam). From an Indian perspective, only limited number of strong opioids are available, commonly used are morphine, fentanyl, buprenorphine and pethidine [8].

In a study conducted in four regional cancer centres in India, 88% patients reported to have experienced pain for 7 days and 60% patients reported that their worst pain was severe [9]. Opioids are the mainstay treatment for patients with advanced or metastatic cancer and palliative care. Due to regulatory barriers introduced by policy makers, limited number of opioids available in the country have all made it difficult for the prescribers to prescribe opioids to patients with legitimate pain leading to inadequate and inconsistent pain relief.

The primary objective of the study includes the role of opioids in managing cancer pain and also check for dose titrations, ADRs of opioids and its management and the role of Co-Analgesics used in Cancer Pain Management. The purpose of the study is to highlight the importance of opioids in pain relief and a retrospective look into the trends in the prescribing pattern of opioids in a tertiary healthcare setting in south India.

## MATERIALS AND METHODS

### Methodology

The study was conducted in the Oncology department of Lourdes hospital, Kochi which is a tertiary care multi-speciality hospital with 500 beds. It is a referral, teaching hospital which provides a wide range of services. A retrospective single centre observational study of 5 years from 1<sup>st</sup> June 2016 to 31<sup>st</sup> May 2021. Patients admitted in the oncology department who were taking opioids for their cancer pain management were included based on the inclusion criteria and were evaluated using data collected from the patient's case files. The patient's pain scores were taken from the pain assessment form and nurses daily notes.

Study sample was selected on the basis of inclusion and exclusion criteria. All patients regardless of age limit who were taking opioids and whose pain was assessed accurately by nursing team were included in the study. Patients with incomplete data and who were discharged against medical advice were excluded from the study.

Approval from the institution's ethical committee was obtained. The Institutional Ethics Committee, Lourdes Hospital, Postgraduate Institute of Medical Science and Research, Ernakulam, Kerala, India has approved the study protocol vide their letter no LH/EC/2021-12 dated 7-10-2021.

Sample size obtained was 91 which was calculated by using the Sample Size Formula for Descriptive Studies. Patients who were taking opioids were identified from the Lourdes Mediware System. The charts of these patients were obtained and thoroughly reviewed. Data of the patients were collected using a specially designed data collection form. Patient's demographics, diagnosis, haemoglobin, total count, platelet and the pain medications along with the pain score before and after taking the respective medicine, any ADR to the opioids were included in the data collection form.

### DESCRIPTIVE STATISTICAL ANALYSIS

The collected data were compiled using Microsoft excel and were presented in graphical format using pie chart and bar graphs. Calculation of mean, standard deviation and t-test were done using statistical calculators. Statistical software SPSS was used for

analysis of the data. The data were tabulated, analysed, and compared with relevant studies.

## RESULTS

### Demographic details

Among cancer patients hospitalized between June 2016 and May 2021 at Lourdes hospital Ernakulam, 98 cases were randomly selected and a retrospective observational study was conducted. The mean age of the patients was 57.78 years (SD  $\pm$  12.22) with 52 (53%) males and 46 (47%) females. The table 1 depicts the distribution of male and female patients in a sample population according to their age category. Also, the association between cancer and sex, it was analyzed using chi-square test and yielded a table value of 2.85 which corresponds to a p value of  $p > 0.001$ , which shows that there is no correlation between the gender of patient and cancer.

**Table 1: Sex distribution of study population according to their age category**

Age in category	Sex of patient				Total
	Male		Female		
	f	%	f	%	
<20	1	1.02	0	0	1.02%
21-40	0	0	5	5.1	5.1%
41-60	25	26.5	24	24.4	50.9%
61-80	26	27.5	15	15.3	40.04%
>80	0	0	2	2.04	2.04%
<b>Total</b>	52	53.1	46	46.9	100%
Chi square test= 2.859				df=3	p value= >0.05

### Gender wise cancer distribution of study population

Out of the 98 patients admitted in the hospital, 52 were males and 46 were females. The most prevalent type of cancer in females was breast cancer in 22 patients (22.4%), the second most prevalent cancer was ovarian cancer in 6 patients (6.1%). Rectal cancer accounted for 2 females (2%) and lung cancer in 6 females (6.1%). Liver, cervical and multiple myeloma accounted for 2 patients each (2% each). Low grade B cell lymphoma, non-Hodgkin's lymphoma, osteosarcoma and urinary bladder cancer (1% each). The most prevalent type of cancer in males was found to be lung cancer in 23 patients (23%). Pancreatic cancer, multiple myeloma, hypopharyngeal cancer and oesophageal cancer accounted for 2 patients each (2% each). Prostate cancer was the second most prevalent cancer in men (6%). Ca stomach was seen in 5 patients (5%). Ca buccal mucosa was seen in 3 patients (3%). Non hodgkins lymphoma, ca urinary bladder, ca

rectum, ca tonsil, ca tongue, ca renal cell and colon cancer each accounted for 1 person each (1% each).

### 1) ROLE OF OPIOIDS IN MANAGING CANCER PAIN

#### COMPARISON OF PRE-TEST POST-TEST PAIN

Out of 98 people admitted at the hospital, there were no patients without the complaints of Pain. About 20 (20.4%) people were categorized with mild pain, 76 people with moderate pain (77.6%) and 2 people with severe pain (2.0%)(figure 1). After the administration of opioids with or without co-analgesics the number of people with No pain was 11 (11.2%), with Mild pain was 86 (87.8%), with Moderate pain was 1 (1.0%) and with severe pain was 0 (0.0%). The levels of pain were categorized by the patient's pain score which is given as No pain (0), Mild pain (<3), Moderate pain (4-7), Severe pain (>7). As shown in Figure 1.

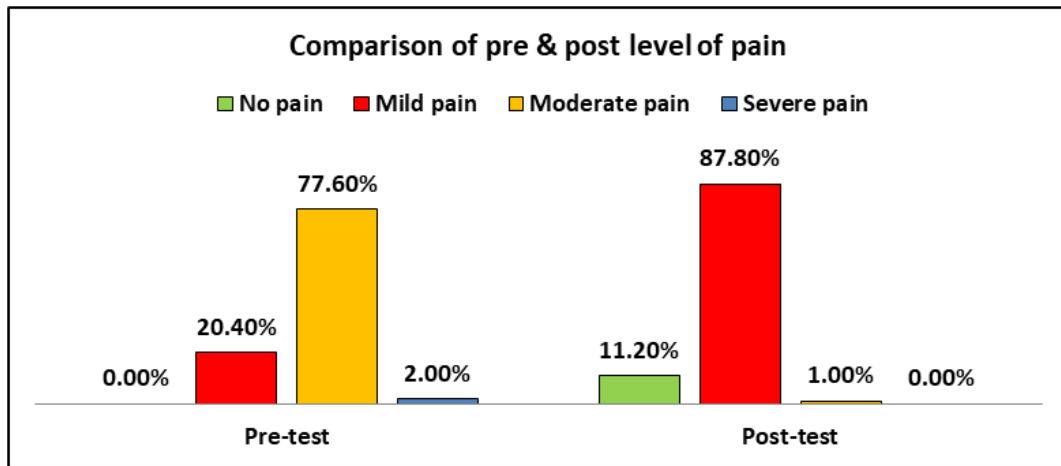


Figure 1: Pain intensity or level of pain before and after opioid administration

Table 2: Mean, Standard deviation and t-value comparing the pain before and after taking the opioids

Test	Mean	SD	Mean change	n	t	df	p-value
Pre-test	4.5	1.33	3.1	98	27.497	97	p < 0.001
Post-test	1.4	0.83					

Table 2 depicts the Mean ,Standard deviation and t-value comparing the pain before and after taking the opioids. The *t-value*, 27.497 and the *p < 0.001*, there is a significant difference existing between the pre-test and post-test pain among cancer patients before and after taking opioids. This proves that there is a significant reduction in pain after taking opioids.

### 2) ADEQUATE DOSE TITRATION WHEN OPIOIDS ADMINISTERED

Titration refers to adequate dose adjustment of opioids according to their pain intensity for cancer pain management. During the course of the study in the hospital of the 98 patients who received opioid analgesics, all patients received adequate dose titration (100%) (Table 3).

Table 3: Dose titration of opioids

Dose titration while taking opioids	f	%
Not titrated	0	0.0%
Titrated	98	100.0%

### 3) ADR OF OPIOIDS AND ITS MANAGEMENT

A total of 98 patients were analyzed, the frequency of occurrence of ADR were in the ratio of 1:0.28. The main ADR recorded was constipation with a frequency of occurrence of f = 22 which was 22.4% of the total number of patients, while the majority of the subjects did not have any noticeable ADR to show with a f=76 which was 77.6% of the total. The offending

agents that caused the ADR were mainly Morphine and Tramadol with a count of 21 (21.6%) and 1 (1.0%) respectively while the patients with no Moderate or Major ADR overwhelmed the study with a f (frequency) value of 76 (77.6%). The severity of the ADR's was analyzed using Naranjo scale shows in table 4.

Table 4: Severity classification using Naranjo scale

Naranjo category	f	%
Definite	0	0.0%
Probable	0	0.0%
Possible	22	22.4%
Doubtful	0	0.0%
No ADR	76	77.6%

A cross tabulation was performed between the ADR's that occurred and the Management that was given to solve the ADR. It was found that out of the 22 subjects that reported ADR all of the patients received a management to solve the ADR (22.4%). The rest of the

subjects that accounted for 77 people were with no ADR was reported and hence did not receive any sort of management (77.4%). Simultaneously a chi-square test was also performed to prove that the Management was given to all the patients experiencing ADR (Table 5). A

value of 98.000 was obtained with a p value  $p < 0.001$ , which proves that there was a significant change in patients that received medication with ADR and patients that did not receive medication without any

ADR. Therefore, all the patients whose ADR was reported did receive appropriate treatment for the corresponding ADR.

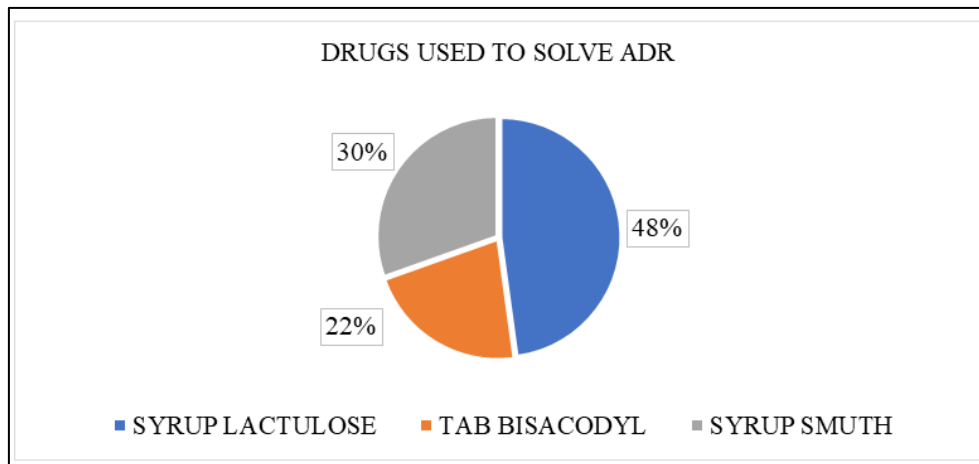
**Table 5: Association between ADR occurred and management given to solve the ADR**

ADR occurred	Management given to solve the ADR		Total
	No	Yes	
Yes	0	22(22.4%)	22.4%
No	76(77.4%)	0	77.
Chi square value =98.000		df=1	p value <0.001

**DRUGS USED TO TREAT ADR OF OPIOIDS**

22 out of 98 patients experienced an ADR and all the patients that reported ADR received appropriate

management. Figure 2 shows the drugs used to treat ADR of opioids.



**Figure 2: Medications used for the management of ADR**

**4) ROLE OF CO-ANALGESICS IN CANCER PAIN MANAGEMENT**

Adjuvant analgesics or co-analgesics are medications whose primary indication is the management of a medical condition with secondary effects of analgesia. Adjuvant analgesics used in conjunction with opioids have been found to be beneficial in the management of moderate to severe cancer pain. Antidepressants, anticonvulsants, local anesthetics, topical agents, steroids, bisphosphonates and calcitonin are all adjuvants which have been

showed to be effective in the management of cancer pain. The role of co-analgesics in cancer pain management was investigated and the statistical analysis is conducted shows the Table 6. Since the t value is 12.929 shows a  $p < 0.001$  which shows a significant difference between the pre pain without co-analgesics and post pain after taking co-analgesic. Therefore, it is evident that use of co-analgesics significantly plays a role in mitigating the pain intensity in patients with cancer.

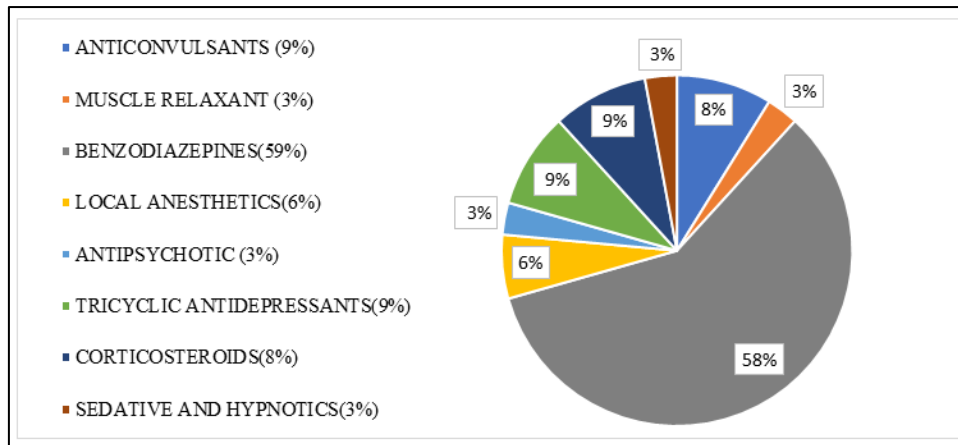
**Table 6: Comparison of Pre-test Post-test pain of patients before and after taking co-analgesic**

Test	Mean	SD	Mean change	SD	n	t	df	p-value
Pre test	4.08	1.50	2.4	0.93	24	12.92	23	$p < 0.001$
Post-test	1.6	1.24						

34 Patients received co-analgesics out of the 98 patients. Co-analgesics when administered along with opioids were found to be a significant factor in managing pain. There are many co-analgesics used

along with opioids but the main co-analgesics that were used throughout the study were found to belong to 8 Main categories. A graphical representation of the prescribed co-analgesics is given in Figure 3.





**Figure 3: Distribution of co analgesics used in cancer pain management**

## DISCUSSION

A study conducted by Kendall K. Morgan – ‘Cancer Incidence Rates by Age [10]’ similar results regarding the distribution of cancer across various ages. This study found that out of 10 cancer patients, 9 patients are generally diagnosed above the age of 45. The distribution of cancer across the various age categories were <20 years of age had an incidence of 1%, 20-30 years of age had an incidence of 3%. 35-44 age category had a 5% chance. 45-54 age category had an incidence of 14%. 55-64 years of age had an incidence of being diagnosed with cancer at 24%. 65-74 age category had 25%. 75-84 age category had a chance of 20% and >85 an 8% chance. This value coincides with our study. The peak ages where cancer was diagnosed were similar in both studies. The study by Kendall K. Morgan had maximum number of cases diagnosed in the age group of 45-84 years which coincidentally coincides with our study.

Hyuna Sung PhD *et al.*, conducted a similar study in 2021 where the most commonly diagnosed cancer in male population was lung cancer, followed by prostate cancer. In females, the most common was breast cancer, followed by ovarian cancer which is analogous to our study [11].

In a review published by Philip J Wiffen *et al.*, on ‘Opioid for Cancer Pain – an overview of Cochrane review [12]’ which analyzed 152 studies along with 9 reviews found that about 19 out of 20 patients with moderate or severe pain can tolerate opioids and will have their pain reduced to mild or no pain within 14 days. But the author concluded with the remark that there is not enough evidence around the use of opioid analgesic for the treatment of cancer pain and the number of evidences presented are disappointingly low [12]. This is also in alignment with the objective of our study which found that there is significant difference between pre and post test using opioid analgesics as a pain management medication. The pre test had patients with moderate and severe pain, with moderate pain being 77.6% of the total subject population. After the

post test ie, after the administration of opioids, the pain intensity mainly fell into mild pain which accounted for about 87.8% and no pain was 11.2%. Therefore the evidence of this study also back ups the claims of the review by Philip J Wiffen.

Choice of opioid and the dose titration are important to achieve an optimum balance between analgesia and unwanted side effects. A normal release formulation of morphine, with a rapid onset and short duration of action is preferred for dose titration. The simplest method is to prescribe a regular 4 hourly dose and adjusted as necessary. Adequate dose titration can refer to different standards depending on the hospital and the guidelines they follow, it can also depend on the country and the specific population that receives the treatment. In this study, the dose was titrated according to the patient’s pain intensity that being the more the pain the higher the opioid dose and the lesser the pain the lower the dose.

Opioid analgesics are known to cause constipation and nausea as the most common type of ADR as shown in a review by Ramsin Benyamin *et al.* in a study by Raja SN *et al* comparing opioids and antidepressants, opioid analgesics were shown to cause more constipation [13].

In a 2009 study Timothy J. Bell *et al.*, on ‘Prevalence, severity, and impact of opioid induced bowel dysfunctions’ it was found that out of 322 patients 81% of the patients reported with constipation and 58% with straining to pass a bowel movement [14]. The patients were treated with laxatives which comprised of stimulants, hyperosmotic and bulking agents for relief. These studies correlate with the study conducted at Lourdes hospital as the main side effect noted was constipation and all the reported cases were treated with a laxative. Therefore, the number of studies and evidences have monumental value in helping patients with these ADR’s.

## CONCLUSION

Cancer pain management is a complicated subject due to the presence of various external factors. Our study tried to answer some of the main questions regarding cancer pain management. The study found that opioid therapy is a cornerstone in cancer pain management. Dose titrations when done correctly are effective in mitigating the pain intensity of the suffering patients. Constipation is one the main ADR's that was reported when using opioid analgesics and it was mitigated using laxatives. The use of co-analgesics was found to be helpful in cancer pain management as it reduces pain in the patients.

## LIMITATIONS

- ❖ First, the study was single centred retrospective study, devoid of patient interaction. And also since pain is subjective the pain intensity of the patient may vary from subject to subject and an accurate representation of the pain will fall within the speculation of pain for the particular patient.
- ❖ The study also takes into account only inpatient subjects and does not reflect any out-patient status
- ❖ And finally, the accuracy of the ADR reported might be inconclusive due to the already ongoing chemotherapy which is well established to cause ADR's and as such many of the ADR's might be difficult to differentiate between the ADR of opioids.
- ❖ This is a retrospective study hence hypothesis generated and the outcomes should be confirmed in a large randomized prospective study.

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