

# Factors Influencing the Initiation of Strong Opioids in Cancer Patients on Palliative Care: An Audit from a Tertiary Cancer Center in India

Ankita Gupta, Bhushan Parmar<sup>1</sup>, Minni Hurria Arora, Raviteja Miriyala, Neeru Anand, Sushmita Ghoshal

Department of Radiotherapy and Oncology, Post Graduate Institute of Medical Education and Research, Chandigarh, <sup>1</sup>Department of Radiotherapy and Oncology, Pt. JLNMGCH, Chamba, Himachal Pradesh, India

## Abstract

**Aim:** This audit was done to analyze the factors influencing the use of strong opioids in cancer patients receiving comprehensive palliative care from a tertiary institute. **Materials and Methods:** Case records of patients registered for palliative care at our center in 3 months were retrospectively reviewed and followed up throughout the course of their illness. Demographic factors, prior treatments, social support system, analgesic use at registration, and use of radiation and adjuvant analgesics were recorded. Strong opioid use and their time of initiation were evaluated, and multivariate analysis was used to identify the factors correlating with the above. **Results:** After registration, strong opioids were initiated in 16% of the patients. It was observed that patients younger than 55 years and those with visceral metastases and history of use of weak opioids at the time of registration had a higher probability of being started on strong opioids. Factors associated with a significantly longer strong opioid-free interval were having spouse as primary caregiver, presence of skeletal metastases, use of palliative radiotherapy, and low socioeconomic status. **Conclusion:** It is certain that the use of strong opioids for adequate analgesia is a necessity for palliative-care patients. However, optimal utilization of adjunctive analgesic modalities, coupled with good supportive care, can minimize the requirement and duration of strong opioid use, especially in developing countries with limited access to specialist palliative care.

**Keywords:** Cancer, palliative care, strong opioids

## BACKGROUND

Incidence of cancer in developing countries is on the rise. However, due to delayed diagnosis, a significant proportion of cancer patients in these countries are diagnosed at advanced stages, requiring specialist palliative care.<sup>[1]</sup>

Pain is commonly experienced by cancer patients, especially in the advanced stage of disease with a prevalence of more than 70%,<sup>[2]</sup> resulting in poor physical and emotional well-being. A comprehensive systematic review indicates pain prevalence of 33% in cancer patients after curative treatment, 59% in patients on anticancer treatment, and 64% in patients with metastatic, advanced, or terminal disease.<sup>[3]</sup> The intensity of pain in such patients also varies, generally increasing with the progression of cancer.

The general guidelines provided by the World Health Organization (WHO) provide a rational basis for oncologists

and palliative-care physicians. Apart from facilitating a comprehensive stepwise approach for pain management, the WHO analgesic ladder helps in utilizing the available resources effectively without overtreatment or undertreatment. This has especially useful implications for developing countries where availability of strong opioids barely suffices the requirement.<sup>[4]</sup> Since access to strong opioids such as morphine and fentanyl is strictly regulated by legal constraints, it would be prudent to evaluate the strong opioid needs of palliative-care patients to ensure their optimal utilization. The purpose of this audit is to

**Address for correspondence:** Dr. Raviteja Miriyala,  
Department of Radiotherapy and Oncology, Post Graduate  
Institute of Medical Education and Research, Chandigarh, India.  
E-mail: ravitejamiriyala@gmail.com

**Submitted:** 31-May-19 **Revised:** 30-Aug-19

**Accepted:** 02-Nov-19 **Published:** 28-Jan-20

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Gupta A, Parmar B, Arora MH, Miriyala R, Anand N, Ghoshal S. Factors influencing the initiation of strong opioids in cancer patients on palliative care: An audit from a tertiary cancer center in India. *Indian J Palliat Care* 2020;26:66-70.

### Access this article online

#### Quick Response Code:



**Website:**  
www.jpalliativecare.com

**DOI:**  
10.4103/IJPC.IJPC\_89\_19

analyze the factors influencing the initiation and duration of use of strong opioids in cancer patients receiving comprehensive palliative care from a tertiary institute.

## MATERIALS AND METHODS

All cancer patients registered in our palliative-care clinic in 3 months were included in this study. The palliative-care clinic runs simultaneously with the outpatient services of the Department of Radiotherapy, PGIMER, Chandigarh, and all patients requiring palliative care are seen jointly by the oncologist and the palliative-care specialist. A preliminary general consent for research was taken from all patients. Their case records were retrospectively reviewed and followed up throughout the course of their illness. Those patients who were terminally ill and expired within 2 days of admission to our hospice were censored from the analysis. Along with demographic factors, variables such as site and extent of disease, prior treatments, social support system and analgesic usage at the time of registration, use of radiation and adjuvant analgesics such as amitriptyline or pregabalin were recorded. Strong opioid use and their time of initiation were evaluated, and multivariate analysis was used to identify the factors correlating with the probability and time of initiation of strong opioids.

## RESULTS

Among the 208 cases registered in 3 months, 187 records were considered suitable for analysis. The median age of the patients was 55 years, ranging from 18 to 79 years. Males constituted 60% of the cases, while females were 40%. 85% of the patients were married, and 65% had their spouse as the primary caregiver; while children or siblings were the primary caregivers in the rest. Two-thirds of the patients belonged to low socioeconomic status [Table 1].

Disease burden at the time of registration was categorized as locally advanced, metastatic, or both and was observed in 40%, 35%, and 25%, respectively. There was a uniform distribution among the common malignancies such as head and neck, breast, cervical, lung, ovarian, prostatic, neurological, and gastrointestinal primaries. However, site-wise analysis was not feasible due to small sample size in each subset. 46% of the patients had previously untreated skeletal or soft tissue metastases at the time of registration, while 38% had visceral metastases [Table 1].

Pain was recorded in 84.5% cases, with about half of them reporting moderate-to-severe pain. Analgesic usage was observed in 90% of the cases registered – 30% using step 1 analgesics alone and 60% using a combination of step 1 and step 2 analgesics.

As a departmental protocol, strong opioids were not prescribed outside the palliative-care clinic. Nonsteroidal anti-inflammatory drugs were the most common step 1 analgesics used at the time of registration, while weak opioids

such as tramadol and codeine were the step 2 analgesics predominantly prescribed. Adjuvant analgesics such as pregabalin and amitriptyline were sparsely used in less than 5% of the cases at the time of registration [Table 2].

The median follow-up period after registration in palliative-care clinic was 78 days, ranging from 1 week to 4 months. After registration, strong opioids were initiated in 16% of the patients. Morphine was the most common, constituting 93% of strong opioids prescribed, followed by fentanyl in the rest. Radiotherapy was used for palliation of symptoms in 65% of the patients, after registration. Among these, 86% of patients were given two to three repeated courses of large single fraction, most commonly 8 Gy, while the rest received fractionated radiation (20–30 Gy in 5–10 fractions). Adjuvant analgesics were prescribed in 35% of the patients, most common being pregabalin, followed by amitriptyline and duloxetine [Table 2].

Among the 16% of patients who received strong opioids, the median duration between registration and initiation of strong

**Table 1: Patient and disease characteristics**

Characteristic	N (%)
Total number of patients, <i>n</i>	187
Median age (years)	55 (18-79)
Marital status, <i>n</i> (%)	
Married	159 (85)
Unmarried	28 (15)
Primary caregiver, <i>n</i> (%)	
Spouse	121 (65)
Children/siblings	66 (35)
Socioeconomic status, <i>n</i> (%)	
Low	123 (66)
Disease status, <i>n</i> (%)	
Locally advanced	75 (40)
Metastatic	65 (35)
Both	47 (25)
Site of metastasis (%)	
Skeletal/soft tissue	46
Visceral	38

**Table 2: Pattern of pain management at and after registration in palliative care clinic**

Management pattern	(%)
Pain at presentation (%)	84.5
Analgesic usage at baseline (%)	90
Step 1 alone	30
Step 1 and 2	60
Strong opioid use after palliative care registration (%)	16
Morphine	93
Fentanyl	7
Palliative RT for pain management (%)	65
8 Gy SFRT (2-3 courses)	86
Fractionated RT (20/30 Gy in 5/10#)	15
Adjuvant analgesics (%)	35 (MC pregabalin)

RT: Radiotherapy, SFRT: Single fraction radiotherapy, MC: Most common

opioids was 29 days, ranging from 1 to 120 days. The median duration of treatment with strong opioids in this group was 47.5 days.

On univariate analysis, age less than 55 years, absence of radiotherapy use, visceral metastases, and use of weak opioids at the time of registration significantly correlated with the initiation of strong opioids in our patients. However, on multivariate analysis, it was observed that patients younger than 55 years (odds ratio = 0.60; 95% confidence interval [CI], 0.30–0.95), those with visceral metastases (odds ratio = 0.80; 95% CI, 0.68–0.97), and history of use of weak opioids at the time of registration (odds ratio = 0.4; 95% CI, 0.3–0.5) had higher probability of being started on strong opioids, than their complementary groups [Table 3].

Among those who received strong opioids during their course of illness, factors associated with a significantly longer strong opioid-free interval (more than 1 month vs. less than 1 month) on univariate analysis were age more than 40 years, having spouse as primary caregiver, low socioeconomic status, skeletal or soft tissue metastases, nonusage of strong opioids at the time of registration, and use of palliative radiotherapy. On multivariate analysis, having spouse as primary caregiver (odds ratio = 0.8; 95% CI, 0.65–0.95), presence of skeletal metastases (odds ratio = 0.6; 95% CI, 0.3–0.8), use of palliative radiotherapy (odds ratio = 0.5; 95% CI, 0.3–0.65), and low socioeconomic status (odds ratio = 0.8; 95% CI, 0.65–0.95) were observed to be associated with delayed initiation of strong opioids [Table 4].

## DISCUSSION

Most pain in cancer responds to pharmacological management using orally administered analgesics and adjuvants. Current treatment is based on the WHO's concept of an "analgesic ladder," which involves a stepwise approach to the use of analgesic drugs. Although progress has occurred in the management of cancer pain, undertreatment prevails.

**Table 3: Factors affecting strong opioid use on multivariate analysis**

Variable	OR	95% CI
Age <55 years	0.60	0.30-0.95
Visceral metastasis	0.80	0.68-0.97
Use of weak opioids at registration	0.40	0.30-0.50

OR: Odds ratio, CI: Confidence interval

**Table 4: Factors associated with delayed initiation of strong opioids on multivariate analysis**

Variable	OR	95% CI
Spouse as primary caregiver	0.80	0.65-0.95
Skeletal metastasis	0.60	0.30-0.80
Use of palliative RT	0.50	0.30-0.65
Low socioeconomic status	0.80	0.65-0.95

OR: Odds ratio, CI: Confidence interval, RT: Radiotherapy

Worldwide, 8.2 million people die of advanced cancer each year, and it has been estimated that around 6 million of these patients have suboptimal or no access to strong opioids largely owing to their lack of availability, especially in developing countries.<sup>[5]</sup> Unfounded fears associated with opioid use, strict government regulations that dictate access to these drugs, and lack of systematic education of health-care workers about cancer pain management are the challenges that surround strong opioid use.<sup>[4]</sup> Even in developed countries in which there is good access to opioids, at least 32% of patients with cancer are undertreated for their pain.<sup>[6]</sup> Therefore, it becomes imperative to analyze the strong opioid needs of cancer patients so as to ensure optimal utilization of these drugs for cancer pain management. Through this audit, we investigated the factors associated with strong opioid use in patients registered in our palliative-care clinic.

We found that 16% of our patients required strong opioids with morphine being the most commonly used analgesic. Factors associated with a higher probability of being initiated on strong opioids included age less than 55 years, presence of visceral metastases, and use of weak opioids at the time of registration.

Among those patients who received strong opioids, the median duration between registration and initiation of strong opioids was 29 days and these were used for a median duration of 47.5 days. Factors associated with a longer strong opioid-free interval were having spouse as primary caregiver, presence of skeletal metastases, use of palliative radiotherapy, and low socioeconomic status.

Our results are in line with a retrospective review that analyzed the characteristics and patterns of opioid use in terminal cancer patients, wherein increasing age was associated with decreasing opioid doses. However, in the same study, patients with spinal metastases required higher doses of opioids while those with lung metastases required lower doses.<sup>[7]</sup>

Another retrospective analysis of the factors associated with usage of higher morphine doses identified that morphine dosage was negatively associated with age. Male patients and non-White patients required slightly higher dosages than others. Primary breast and genitourinary cancers, as well as metastases to bone and spinal diseases, were associated with higher morphine dosages.<sup>[8]</sup>

The decreasing requirement of strong opioids with age could be due to decreased hepatic metabolism and renal excretion in these patients, as well as a reduced number of opioid receptors due to brain atrophy, resulting in increased sensitivity to opioids.<sup>[9]</sup>

Site-wise analysis was not feasible in our study due to small sample size in each subset, and on the contrary, patients with skeletal metastasis had a relatively longer strong opioid-free interval in our study, likely due to utilization of palliative radiotherapy in a majority of these patients.

Radiotherapy is highly effective in the management of metastatic bone pain and in metastatic spinal cord

compression.<sup>[10]</sup> Numerous randomized, prospective trials show improvements in pain relief in 60%–80% of patients after radiotherapy, with complete responses (no pain and no increase in analgesic requirements) in up to 30%.<sup>[11]</sup> Radiotherapy was used for palliation of symptoms in 65% of our patients.

Although no significant association was demonstrated with the use of adjuvant analgesics in our study, these could be responsible for alleviation of symptoms in some patients. 35% of the patients in our study group were prescribed adjuvant analgesics in addition to opioids. A narrative analysis from eight studies including five randomized controlled trials concluded that adjuvants improved pain control within 4–8 days when added to opioids for cancer-related neuropathic pain, with the strongest evidence supporting gabapentin.<sup>[12,13]</sup>

Another study examining site-wise distribution of pain reported that cancer of the cervix was frequently (68%) associated with severe pain, followed by prostate (52%) and rectosigmoid tumors (49%). It also demonstrated that severe pain was more prevalent in those with bone metastasis, in those admitted from home, and in those younger than 55 years of age. The majority (71.7%) of patients had a stable dosing pattern, and only 4.2% of the patients required dose increases of at least 10% per day.<sup>[14]</sup> We did not analyze change in dosing pattern of strong opioids in our patients.

Because pain is a somatopsychic experience, its intensity is modified by the patient's mood and morale. Therefore, the critical role played by caregivers in pain management of cancer patients cannot be understated.<sup>[15]</sup> Our study demonstrated a statistically significant difference in strong opioid-free interval in cancer patients who had spouse as the primary caregiver. A preliminary study tested the efficacy of a partner-guided cancer pain management protocol for terminally ill cancer patients and stated that such protocol may have benefits in the context of cancer pain at the end of life.<sup>[16]</sup>

Another factor that was associated with a greater requirement of strong opioids in our patients was the prior use of weak opioids at the time of registration. This could be explained by the phenomena of opioid desensitization and hypersensitization of NMDA receptors from prolonged opioid therapy, which may contribute to an apparent decrease in analgesic efficacy, regardless of progression of the pain, thereby, increasing the probability of being initiated on strong opioids.<sup>[9]</sup>

It was seen that poor socioeconomic status was associated with delayed initiation of strong opioids in our patients. This factor holds relevance in our setup where a majority of patients come from low socioeconomic background and travel long distances for supportive care. Long-term regular follow-up and traveling large distances for their strong opioid requirement may not be feasible for them.

Likewise, a systematic content analysis of policy barriers to opioid access in 12 European countries (ATOME) identified affordability as one of the main factors that hamper access to opioid medication.<sup>[17]</sup>

Through this audit, we demonstrated the factors that affected strong opioid needs in our patients. Identification of such factors is critical to delivering effective pain management and quality palliative care in cancer patients. This is expected to provide a basis for optimal utilization of strong opioids, especially in a background of limited opioid availability and palliative-care services.

## CONCLUSION

It is certain that the use of strong opioids for adequate analgesia is a necessity for palliative-care patients. However, optimal utilization of adjunctive analgesic modalities, coupled with good supportive care, can minimize the requirement and duration of strong opioid use, especially in developing countries with limited access to specialist palliative care.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

- Saini S, Bhatnagar S. Cancer pain management in developing countries. *Indian J Palliat Care* 2016;22:373-7.
- Portenoy RK. Treatment of cancer pain. *Lancet* 2011;377:2236-47.
- van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: A systematic review of the past 40 years. *Ann Oncol* 2007;18:1437-49.
- Manjiani D, Paul DB, Kunnumpurath S, Kaye AD, Vadivelu N. Availability and utilization of opioids for pain management: Global issues. *Ochsner J* 2014;14:208-15.
- Berterame S, Erthal J, Thomas J, Fellner S, Vosse B, Clare P, *et al.* Use of and barriers to access to opioid analgesics: A worldwide, regional, and national study. *Lancet* 2016;387:1644-56.
- Greco MT, Roberto A, Corli O, Deandrea S, Bandieri E, Cavuto S, *et al.* Quality of cancer pain management: An update of a systematic review of undertreatment of patients with cancer. *J Clin Oncol* 2014;32:4149-54.
- Radha Krishna LK, Poulouse JV, Tan BS, Goh C. Opioid use amongst cancer patients at the end of life. *Ann Acad Med Singapore* 2010;39:790-7.
- Bercovitch M, Waller A, Adunsky A. High dose morphine use in the hospice setting. A database survey of patient characteristics and effect on life expectancy. *Cancer* 1999;86:871-7.
- Nersesyan H, Slavin KV. Current approach to cancer pain management: Availability and implications of different treatment options. *Ther Clin Risk Manag* 2007;3:381-400.
- Chow R, Hoskin P, Hollenberg D, Lam M, Dennis K, Lutz S, *et al.* Efficacy of single fraction conventional radiation therapy for painful uncomplicated bone metastases: A systematic review and meta-analysis. *Ann Palliat Med* 2017;6:125-42.
- Lutz S, Berk L, Chang E, Chow E, Hahn C, Hoskin P, *et al.* Palliative radiotherapy for bone metastases: An ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011;79:965-76.
- Kane CM, Mulvey MR, Wright S, Craigs C, Wright JM, Bennett MI. Opioids combined with antidepressants or antiepileptic drugs for cancer pain: Systematic review and meta-analysis. *Palliat Med* 2018;32:276-86.
- van den Beuken-van Everdingen MH, de Graeff A, Jongen JL, Dijkstra D, Mostovaya I, Vissers KC, *et al.* Pharmacological treatment of pain in cancer patients: The role of adjuvant analgesics, a systematic review. *Pain Pract* 2017;17:409-19.

14. Brescia FJ, Portenoy RK, Ryan M, Krasnoff L, Gray G. Pain, opioid use, and survival in hospitalized patients with advanced cancer. *J Clin Oncol* 1992;10:149-55.
15. Ferrell BR, Ferrell BA, Rhiner M, Grant M. Family factors influencing cancer pain management. *Postgrad Med J* 1991;67 Suppl 2:S64-9.
16. Keefe FJ, Ahles TA, Sutton L, Dalton J, Baucom D, Pope MS, *et al.* Partner-guided cancer pain management at the end of life: A preliminary study. *J Pain Symptom Manage* 2005;29:263-72.
17. Larjow E, Papavasiliou E, Payne S, Scholten W, Radbruch L. A systematic content analysis of policy barriers impeding access to opioid medication in central and Eastern Europe: Results of ATOME. *J Pain Symptom Manage* 2016;51:99-107.