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Safe practices for legitimate medical use of opioids: a study of trends in opioids prescription over a decade

Abstract

Background: An unwavering availability of opioids is crucial for effective pain and palliative care and for managing opioid dependence. This study aims to study the pattern of morphine consumption and the use of safety protocols for prescribing opioids in a tertiary cancer hospital in India.

Patients and methods: The medical and pharmacy records were studied retrospectively to investigate the pattern of oral Morphine consumption and distribution from 2008 to 2020.

Results: The number of new cancer patients visiting the hospital, the number of re-visits of these patients, and inpatient admissions to palliative care services increased unswervingly from 2008 to 2019 with a sharp fall in 2020 owing to the COVID pandemic. Annual oral morphine consumption showed a steady increase from 4.89 kg in 2008 to 11.53 kg in 2019 with a fall to 5.68 kg in 2020. However, the trend for oral morphine dispensed per patient per visit showed a mild increase from 1.1 grams in 2008 to 2.06 grams in 2012, followed by a gradual decline to 0.89 grams in 2020. Opioid diversion incidence was found to be zero.

Conclusions: Comprehensive interventions alongside safety protocols for prescriptions of opioids and effective integration of palliative care can help prevent opioid use disorders.

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Key words: opioid prescribing patterns, morphine consumption, patient safety protocols, substance use disorder, cancer pain

Introduction

Morphine was included in the World Health Organization (WHO) Model List of Essential Medicines in 1977 [1]. It is an indispensable drug for managing cancer pain. An unwavering availability

of opioids is crucial for effective pain and palliative care and for managing opioid dependence [2, 3]. Conversely, opioids have been legally classified as controlled drugs due to abuse and dependence potential, posing a barrier to their legitimate medical use.

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Barriers to access to morphine are especially high in Low Middle-Income Countries [4]. In India, more than 1 million new cases of cancer are detected annually, with pain and its inadequate management being a frequently prevalent problem [5], although India perceives several narcotic drugs as essential [6]. The Lancet Commission's report of 2017 quantified the inequalities in medicinal opioid availability access across the globe. India distributed 43 mg morphine equivalent which was enough to meet only 4% of the total palliative care needs [7]. Moreover, stringent regulations on the medical use of opioids and a lack of formal pain management training present an enormous impediment to the safe and effective use and prescription of opioids [8].

On the other hand, in the Western world, a remarkable rise in opioid use to treat chronic pain, and the ensuing rise in opioid abuse have amassed concern from the public health sector [9]. There has been a dismal panic originating from the various reports of addiction and opioid-related deaths [10–12]. Between 2001 and 2014, in the United States of America, opioid prescription-related deaths have soared from 1.9 to 5.9 per 100,000 [13]. Nevertheless, even the most developed nations faced severe shortages in the supply of opioids due to the challenges during the COVID-19 pandemic [14].

A survey conducted in 2007 concluded that difficulty with procurement and distribution due to restraining laws, costs, bureaucracy, and concerns of addiction, have constrained the legitimate medical use of opioids [15]. An exigency due to the precipitous increase in the occurrence of opioid-related deaths is further complicated by insufficient training and physician education regarding opioid prescribing [16].

However, such fear of opioid addiction and overdose can have grievous consequences for cancer patients suffering from severe undertreated pain. Therefore the pattern of morphine consumption was studied for over a decade and so was the use of safety protocols for prescribing opioids, followed in a tertiary cancer hospital in New Delhi.

Patients and methods

We performed a retrospective study to analyse the pattern of morphine consumption from 2008 to 2020, in a tertiary cancer hospital in New Delhi, India. The hospital has a dedicated tertiary-level palliative care department with monthly audits and frequent reviews of safety protocols and prescription practices. Data on patient registrations and revisits in the hospital, and with the Department of Palliative care and inpatient admissions to the Pain and palliative care

ward were collected from Medical Records Section. Data relating to morphine consumption was retrieved from the Outpatient Pharmacy retrospectively. Total oral morphine dispensed over thirteen years, and morphine consumption per visit was calculated and studied. Ethics committee approval was obtained from the Institute Ethics Committee (IEC-616/03.09.2021).

Results

Patient data

The number of new cancer patients visiting the hospital increased every year, from 8793 patients in 2008 to 13008 patients in 2019 but fell to 7093 patients in 2020. Out of these, patients with high symptom burden or poor performance status or advanced disease were primarily registered with the palliative care clinic. The number of such patients also increased from 295 patients in 2008 to 1120 patients in 2019 but were fewer in 2020. All other patients also received palliative care consultations. Justifiably, the number of visits of these patients to the hospital and the pain clinic also increased every year. Inpatient admissions to the palliative care ward, as recorded since 2010 increased consistently (Table 1).

Oral morphine consumption data

Morphine consumption showed a continual rise from 4.89 kg in 2008 to 11.53 kg in 2019 but showed a drastic fall to 5.63 kg in 2020 (–50% annual change) (Table 1, Fig. 1). The steady incline was accompanied by a corresponding rise in out-patient attendance to pain and palliative care clinic from 4457 patient-visits in 2008 to 17857 visits in 2019, with a sharp decline to 6398 patients in 2020. Notwithstanding the rise in patient footfall in the hospital, the trend for total oral morphine consumption as well as the oral morphine dispensed per patient per visit showed an increase from 1.1 grams in 2008 to 2.06 grams in 2012, followed by a gradual decline to 0.89 grams of oral morphine prescribed per patient visit in 2020 (Fig. 2). Divergence incidence reported was nil [17].

Discussion

With the rising incidence of cancer as well as opioid-related deaths reported worldwide, it was decided to perform a survey of the opioid-use data of the past thirteen years spanning the journey since the initiation of dedicated palliative services at the study institute till the current integrated structure. The number of new cancer patients and hospital visits to the cancer centre soared unswervingly. With the establishment of dedicated palliative care services and a dedicated

Table 1. Patient registrations and morphine consumption

Year	New cancer patients (n)	New patients registered with the palliative care team (n)	Revisits per year to the cancer hospital (n)	Revisits per year to the pain clinic (n)	Admissions in palliative care ward (n)	Oral morphine consumed per year [kg]	Oral morphine consumed per visit [gm]
2008	8793	295	74280	4457	–	4.89	1.1
2009	8504	404	74080	5174	–	7.17	1.39
2010	8679	408	82597	4906	603	8.1	1.65
2011	8633	421	85070	4793	383	7.41	1.55
2012	9059	410	91100	6030	494	12.44	2.06
2013	10084	428	106261	7144	608	10.28	1.44
2014	11000	362	138125	10539	619	10.15	0.96
2015	11099	640	146688	11584	729	14.05	1.21
2016	12372	671	157884	14443	908	13.84	0.95
2017	13260	725	171778	15530	1022	9.37	0.6
2018	13186	963	181566	17240	1227	9.6	0.56
2019	13008	1120	178700	17857	1514	11.53	0.65
2020	7093	723	82392	6398	479	5.68	0.89

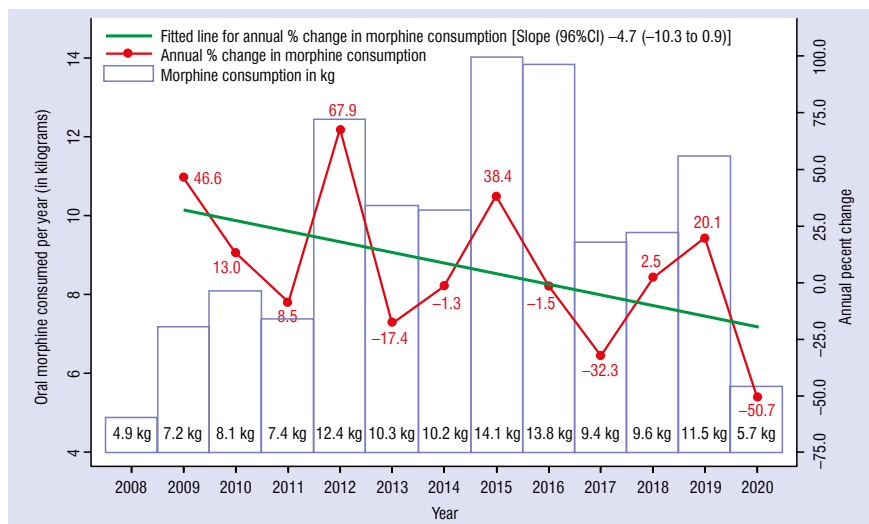


Figure 1. Annual percent change in morphine consumption from years 2008–2020

pain and palliative care ward, well equipped with a fluoroscopy-enabled intervention room, the number of patients admitted to the ward also showed a constant upsurge. Over the years, the department has held monthly clinical audits and updated and monitored the safety protocols for opioid prescription.

Despite various studies quoting opioid-sparing properties of adjuvant drugs and neurolytic blocks and behavioural intervention, the morphine consumption trend has, often, been used to gauge advances in the quality of pain management services [18, 19]. In the present observational study, oral morphine consumption dispensed on an outpatient basis was

used instead of total opioid consumption in the hospital, to evade bias owing to distinct clinical uses of opioids (e.g., intravenous fentanyl and morphine for perioperative care).

We found morphine consumption showed a continual rise from 4.89 kg in 2008 to 11.53 kg in 2019. This increase was accompanied by a parallel rise in out-patient attendance to pain and palliative care clinics from 4457 patient visits in 2008, to 17857 patient visits in 2019. This constant and parallel rise can be ascribed to advances in palliative care [20–22], growth of educational opportunities for healthcare professionals involved in pain and opioid prescribing

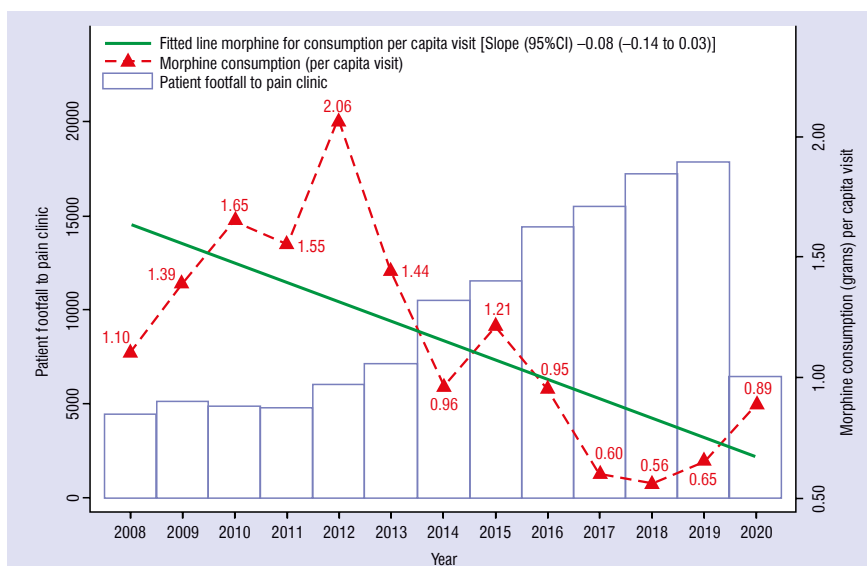


Figure 2. Morphine consumption in grams per capita visit for years 2008–2020

[23–25], and initiation of clearer policies governing the medical use of opioids. However, owing to the COVID-19 pandemic, ensuing nationwide lockdowns, and resulting barriers [26] to access to healthcare, patient attendance as well as morphine dispensed in the hospital saw a sharp fall.

To avoid being misled by the wavering trend in total oral morphine consumption in the backdrop of an increasing number of patients and revisits, the authors calculated and plotted the trend for oral morphine dispensed per patient visit. However, this trend, over thirteen years, was unmatched: although morphine consumption had increased, the consumption pattern per patient visit did not show a similar consistent rise. In cases of addiction or dependence or increased dosing, opioid consumption is expected to increase. However, the present data show an irregular fluctuating pattern of demand and supply of morphine, with an eventual decline over more than a decade of quality improvement measures, suggestive of the judicious use of opioids.

A separate cross-sectional observational study conducted at the study centre interviewed patients who were receiving uninterrupted morphine for chronic cancer pain for ≥ 12 months; the most recent prescription showed a morphine equivalent dosage of ≥ 60 mg. Patients were screened for the presence of comorbid mental disorders or probable substance use disorders. None of the participants had psychiatric or substance use disorder [17]. Meticulous prescription practices are followed at the study centre to reinforce the responsible and judicious use of oral morphine for cancer pain, and to prevent drug abuse (Fig. 3). Safe prescription protocols are followed at the institute.

Palliative care referrals

- An “automatic-referral model” [27] is followed at the institute wherein all patients are referred for palliative care consultations to the outpatient clinic. This helps to streamline access to palliative care and standardize care using routine screening.
- Patients presenting with high symptom burden or advanced disease are primarily registered with the palliative care team. Those requiring emergent care for the relief of symptoms are admitted to the pain and palliative care ward.

Integration of palliative oncology

- An “integrated-care model” [28] of palliative care is followed, wherein the oncologist and other specialists diligently work in collaboration with the palliative care team to provide complete cancer care.
- A palliative care trained doctor is posted in the emergency department to provide palliative care and counselling to patients with chronic diseases including cancer, presenting in the emergency.
- Training and collaboration with departments managing non-oncological chronic diseases (pulmonary, neurologic, geriatric).
- Collaboration with addiction psychiatry, and the department of physical and medical rehabilitation.

Education

- All health care professionals working in onco-anaesthesia, pain and palliative care department complete a certified training program in palliative care services and prescription of opioids.
- The department also started a 3-year M.D. course in Palliative Medicine in 2016.

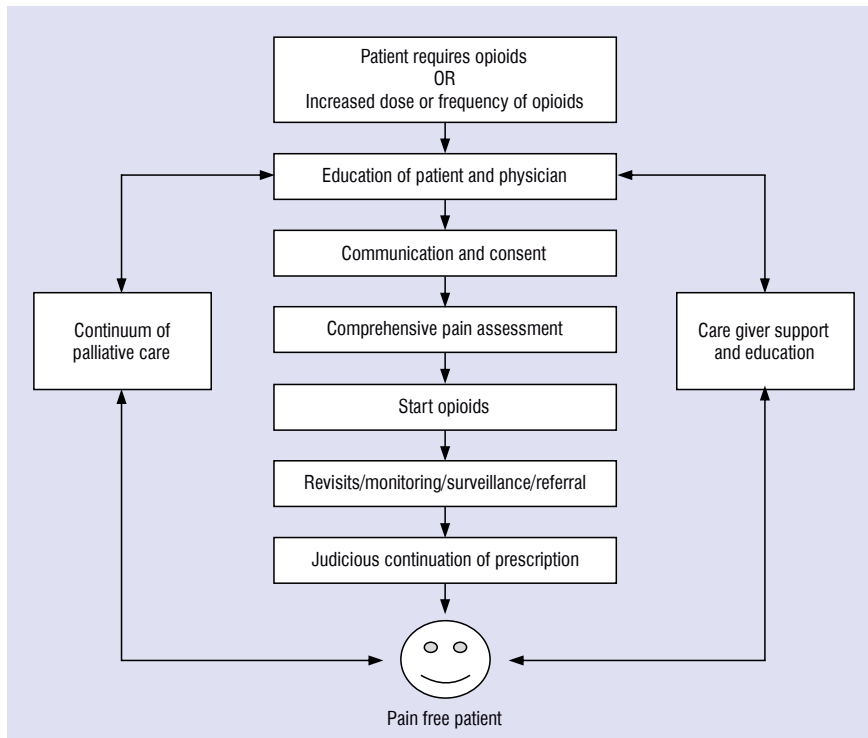


Figure 3. Comprehensive management of 'total pain'

Communication

- Patients are interviewed about their concerns regarding opioid addiction, tolerance, side effects and fears.
- Patients and caregivers are educated about opioids, both verbally and through written handouts in their language. They are informed about the safe use and storage of opioids, the signs and symptoms of overdose, and the importance of follow-ups.
- A 24-hour helpline number is provided to all patients for telemedicine family conference or consultation contact out of hours, particularly during the initiation of treatment or for palliative care counselling during the last phase of life.

Screening

- Patients are screened on each visit about social and psychological factors associated with pain.
- Patients suffering from altered liver or kidney functions are categorized as high risk.
- All adult patients who have received oral opioids uninterruptedly for more than one year or are receiving an equivalent morphine dose of 60 mg/day or more, in the latest prescription are examined for signs of dependence or addiction [17].
- In case of suspicion, evaluation is completed by a qualified specialist in addiction psychiatry.

- There have been occasional instances where patients were admitted for comprehensive psychiatric evaluation and observation of drug-seeking behaviour. To date, no diversion incidence has been reported in the practice [17].

Starting opioids

- Comprehensive pain assessment (nature and severity of pain, aetiology of pain, appropriate tests if required) (Fig. 4). A holistic assessment of pain ought to include the social and psychological elements of distress. Before starting or increasing the dose of opioids, patients should be assessed for potential risk factors for addiction such as long-term opioid use (> 3 months) [29, 30], age > 65 years [31], adolescence [32], sleep-disordered breathing [33], renal or hepatic impairment [34], depression [35], substance-use disorder (including alcohol) [36], history of overdose [37].
- If a patient needs emergent management of pain for acute or severe pain, the patient is admitted under the care of a palliative medicine physician for titration of opioid therapy using intravenous or immediate-release oral morphine (Fig. 4).
- Appropriate adjuvant drugs are started.
- Step IV of the WHO analgesic ladder (intervention techniques) are considered early and when feasible.

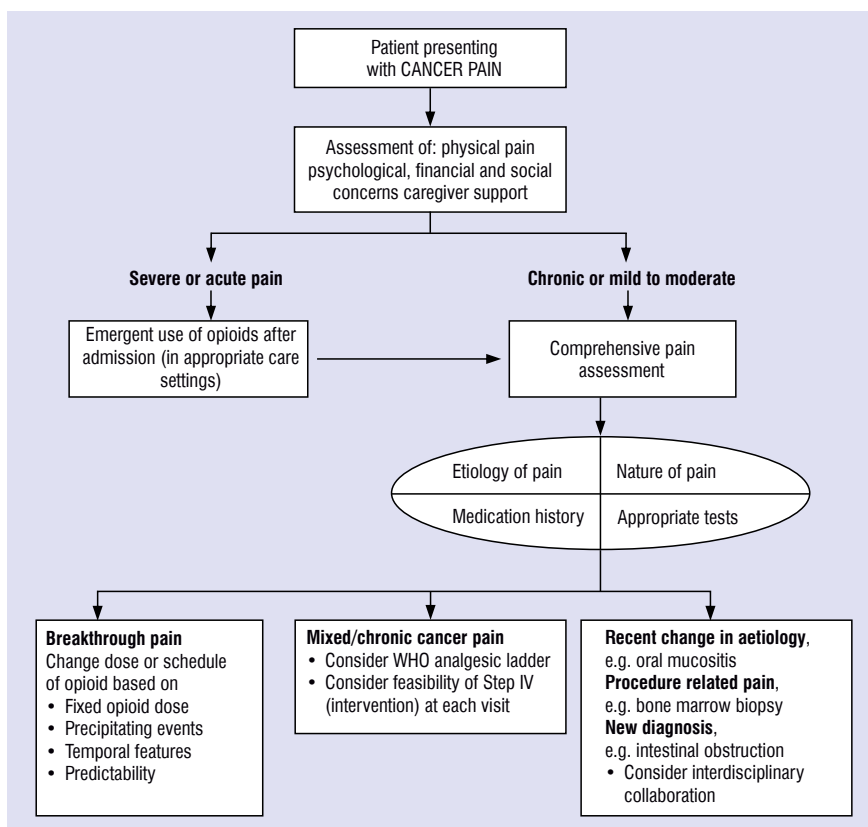


Figure 4. Management protocol for patients presenting with cancer pain

Prescription

- Opioid-naïve patients are prescribed opioids for seven days only, after which the patient is required to visit the pain clinic for re-assessment.
- On subsequent visits, opioids are prescribed for 15 days, after which the prescription needs to be renewed during a visit to the pain clinic in person.
- Patients are taught about the management of opioid doses for breakthrough pain.
- Prescription Drug Monitoring Performa are filled by the pain physician at each visit. This helps to inform the physician about drugs’ side effects, escalating doses of opioids, and to identify safety, risk, abuse, diversion, and doctor-shopping behaviour.
- If any patient is unable to visit the hospital due to disease or debility, a home-care palliative care team (including a doctor, a nurse, and a social worker) is deployed to visit the patient at home.
- Alternatively, any registered medical practitioner may contact the pain-care team to explain the health status of the patient. These procedures facilitate the safe supply of opioids to those who need them for legitimate medical use.

Multimodal techniques

- Weekly inter-departmental meetings are held between radiologists, anaesthesiologists, and surgical oncologists, to assess the feasibility of interventions to reduce pain and provide palliation.
- Interventional pain management such as neurolytic blocks and radiofrequency ablation of nerves are employed when appropriate (Fig. 4).
- Palliative radiotherapy or chemotherapy or surgery is given to appropriate candidates to reduce symptom burden.
- Non-pharmacological methods: scrambler therapy, physiotherapy and physical and medical rehabilitation, nutritional counselling are also offered when deemed necessary, to improve the functional status of the patient.

Changes made during the COVID-19 pandemic

- Telemedicine consultations for new patients as well as revisits. A digital database for formed for the documentation of contact details of outpatients.
- Educating patients and caregivers about home care and identifying worrying symptoms early to prevent hospitalizations.

- All medications were dispensed for 1 month instead of 15 days, to prevent the need for unnecessary travel and to minimize patients' frequent visits to the hospital during the difficult lockdown period.
- Palliative care physicians were included in the COVID-19 treating teams to ensure pain and palliative care for cancer patients suffering from COVID-19.

Conclusions

To optimize opioid use we need to educate health-care professionals, caregivers, and policymakers. The present study was limited by the inherent nature of the study design that did not consider individual patient data or any clinical variables such as relief in pain or other symptoms in cancer patients. Lower potency opioids such as tramadol were not studied.

Morphine consumption can be a deceptive marker for quality and access to palliative care. This study highlights the importance of multidisciplinary actions and interventions to achieve pain relief and palliation of symptoms which thereby reduce morphine consumption.

Apprehension amongst doctors, due to reports of opioid overdose and abuse should not deprive patients of adequate pain relief. Appropriate opioid prescriptions should always be accompanied by immaculate assessment and continuing education of the patient, caregivers, and health care professionals.

The COVID-19 pandemic and ensuing travel restrictions have added health-related suffering of vulnerable populations highlighting the role of policy decisions and strategic interventions to ensure the availability, accessibility, and affordability of essential medicines for primary, intensive, and palliative care [38].

Declarations

Authorship: AP is the chief investigator; AP with critical input from all authors, wrote the protocol for the study. AP and SB coordinated data collection, with input from all authors. HKR analysed the data. All authors had access to all study data, discussed the interpretation of findings and take responsibility for data integrity and analysis. AP and SB drafted the manuscript. All authors contributed to the analysis plan and provided critical revision of the manuscript for important intellectual content.

Ethics

Ethics committee approval was obtained from the Institute Ethics Committee, AIIMS, New Delhi (IEC-616/03.09.2021)

Data sharing

The data that supports the findings of this study are available at Medical Records Section, All India Institute of Medical Sciences, New Delhi and available on request from the first and last authors. The data are not publicly available due to privacy and ethical restrictions.

Declaration of conflict of interest

The authors declare that there is no conflict of interest.

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References

1. World Health Organization. Comparative table of medicines on the World Health Organization Essential Medicines Lists from 1977-2011. http://www.who.int/entity/medicines/publications/essentialmedicines/EMLsChanges1977_2011.xls (21.10.2022).
2. Fallon M, Cherny NI, Hanks G. Opioid analgesic therapy. In: Fallon M, Cherny NI, Christakis NA. ed. *Oxford Textbook of Palliative Medicine*, 4th ed. Oxford University Press, New York 2010: 661–698.
3. Joranson DE, Ryan KM, Maurer M. Opioid policy, availability, and access in developing and non-industrialized countries. In: Fishman SM, Ballantyne JC, Rathmell JP. ed. *Bonica's Management of Pain*, 4th ed. Lippincott Williams & Wilkins, Baltimore 2010: 194–208.
4. Milani B, Scholten W. Access to controlled medicines. In: World Health Organization (ed.) *The world medicines situation 2011*. 3rd ed. World Health Organization, Geneva 2011: 1–20.
5. Doyle KE, El Nakib SK, Rajagopal MR, et al. Predictors and prevalence of pain and its management in four regional cancer hospitals in India. *J Glob Oncol*. 2018; 4: 1–9, doi: [10.1200/JGO.2016.006783](https://doi.org/10.1200/JGO.2016.006783), indexed in Pubmed: [30241192](https://pubmed.ncbi.nlm.nih.gov/30241192/).
6. Human Rights Watch. Country Chapters, World Report. 2014. <http://www.hrw.org/world-report/2014/country-chapters/india?page=3> (21.10.2022).
7. Knaul F, Farmer P, Krakauer E, et al. Alleviating the access abyss in palliative care and pain relief — an imperative of universal health coverage: the Lancet Commission report. *Lancet*. 2018; 391(10128): 1391–1454, doi: [10.1016/s0140-6736\(17\)32513-8](https://doi.org/10.1016/s0140-6736(17)32513-8).
8. Singh S, Prasad S, Bhatnagar S, et al. A cross-sectional web-based survey of medical practitioners in India to assess their knowledge, attitude, prescription practices, and barriers toward opioid analgesic prescriptions. *Indian J Palliat Care*. 2019; 25(4): 567–574, doi: [10.4103/ijpc.ijpc_83_19](https://doi.org/10.4103/ijpc.ijpc_83_19), indexed in Pubmed: [31673214](https://pubmed.ncbi.nlm.nih.gov/31673214/).
9. Scholten WK, Christensen AE, Olesen AE, et al. Quantifying the adequacy of opioid analgesic consumption globally: an updated method and early findings. *Am J Public Health*. 2019; 109(1): 52–57, doi: [10.2105/AJPH.2018.304753](https://doi.org/10.2105/AJPH.2018.304753), indexed in Pubmed: [30496006](https://pubmed.ncbi.nlm.nih.gov/30496006/).
10. Barry CL, Kennedy-Hendricks A, Gollust SE, et al. Understanding Americans' views on opioid pain reliever abuse. *Addiction*. 2016; 111(1): 85–93, doi: [10.1111/add.13077](https://doi.org/10.1111/add.13077), indexed in Pubmed: [26212522](https://pubmed.ncbi.nlm.nih.gov/26212522/).

11. Herzberg D, Guarino H, Mateu-Gelabert P, et al. Recurring epidemics of pharmaceutical drug abuse in america: time for an all-drug strategy. *Am J Public Health*. 2016; 106(3): 408–410, doi: [10.2105/AJPH.2015.302982](https://doi.org/10.2105/AJPH.2015.302982), indexed in Pubmed: [26794163](https://pubmed.ncbi.nlm.nih.gov/26794163/).
12. Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu Rev Public Health*. 2015; 36: 559–574, doi: [10.1146/annurev-publ-health-031914-122957](https://doi.org/10.1146/annurev-publ-health-031914-122957), indexed in Pubmed: [25581144](https://pubmed.ncbi.nlm.nih.gov/25581144/).
13. Rudd RA, Aleshire N, Zibbell JE, et al. Increases in drug and opioid overdose deaths — United States, 2000–2014. *MMWR Morb Mortal Wkly Rep*. 2016; 64(50–51): 1378–1382, doi: [10.15585/mmwr.mm6450a3](https://doi.org/10.15585/mmwr.mm6450a3), indexed in Pubmed: [26720857](https://pubmed.ncbi.nlm.nih.gov/26720857/).
14. Reuters, personal communication, 2020. Exclusive: Opioid supply crunch for U.S. coronavirus patients prompts appeal to relax limits. [https://www.reuters.com/article/us-health-coronavirus-usa-opioids-exclus-idUSKBN21K2ZJ\(21.10.2022\)](https://www.reuters.com/article/us-health-coronavirus-usa-opioids-exclus-idUSKBN21K2ZJ(21.10.2022)).
15. International Narcotics Control Board. Report of the International Narcotics Control Board on follow-up to the twentieth special session of the general assembly, 2008. New York: United Nations 2009.
16. Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research* [Internet]. Washington (DC): National Academies Press (US); 2011 [cited 2020 Sep 25]. (The National Academies Collection: Reports funded by National Institutes of Health). <http://www.ncbi.nlm.nih.gov/books/NBK91497/> (21.10.2022).
17. Choudhary N, Singh S, Rathore P, et al. Opioid use disorders among patients on long-term morphine for management of chronic cancer pain: a pilot study from a tertiary palliative care facility. *Indian J Palliat Care*. 2021; 27: 264–268, doi: [10.25259/ijpc_358_20](https://doi.org/10.25259/ijpc_358_20).
18. Seya MJ, Gelders SF, Achara OU, et al. A first comparison between the consumption of and the need for opioid analgesics at country, regional, and global levels. *J Pain Palliat Care Pharmacother*. 2011; 25(1): 6–18, doi: [10.3109/15360288.2010.536307](https://doi.org/10.3109/15360288.2010.536307), indexed in Pubmed: [21426212](https://pubmed.ncbi.nlm.nih.gov/21426212/).
19. Foley KM. How well is cancer pain treated? *Palliat Med*. 2011; 25(5): 398–401, doi: [10.1177/0269216311400480](https://doi.org/10.1177/0269216311400480), indexed in Pubmed: [21708847](https://pubmed.ncbi.nlm.nih.gov/21708847/).
20. García del Pozo J, Carvajal A, Viloria JM, et al. Trends in the consumption of opioid analgesics in Spain. Higher increases as fentanyl replaces morphine. *Eur J Clin Pharmacol*. 2008; 64(4): 411–415, doi: [10.1007/s00228-007-0419-9](https://doi.org/10.1007/s00228-007-0419-9), indexed in Pubmed: [18157671](https://pubmed.ncbi.nlm.nih.gov/18157671/).
21. García del Pozo J, Carvajal A, Rueda de Castro AM, et al. Opioid consumption in Spain — the significance of a regulatory measure. *Eur J Clin Pharmacol*. 1999; 55(9): 681–683, doi: [10.1007/s002280050693](https://doi.org/10.1007/s002280050693), indexed in Pubmed: [10638399](https://pubmed.ncbi.nlm.nih.gov/10638399/).
22. Wright M, Wood J, Lynch T, et al. Mapping levels of palliative care development: a global view. *J Pain Symptom Manage*. 2008; 35(5): 469–485, doi: [10.1016/j.jpainsymman.2007.06.006](https://doi.org/10.1016/j.jpainsymman.2007.06.006), indexed in Pubmed: [18243637](https://pubmed.ncbi.nlm.nih.gov/18243637/).
23. Harding R, Powell RA, Kiyange F, et al. Provision of pain- and symptom-relieving drugs for HIV/AIDS in sub-Saharan Africa. *J Pain Symptom Manage*. 2010; 40(3): 405–415, doi: [10.1016/j.jpainsymman.2009.12.025](https://doi.org/10.1016/j.jpainsymman.2009.12.025), indexed in Pubmed: [20685071](https://pubmed.ncbi.nlm.nih.gov/20685071/).
24. Zenz M, Zenz T, Tryba M, et al. Severe undertreatment of cancer pain: a 3-year survey of the German situation. *J Pain Symptom Manage*. 1995; 10(3): 187–191, doi: [10.1016/0885-3924\(94\)00122-2](https://doi.org/10.1016/0885-3924(94)00122-2), indexed in Pubmed: [7629412](https://pubmed.ncbi.nlm.nih.gov/7629412/).
25. Jarlbaek L, Andersen M, Hallas J, et al. Use of opioids in a Danish population-based cohort of cancer patients. *J Pain Symptom Manage*. 2005; 29(4): 336–343, doi: [10.1016/j.jpainsymman.2004.07.010](https://doi.org/10.1016/j.jpainsymman.2004.07.010), indexed in Pubmed: [15857736](https://pubmed.ncbi.nlm.nih.gov/15857736/).
26. Khurana R, Varshney M, Mishra S, et al. Opioid dispensing patterns from a tertiary care cancer hospital during the nationwide lockdown in COVID-19 pandemic. *Indian J Palliat Care*. 2020; 26(Suppl 1): S70–S75, doi: [10.4103/IJPC.IJPC_179_20](https://doi.org/10.4103/IJPC.IJPC_179_20), indexed in Pubmed: [33088092](https://pubmed.ncbi.nlm.nih.gov/33088092/).
27. Bruera E, Hui D. Conceptual models for integrating palliative care at cancer centers. *J Palliat Med*. 2012; 15(11): 1261–1269, doi: [10.1089/jpm.2012.0147](https://doi.org/10.1089/jpm.2012.0147), indexed in Pubmed: [22925157](https://pubmed.ncbi.nlm.nih.gov/22925157/).
28. Bruera E, Hui D. Integrating supportive and palliative care in the trajectory of cancer: establishing goals and models of care. *J Clin Oncol*. 2010; 28(25): 4013–4017, doi: [10.1200/JCO.2010.29.5618](https://doi.org/10.1200/JCO.2010.29.5618), indexed in Pubmed: [20660825](https://pubmed.ncbi.nlm.nih.gov/20660825/).
29. Edlund MJ, Martin BC, Russo JE, et al. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. *Clin J Pain*. 2014; 30(7): 557–564, doi: [10.1097/AJP.000000000000021](https://doi.org/10.1097/AJP.000000000000021), indexed in Pubmed: [24281273](https://pubmed.ncbi.nlm.nih.gov/24281273/).
30. Paulozzi LJ, Zhang K, Jones CM, et al. Risk of adverse health outcomes with increasing duration and regularity of opioid therapy. *J Am Board Fam Med*. 2014; 27(3): 329–338, doi: [10.3122/jabfm.2014.03.130290](https://doi.org/10.3122/jabfm.2014.03.130290), indexed in Pubmed: [24808111](https://pubmed.ncbi.nlm.nih.gov/24808111/).
31. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract*. 2008; 8(4): 287–313, doi: [10.1111/j.1533-2500.2008.00204.x](https://doi.org/10.1111/j.1533-2500.2008.00204.x), indexed in Pubmed: [18503626](https://pubmed.ncbi.nlm.nih.gov/18503626/).
32. Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *Am J Psychiatry*. 2003; 160(6): 1041–1052, doi: [10.1176/appi.ajp.160.6.1041](https://doi.org/10.1176/appi.ajp.160.6.1041), indexed in Pubmed: [12777258](https://pubmed.ncbi.nlm.nih.gov/12777258/).
33. Cheatle MD, Webster LR. Opioid therapy and sleep disorders: risks and mitigation strategies. *Pain Med*. 2015; 16 Suppl 1: S22–S26, doi: [10.1111/pme.12910](https://doi.org/10.1111/pme.12910), indexed in Pubmed: [26461072](https://pubmed.ncbi.nlm.nih.gov/26461072/).
34. Beaudoin FL, Merchant RC, Janicki A, et al. Preventing iatrogenic overdose: a review of in-emergency department opioid-related adverse drug events and medication errors. *Ann Emerg Med*. 2015; 65(4): 423–431, doi: [10.1016/j.annemergmed.2014.11.016](https://doi.org/10.1016/j.annemergmed.2014.11.016), indexed in Pubmed: [25534653](https://pubmed.ncbi.nlm.nih.gov/25534653/).
35. Boscarino JA, Rukstalis M, Hoffman SN, et al. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. *Addiction*. 2010; 105(10): 1776–1782, doi: [10.1111/j.1360-0443.2010.03052.x](https://doi.org/10.1111/j.1360-0443.2010.03052.x), indexed in Pubmed: [20712819](https://pubmed.ncbi.nlm.nih.gov/20712819/).
36. Jones CM, Paulozzi LJ, Mack KA, et al. Centers for Disease Control and Prevention (CDC). Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department visits and drug-related deaths — United States. *MMWR Morb Mortal Wkly Rep*. 2014; 63(40): 881–885, indexed in Pubmed: [25299603](https://pubmed.ncbi.nlm.nih.gov/25299603/).

37. Hasegawa K, Brown DFM, Tsugawa Y, et al. Epidemiology of emergency department visits for opioid overdose: a population-based study. *Mayo Clin Proc.* 2014; 89(4): 462–471, doi: [10.1016/j.mayocp.2013.12.008](https://doi.org/10.1016/j.mayocp.2013.12.008), indexed in Pubmed: [24629443](https://pubmed.ncbi.nlm.nih.gov/24629443/).
38. Pettus K, Cleary JF, de Lima L, et al. Availability of internationally controlled essential medicines in the COVID-19 pandemic. *J Pain Symptom Manage.* 2020; 60(2): e48–e51, doi: [10.1016/j.jpainsymman.2020.04.153](https://doi.org/10.1016/j.jpainsymman.2020.04.153), indexed in Pubmed: [32387575](https://pubmed.ncbi.nlm.nih.gov/32387575/).