International Journal of Integrated Medical Research
Volume 11 Issue 01 January-February-March 2024
https://doi.org/10.57181/ijoimr/vol11i01/166
ISSN (Online): 2393-9869, ISSN (Print): 2350-0360

RESEARCH ARTICLE

INCIDENCE OF ADVERSE EFFECTS ASSOCIATED WITH STRONG OPIOIDS TREATMENT FOR ONCOLOGICAL PAIN

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ABSTRACT

Background: Opioids are the most commonly drugs used in oncological pain treatment due to its potency and availability and the mechanism underlying their adverse effects is secondary to the activation of the subtypes of opioids receptors. The incidence of adverse effects due opioid treatment varies according on the population, drug dosage and individual comorbidities, being the most common ones: Constipation, nausea and vomiting, dyspnea, drowsiness and opioid use disorder. The presence of adverse effects may be crucial in the context of treatment failure, the goal of this research is to report the incidence of adverse effects associated with the use of strong opioids in diagnosed cancer population.

Materials and Methods: This research is conducted with outpatients from the "Instituto nacional de cancerología", the national reference center of oncology in Mexico, from march to september 2023. From the total of 1230 cases that were reviewed, 467 of them met the inclusion criteria. We consider as strong opioids: Morphine, Buprenorphine, Tapentadol, Oxycodone, Fentanyl and Methadone. For the assessment of the incidence of adverse effects, we employ the Edmonton Symptom Assessment Scale, which is standardized on a numerical scale ranging from 0 to 10 points based on the intensity of the adverse effects.

Results: In the studied sample, 59,1% are women. The mean age is 57,6 ± 13,7 years with a mean BMI of 26,5 ± 5,8 kg/m2. The most common adverse effect associated with the use of opioids in cancer patients is constipation, occurring in 25,9% of the cases, followed by nausea and vomiting at 19,1%, respiratory depression at 1,7%, erythema at 1,3% and drowsiness at 1,3%. Fentanil shows the highest incidence of adverse effects, with constipation occurring in 46,7% of cases and nausea and vomiting at 26,7%. Oxycodone follows closely behind with a 41,7% incidence rate for both variables.

Conclusion: The adverse effects in order or frequency were: Constipation, nausea and vomiting, respiratory depression, erythema and drowsiness, exhibiting a minor incidence compared to other reviews. This enables us to understand the influence of our treatments and the precautions to consider in order to prevent an adverse effect from being the cause of opioid treatment failure, especially in oncologic patients with refractory pain.

KEYWORDS: Adverse effects, Constipation, Incidence, Nausea and vomiting, Opioids.

INTRODUCTION

Opioids are the most commonly drugs used in oncological pain treatment due to its potency and availability, they work through the opioid receptor, found in several structures of the nervous system. The mechanism underlying their adverse effects is secondary to the activation of the subtypes of opioids receptors, primarily

Mu (MOR), Kappa (KOR) and Delta (DOR) [1,2]. The incidence of adverse effects due opioid treatment varies according on the population, drug dosage and individual comorbidities, being the most common ones: Constipation, nausea and vomiting, dyspnea, drowsiness and opioid use disorder [3,4].

Among the most frequently reported adverse effects, we can find:

Constipation: It occurs through the activation of MOR and KOR receptors found in the intestinal submucosal and myenteric plexus, resulting in cellular hyperpolarization by activating potassium channels, reducing neurotransmission, and thereby intestinal motility [5]. The diagnosis is made based on the Rome IV criteria for functional constipation [6]. The treatment relies on education and non-pharmacological strategies such as nutrition and hydration, along with the use of medications and assessment of the possibility of intestinal obstruction and hydro electrolytic disorders [7].

Nausea and vomiting: The etiology of this adverse effect is multifactorial, making it difficult to ascertain the precise reason, meanwhile, it significantly impacts the patient's quality of life. The mechanism of production is explained through three possible causes: Direct stimulation of opioid receptors in the chemoreceptor trigger zone of the medulla oblongata, increased vestibular sensitivity through activation of opioid receptors at the same level, and decreased gastric emptying due to lowered intestinal motility induced by opioids [8,9]. The treatment focuses on optimizing the detection and management of other underlying causes, while using first-line antiemetic agents in case of their occurrence and second-line agents in refractory cases, taking into consideration other potential causes [7].

Opioid-induced respiratory depression: It has been mainly described in the immediate postoperative context, where high doses are used, with an incidence ranging from 0.1% to 37%. The most frequently employed opioids in this case report were Morphine and Fentanyl [10]. The mechanism relies on its effect on MOR receptors in the respiratory centers of the brainstem, reducing the physiological response to hypoxia, hypercarbia, and acidosis. The treatment relies on monitoring these effects, discontinuing opioid administration, providing supportive care, and employing opioid antagonists [11].

Other adverse effects associated with the opioid treatment include: drowsiness and sedation due to the suppression of neurons in the central nervous system, including the cerebral cortex, tolerance phenomena because of to the internalization of the receptor complex, dependence resulting from the rewarding effect, especially produced by full opioid agonists [12], urinary retention, delirium, opioid-induced endocrinopathy with deficiency of androgens, testosterone, estrogens, and progesterone, immunosuppressive effect on the humoral and cellular immune system, and cardiovascular effects mediated by histamine release [13].

The categorization of opioids into strong and weak is based on the potency of the molecule and the associated risk, including the potential for developing opioid use disorder. The most frequently used major opioids include Morphine, Hydromorphone, Buprenorphine, Oxycodone, Fentanyl, and Methadone [14].

The presence of adverse effects may be crucial in the context of treatment failure, the goal of the present research is to report the incidence of adverse effects associated with the use of strong opioids in diagnosed cancer population.

MATERIALS AND METHODS

This research was conducted with outpatients from the “Instituto nacional de cancerología”, the national reference center of oncology in Mexico, from march to September 2023. From the total of 1230 cases that were reviewed, 467 of them met the inclusion criteria. Notice that the most prevalent symptoms in oncologic patients include the probable adverse effects of opioids [3,4], therefore, the results of the present research demonstrate the incidence of adverse effects in the described population, without necessarily a direct cause-and-effect relationship with the opioid treatment.

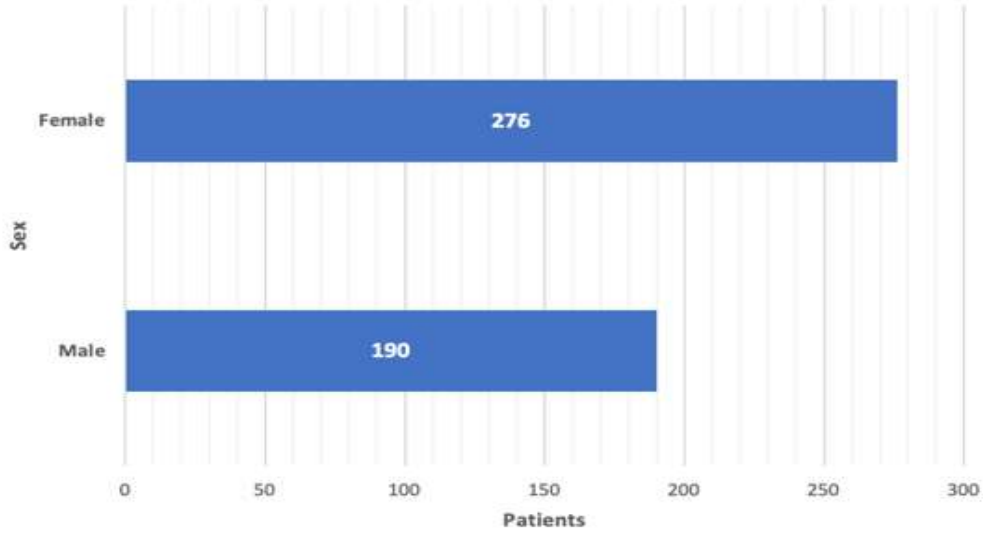
We considered as strong opioids: Morphine, Buprenorphine, Tapentadol, Oxycodone, Fentanyl and Methadone. For the assessment of the incidence of adverse effects, we employ the Edmonton Symptom Assessment Scale, which is standardized on a numerical scale ranging from 0 to 10 points based on the intensity of the adverse effects. This scale is routinely utilized to evaluate all patients attending outpatient therapy and has been validated worldwide [15].

The development of this study adhered to the guidelines of the Good Clinical Practice and the Regulations of the General Health Law on Health Research in Mexico and it

has been approved by the ethics committee of the institute with approval number 2023/159.

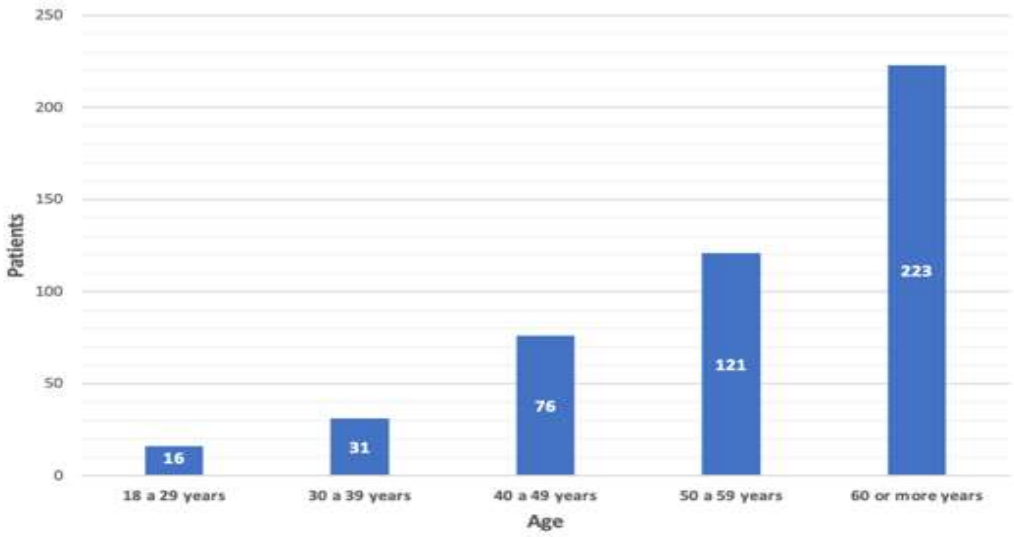
RESULTS

In the studied sample, 59,1% are women. The mean age is 57,6 ± 13,7 years with a mean BMI of 26,5 ± 5,8 kg/m^2. The predominant oncologic diagnoses reveal incidences of 17,6% for breast cancer, 13,1% for prostate cancer and 10,3% for multiple myeloma.



Source: Clinical records, INCAnet.

FIGURE 1- Sex Distribution of the Study Population, INCan, 2023



Source: Clinical records, INCAnet

FIGURE 2- Ago Group Distribution, Study, Population, INCan, 2023

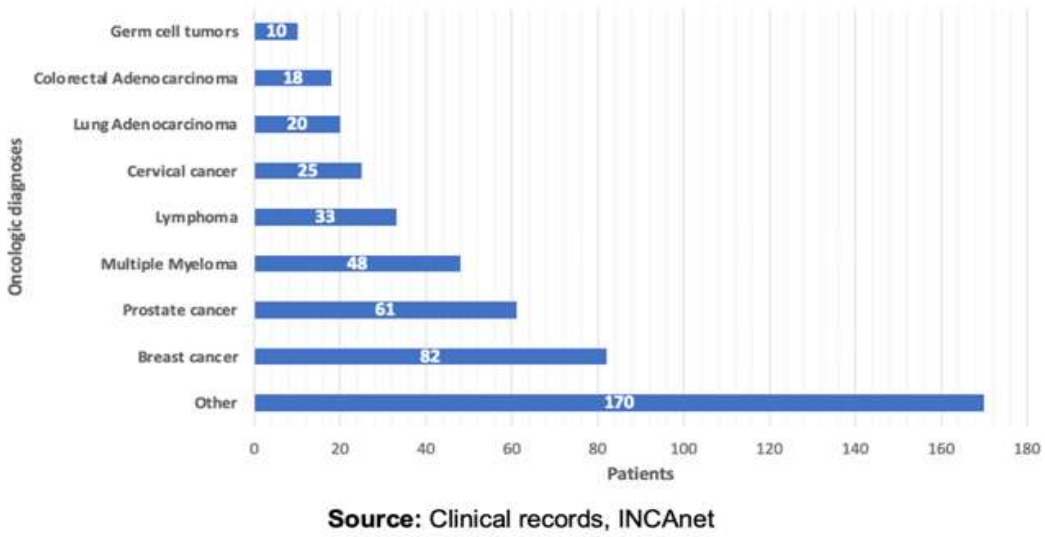


FIGURE 3-Distribution by Oncological Diagnosis, Study Population, INCan, 2023

The most frequently observed algological diagnosis is oncologic axial bone pain, accounting for 21,9% of the sample. Buprenorphine is the most used opioid with a 52,7% of rate use followed by Tapentadol at 31,9%

The most common adverse effect associated with the use of opioids in cancer patients is constipation, occurring in 25,9% of the cases, followed by nausea and vomiting at 19,1%, respiratory depression at 1,7%, erythema at 1,3% and drowsiness at 1,3%. The remaining adverse effects exhibit a low frequency, with incidences below 1%.

TABLE 1- Overall Incidence of Adverse Effects, Study opulation, INCan, 2023

Adverse Effects Incidence		
Adverse Effect	**Cases**	**Percentages**
Constipation	121	25,9
Nauseas	89	19,1
Respiratory Depression	8	1,7
Erythema	6	1,3
Drowsiness	6	1,3
Anxiety Syndrome	5	1,1
Dizziness	2	0,4
Anorexia	1	0,2
Weakness	1	0,2
Pruritus	1	0,2
Angioedema	1	0,2
Insomnia	1	0,2
Abstinence Syndrome	1	0,2
Hallucinations	1	0,2
Tachycardia	1	0,2
Sweating	1	0,2
Tremor	1	0,2

Source: *Clinical Records, INCAnet*

Fentanil shows the highest incidence of adverse effects, with constipation occurring in 46,7% of cases and nausea and vomiting at 26,7%. Oxycodone follows closely behind with a 41,7% incidence rate for both variables. Tapentadol has the lowest incidence of gastrointestinal adverse effects with a rate of 16,7%.

TABLE 2- Incidence of Adverse Effects According to the Specific Opioid, Study Population, INCan in 2023

		Constipation	**Nausea and Vomiting**	**Respiratory Depression**	**Other**
Buprenophine (251 Cases)	Cases	79	49	2	11
	Percentages	31,5	19,5	0,4	4,38
Tapentadol (251 Cases)	Cases	25	26	4	16
	Percentages	16,8	17,5	2,7	10,74
Fentanyl (251 Cases)	Cases	7	4	2	4
	Percentages	46,7	26,7	13,3	26,67
Methadone (251 Cases)	Cases	1	0	0	1
	Percentages	14,3	0	0	14,29
Morphine (251 Cases)	Cases	10	5	0	0
	Percentages	30,3	15,2	0	0
Oxycodone (251 Cases)	Cases	5	5	0	0
	Percentages	41,7	41,7	0	0

Source: *Clinical Records, INCAnet*

DISCUSSION

The use of opioid medications remains the cornerstone of oncologic pain treatment [7]. However, the occurrence of their adverse effects can restrict its use and even jeopardize the patient safety. Therefore, it is crucial for healthcare professionals working in the field of pain medicine to knowledge of the incidence of these effects [16].

The current research reveals a sociodemographic distribution with a higher incidence of pain in females and a direct proportional incidence increase for each decade of life, which aligns with current literature. Nicholas H. et al, in their report from the Mayo Clinic, describe an incidence of 25 to 76% in patients over the age of 65. Furthermore, this incidence is even higher in older adults residing in residential homes or nursing homes [17]. Breast cancer and prostate cancer, lead different prevalence studies worldwide, according to the 2020 GLOBOCAN report, an online platform for global cancer information and statistics in 138 countries, breast cancer had an incidence of 46.3 cases per 100,000 population, while prostate cancer had an incidence of 29.3 cases per 100,000 population. Lung cancer and cervical cancer followed closely behind. Thus, it may be concluded that oncology patients suffering a painful syndrome in our study exhibit similar statistical trends that are observed globally [18].

As previously described, the most common painful syndrome was oncologic axial bone pain, which represented 21.9% of the overall sample. Renata Z. et al conducted a review on the incidence of bone pain in cancer patients, which was shown to be 60%, with a higher prevalence in patients with advanced cancer. The most common metastases were found in vertebral bodies (69%), by hematogenous dissemination, corresponding to the most common type of pain of our research [19].

Buprenorphine was the most widely used opioid in the cur rent study, mostly because to its availability, versatility, hi gh adherence, and simplicity of use as a transdermal patch treatment, followed by Tapentadol, aided from its action in neuropathic pain, very common in oncologic pain.

In comparable reviews to the present study, Keith B. et al reported adverse effects related to the use of opioids in cardiovascular pathology, with a potential incidence of 32.4% resulting in increased hospitalization time and costs. However, they do not specify the exact incidence of each effect [20]. Mercadante et al. documented the same adverse effects in the following order of incidence: nausea and vomiting, constipation, dizziness, sleep disorders, cognitive dysfunction, and others [21]. In their review, Paul

A. et al described an approximate incidence of 40% for constipation and 20% for nausea and vomiting in patients undergoing chronic opioid treatment. Other mentioned adverse effects such as pruritus, dizziness, and lethargy do not specify their incidence [22]. In a systematic review of oncology patients, McNicol et al. indicate varying incidences of 10 to 40% for nausea and vomiting, and 25 to 50% for constipation. They also mention sedation, confusion, myoclonus, and pruritus as adverse effects, without providing incidence data [23]. Compared to our results, and considering that we only included oncology patients, the adverse effects seem to be lower in percentage, with 25.9% for constipation and 19.1% for nausea and vomiting, regardless of the opioid used. This could be attributed to the prophylactic treatment of adverse effects associated with opioid use, according to guidelines of our institute.

We acknowledge as limitations of the current study the inability to compare different opioids with equal amounts of patients, due to long periods of opioid shortage throughout the year caused by administrative issues. Likewise, in our research, we did not consider the equivalent daily dose to compare its implication in the occurrence of adverse effects, which remains open for subsequent studies.

CONCLUSION

The oncologic population in opioid treatment for chronic cancer pain had a sociodemographic distribution comparable to that described in oncologic patients without it. The adverse effects in order or frequency were: Constipation, nausea and vomiting, respiratory depression, erythema and drowsiness, exhibiting a minor incidence compared to other reviews.

This enables us to understand the influence of our treatments and the precautions to consider in order to prevent an adverse effect from being the cause of opioid treatment failure, especially in oncologic patients with refractory pain.

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