

## OPIOID-INDUCED CONSTIPATION IN PALLIATIVE CARE: STATE OF THE ART

Constipação induzida por opióides em cuidado paliativo: o estado da arte

Presión de vientre induzida por opióides en cuidado paliativo: el estado del arte

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### How to cite this article:

Silva GR, Freitas EC, Silva RS, Milagres MP, Boery RNSO. Opioid-induced constipation in palliative care: state of the art. 2020 jan/dez; 12:1116-1124. DOI: <http://dx.doi.org/10.9789/2175-5361.rpcfo.v12.8008>.

### ABSTRACT

**Objective:** The study's purpose has been to address the state of the art in investigations such as clinical trials, systematic reviews with meta-analysis and case studies, which report how to minimize opioid-induced constipation in patients undergoing palliative care. **Methods:** This is an exploratory study through an integrative review of four databases addressing published articles from 2013 to 2017. **Results:** A total of 117 publications were presented, which 17 presented the inclusion criteria. The studies describe the prevalence of constipation rates induced by the use of opioids. **Conclusion:** Although these drugs alleviate pain, the adverse reactions may generate discomfort and loss of the patient's life quality. There are limited data on the treatment of constipation. It was observed that few authors mentioned diet as a helper on this situation, emphasizing the use of medications. Further studies should be encouraged aiming to find the balance between analgesia and reduction of adverse effects.

**Descriptors:** Morphine, constipation, palliative care, nursing and health, nutrition.

### RESUMO

**Objetivo:** Objetivou-se realizar o estado da arte de publicações que relatem estratégias de como minimizar a constipação induzida pelo uso de opióides, de pacientes em cuidado paliativo. **Método:** Trata-se de um estudo exploratório através de uma revisão integrativa em quatro bases de dados de artigos publicados entre os anos de 2013 a 2017. **Resultados:** Evidenciaram-se 117 publicações, as quais 17 apresentaram os critérios de inclusão da pesquisa. **Conclusão:** Apesar das drogas aliviarem a dor, as reações adversas geram desconforto e perda da qualidade de vida. Existem dados limitados referentes ao tratamento da constipação intestinal em cuidado paliativo. Observou-

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se que poucos autores mencionaram a dieta como auxiliador no quadro, enfatizando o uso de medicamentos. Mais estudos devem ser estimulados no intuito de encontrar o equilíbrio entre analgesia e redução de efeitos adversos causados pelos opióides.

**Descritores:** Morfina; Constipação; Cuidados paliativos.

## RESUMÉN

**Objetivo:** Se objetivó realizar el estado del arte de publicaciones que relatan estrategias de cómo minimizar el constipación inducida por el uso de opioides, de pacientes en cuidado paliativo. **Método:** Se trata de un estudio exploratorio a través de una revisión integrativa en cuatro bases de datos de artículos publicados entre los años de 2013 a 2017. **Resultados:** Se evidenció 117 publicaciones, las cuales 17 presentaron los criterios de inclusión de la investigación. **Conclusión:** A pesar de las drogas aliviar el dolor, las reacciones adversas generan incomodidad y pérdida de la calidad de vida. Existen datos limitados referentes al tratamiento del estreñimiento intestinal en el cuidado paliativo. Se observó que pocos autores mencionaron la dieta como auxiliador en el cuadro, enfatizando el uso de medicamentos. Más estudios deben ser estimulados con el fin de encontrar el equilibrio entre analgesia y reducción de efectos adversos causados por los opioides.

**Descritores:** Morfina; Presión de vientre; Cuidados paliativos.

## INTRODUCTION

Pain is one of the most experienced anxieties in cancer patients. Despite so many beliefs and fears about opioid use, old World Health Organization (WHO) publications<sup>1</sup> supported by recent international guidelines<sup>2,3</sup> for the pharmacological treatment of cancer pain in its moderate to severe stages, suggest that the use of opioids is the best therapy, evidencing the use of morphine<sup>4</sup>. Nevertheless, side effects such as opioid-induced constipation deserve highlighting<sup>5,6</sup>.

Studies report the increased prevalence of neoplasms, Non-communicable Chronic Diseases (NCDs) and other diseases, generating morbidity with sequelae and disabilities, progressing to the association of palliative care<sup>5,7</sup>. Using palliative care treatment against the disease without expectation of cure is still a matter of conflict.

The WHO<sup>8</sup> defines that Palliative Care is active total care with an approach that promotes the quality of life of patients and their families, who face life-threatening diseases and do not respond to curative treatment by preventing and relieving suffering<sup>5,6,9</sup>.

Opioids are the most effective drugs of choice in the treatment of moderate to severe pain, especially in advanced and malignant diseases<sup>2,10</sup>. Opioid receptors are distributed in cells of the body, especially those of the neural and intestinal systems. By activating  $\mu$ -receptors in the intestine, opioids do reduce the release of acetylcholine and other neurotransmitters that control the enteric muscle contractions responsible for propulsive activity, leading to increased fluid absorption and decreasing intestinal secretion that dries out the fecal bolus, reducing the spasms of the colon and anal sphincter, leading to constipation and also gastroparesis. Patients complain of incomplete

bowel movement, abdominal distension, gas accumulation, among others<sup>10</sup>.

Cancer patients may develop severe constipation that is usually aggravated by morphine therapy<sup>11</sup>. The effects of opioids are distressing, to the point that patients prefer to give up the use of these drugs<sup>12,13</sup>. Research has reported that opioid-induced constipation is estimated at 40% to 70% of people receiving opioids. In contrast, there are constipation events in palliative care that are not related to the use of opioids, it is suggested that inappetence, nausea, and vomiting that reduce food intake, evolve to constipation<sup>4,10,14</sup>.

Considering this perspective, the present study aims to perform an integrative literature review of the latest publications between the years 2013 to 2017 of clinical trials, systematic reviews with meta-analysis and case studies that address topics such as minimizing signs and symptoms caused by the use of opioids in patients under palliative treatment.

## METHODS

This is an integrative literature review based on the state of the art. For the bibliographic survey, three controlled descriptors were selected and identified in the Health Sciences Descriptors (DeCS) database of the *Centro Latino-Americano e do Caribe* [Latin American and Caribbean Center] on Health Sciences Information: "Constipation"; "Palliative Care"; "Morphine" and the "and" and "or" Boolean operators following the steps proposed by Ércole et al.<sup>27</sup>. The research question was elaborated as follows: How to reduce the symptoms of opioid-induced constipation in patients undergoing palliative care using morphine?

There were included articles published in peer-reviewed journals using methodologies with randomized clinical trials with children and adults, case studies and systematic reviews with meta-analysis published from 2013 to 2017, in English, Spanish and Portuguese, addressing studies with palliative care patients who use morphine or other opioids as therapy for moderate to chronic pain and who have developed opioid-induced constipation.

Guidelines were excluded, articles that had conflicts of interest and did not have a clinical trial, articles that had restricted access in which the main authors did not respond to the requested electronic correspondences to date (n=5), articles with animal research; bibliographic reviews without meta-analysis; articles dealing with chronic opioid pain but without palliative care; and research that did not match the outcome of the research and did not answer the guiding question proposed.

The search strategies used in the literature were articles available in the databases of the Virtual Health Library (VHL), *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)* [Coordination for the Improvement of Higher Education Personnel], SAGE Journals, PubMed and

to avoid confirmation bias, systematic reviews were used at The Cochrane Library - Cochrane Reviews database over the period from September to October 2017.

To categorize the selected studies, 45 articles were found in the CAPES database; in the VHL 09 articles, 04 in common with those found in CAPES; In SAGE Journals, 61 articles were found, with 09 in common with the CAPES database, 04 reviews in the Cochrane Library database, 03 in common to those found in the CAPES database, and 18 articles found in the PubMed database: 04 in common with the findings in the CAPES database, 01 common in the Cochrane database, 13 new articles, where 07 articles addressing the theme were used. In the end, 117 articles were found in the research databases.

A critical assessment of the located articles was performed and soon after the critical analysis of the 117 articles found, only 17 articles fit the inclusion criteria of the present research, of which 11 studies were clinical trials, 02 case studies and 04 systematic reviews with meta-analysis.

## RESULTS

The articles with clinical trials that have proven opioid-induced constipation in palliative care and suggest some type of therapy for constipation control, and two case reports, are presented in Table 1.

**Table - 1** - Articles showing opioid-induced constipation in palliative care patients.

Authors	Sample	Objective of the study	Methods	Results
GRETTON et al. <sup>5</sup>	228 patients using morphine for more than 30 days.	Investigate the association between plasma morphine concentrations and clinical effects of morphine in cancer patients	Prospective observational clinical trial of cancer patients who use oral morphine for moderate to severe pain.	No significant association was observed between plasma morphine and metabolite concentrations and other side effects (nausea, vomiting, constipation, diarrhea). The authors suggest that side effects are associated with dosing and that interindividual variation in morphine bioavailability may influence these findings.
YEOMANSO, CHOCHAN e MAYER <sup>15</sup>	Male child 03 years old with widely metastatic alveolar rhabdomyosarcoma.	Observe the effects of the drug Methylalntrexone in a child undergoing oncologic treatment with opioid-induced constipation.	Case study of a child using opioids (120 mg intravenous diamorphine/24h continuously infused) evolving with opioid-induced constipation used sodium laxative docusate and sodium picosulfate for a short time because it had an unpleasant taste where it was prescribed Methylalntrexone.	The child experienced a very large volume of stool within 10 minutes of Methylalntrexone (150mcg/kg intravenously), where there was no reduction in opioid half-life while maintaining pain control. It shows the effectiveness of using a constipation controller against opioid treatment.
DHINGRA et al. <sup>16</sup>	169 patients, where 68 had advanced cancer and opioid-induced constipation. Considering the 68 patients, 17 used oral laxatives or enemas for more than 3 days a week and of these only 12 participated in the interview.	Use qualitative research methods to better understand psychological distress and burden associated with opioid-induced constipation and its treatment in advanced cancer patients	Qualitative study with thematic content analysis, with semi-structured interviews with questions that guide the perception of psychological distress of opioid-induced constipation symptoms. Patients had been on opioids daily for more than 4 weeks (Hydromorphone IV; Fentanyl; Oxycodone; Methadone) and had self-reported constipation, where they used oral laxative or enema for more than 3 days a week.	It was observed that the patients had psychological distress such as depressive changes and anticipatory anxiety related to constipation. And they believed in the power of a high-fiber diet to minimize the effects of constipation. The authors suggest the use of medications to minimize opioid side effects.

Authors	Sample	Objective of the study	Methods	Results
NEEFJES et al. <sup>17</sup>	195 Palliative care patient using morphine (n=78), oxycodone (n=78) and fentanyl (n=39) who will receive Methylnaltrexone according to weight for laxation.	The overall objective is to determine the effectiveness of Methylnaltrexone prescribing for the treatment of opioid-induced constipation in patients using morphine, oxycodone and fentanyl, and to explore the effects of methylnaltrexone immunomodulators and antiangiogenics.	A randomized, prospective, parallel multicenter clinical trial will assess the effectiveness of methylnaltrexone among palliative care patient groups using different types of opioids, clinic users, ambulatory clinic and hospital wards in the Netherlands. In patients who did not evacuate within 03 days of the week or no evacuation in the last 24 or 48 hours and who have a clinical indication for methylnaltrexone use.	For the laxative effect of the drug, it was noted that patients treated with morphine sulfate, oxycodone and fentanyl complained of constipation in 70, 75 and 40%, respectively, and after intervention improvements were observed in 60% of morphine patients; 60% of oxycodone patients and 25% of patients in the fentanyl group, and laxation effect at 4 hours after methylnaltrexone use. The anti-angiogenic and immunomodulatory effects of methylnaltrexone were also confirmed.
NALAMACHU et al. <sup>18</sup>	02 groups with 301 and 302 palliative care patients with a life expectancy of 1 to 6 months who developed opioid-induced constipation.	Evaluate the efficacy and tolerability of methylnaltrexone in this population.	02 randomized, double-blind, placebo-controlled clinical trial. The 301-patient group had constipation within 48 hours and used morphine (mean dose <150 mg/day vs ≥ 150 mg/day) and laxatives where 154 were randomized to 0.15 mg/kg subcutaneous methylnaltrexone (n=47) and 0.30 mg/kg (n=55) or placebo (n=52) for 28 days followed by 3 months. The 302 group was randomized to 133 patients who had less than 03 bowel movements per week or no 48-hour bowel movement also on morphine and laxatives receiving subcutaneous methylnaltrexone 0.15 mg/kg (n=62) and placebo (n=71).	From the results, it was observed that 33% of the group that used 0.15 mg/Kg of drug evolved with a lot of constipation against 19% of those receiving 0.30 mg/Kg and placebo 36%. Subcutaneous methylnaltrexone provides a fast, robust and consistent response in patients with advanced disease with a favorable dose of 0.30 mg/kg in the population studied.
TAYLOR et al. <sup>19</sup>	171 chronic bone cancer patients undergoing chronic pain using at least 60 mg/day of oral morphine or equivalent for an average of 325 days.	Investigate prolonged use of Fentanyl Pectin Nasal Spray (FPNS) for the treatment of progressive cancer pain in patients receiving regular opioid therapy.	Clinical trial with 171 chronic cancer pain patients on average 60 mg/day oral morphine use and was conducted using FPNS at 100-800 µg of physician-prescribed doses.	There were 163 patients with documented use of FPNS. The average duration of use was 325 days; 46 patients used FPNS for ≥ 360 days; the maximum duration was 44 months. Seventy percent of patients did not change their dose of FPNS. The most common complaints were insomnia, 9.9%; nausea, 9.4%; vomiting, 9.4%; and peripheral edema, 9.4%. The overall incidence of FPNS-related complaints was 11.1%, the most common being constipation (4.1%), with no apparent dose relationship. Ten patients (5.8%) had mild or moderate nasal complaints.
HUANG et al. <sup>9</sup>	36 cancer patients received a continuous infusion of morphine and ropivacaine via an intrathecal catheter through a subcutaneous port.	Compare the efficacy and safety of a continuous intrathecal infusion of morphine and ropivacaine versus an intrathecal morphine alone for cancer pain.	Double-blind randomized trial.	Constipation was not observed as most patients treated with systemic opioids in this study were treated with an intestinal stimulant, a stool softener or laxatives prior to intrathecal management.

Authors	Sample	Objective of the study	Methods	Results
KURITA et al. <sup>20</sup>	1147 cancer patients on opioid treatment to control cancer pain, including: morphine (n=581), oxycodone (n=298), and fentanyl (n=268), aged 18 to 80 years old.	Analyze whether opioid symptoms and adverse effects of cancer patients are associated with reduced renal function.	Cross-sectional, randomized, multicenter clinical trial of 1,147 opioid-treated patients (morphine/ oxycodone/ fentanyl) from 2005 to 2008 for at least 03 days where weight, height, serum opioid and creatinine concentrations were evaluated, and symptoms progressed: fatigue, nausea, vomiting, pain, loss of appetite, constipation, and cognitive dysfunction.	Severe constipation and loss of appetite associated with poor renal function have been reported only in patients with serum morphine concentrations above ( $\geq 41.89$ nmol/L). The other two opioids from the research appear to be safer in treating cancer pain. Patients who had serum oxycodone concentrations above ( $> 99.58$ nmol/L) were more likely to report severe fatigue. Fentanyl-treated patients had no complaints.
JANKU et al. <sup>13</sup>	229 patients with advanced cancer and 134 with other opioid-treated diseases and all had opioid-induced constipation.	Evaluate the effectiveness of Methylalntrexone-MNTX in opioid-induced palliative care patients.	Placebo-controlled randomized controlled trial. Of the 229 cancer patients, 117 (51%) were treated with MNTX and 112 (49%) were treated with placebo during the double-blind portion of the study.	MNTX-treated patients were more likely to have a response (laxation within 4 hours after the first administration) compared to placebo-treated patients (72/117, 62% versus. 5/112, 4%, $P < 0.001$ ). It is concluded that methylalntrexone, which is used for the treatment of opioid-induced constipation, could positively influence patient survival.
HIGUCHI et al. <sup>21</sup>	A 14-year-old female who developed an intrapelvic tumor from the lumbosacral spinal cord detected since she was 4 years old.	Show the effectiveness of subarachnoid drug use in a continuous infusion pump without sedation.	Case study in which opioid therapy and infusion of subarachnoid drugs for pediatric treatment were followed. High doses of gabapentin, tramadol, and pentazocine were initially used, but could not relieve pain progressing to morphine administration 50 mg per day, and soon after, subarachnoid bupivacaine pump infusion was started.	Although pain improved due to sedation, the adolescent evolved sedated and developed severe constipation due to opioid-induced paralytic ileus. sedation, improved awareness of reading, eating and watching TV, and improved bowel function. In conclusion, continuous infusion of subarachnoid drugs provided effective analgesia, decreased side effects of systemic opioids.
FERNÁNDEZ et al. <sup>22</sup>	99 medical records of children aged 8 years and 64.6% were male on opioids 0.5 mg/kg/h.	Describe the experience of using opioids for pain management in pediatric advanced cancer patients in palliative care.	Retrospective study of patients admitted to the program at Hospital Roberto del Río between 2002 and 2013	Two-thirds of the patients studied required strong opioids, in which adequate pain management was obtained, with no serious complications observed. The use of opioids in this group of patients, following a protocol, is considered effective and safe. Form 66 patients taking strong opioids, 89% required less than 0.5 mg/kg/h. Constipation was the most commonly observed side effect.
ROBERTO et al. <sup>4</sup>	336 cancer patients with moderate to severe pain treated with Transdermal Fentanyl - TDF and oral Oxycodone-Naloxone - OXN (119 TDF and 191 OXN) for 28 days.	It aims to partially bridge the gap between comparing the use of TDF and OXN in pain control and the lower incidence of opioid-induced constipation.	Prospective clinical trial with cancer patients with moderate to severe stage pain enrolled consecutively in two 28-day prospective trials, received TDF or OXN-PR. To compare the efficacy and safety of TDF and OXN-PR, we used propensity score analysis to adjust the heterogeneity between the two patient groups.	The final daily dose of opioid expressed as morphine equivalent was 113.6 mg for TDF and 44.5 mg for OXN-PR. Reports of opioid-induced constipation were observed in both groups (32.6% after TDF vs 24.7% after OXN-PR) being lower in the group than OXN. Gastrointestinal symptoms such as nausea, vomiting and dry mouth were significantly less frequent in the OXN-PR group than in the TDF group.
NOSEK et al. <sup>23</sup>	62 cancer patients treated at home and ambulatory care with a life expectancy of at least 40 days without renal or hepatic dysfunction for 28 days. Only 53 patients completed the survey.	Compare analgesic effect and adverse effects during oral morphine, oral oxycodone, transdermal fentanyl and buprenorphine use in cancer patients with advanced pain.	Randomized clinical trial in which patients used morphine 14, oxycodone 16, fentanyl 15 and buprenorphine 17 for 28 days. All patients received 10 mL of lactulose as constipation prophylaxis.	Considering the effect of pain on patients' overall activity, a slightly better but insignificant effect of morphine is observed compared to other opioids. For bowel function, no significant changes in constipation symptoms were found during the trial, however it is considered that all patients received 10 mL lactulose as prophylaxis.

Source: Articles found in research databases CAPES, VHL, SAGE Journals, Pubmed (2013-2017).

## DISCUSSION

Given the reviews of the studies, it is possible to observe that morphine is the opioid of choice to minimize cancer pain. The authors<sup>5</sup> monitored cancer patients undergoing palliative care using oral morphine and investigated the side effects of morphine according to their serum concentrations, and concluded that the higher the serum drug dosages, the greater the complaints of side effects such as constipation.

Other researchers<sup>20</sup> performed a clinical trial with 1,147 cancer patients receiving opioids (morphine, oxycodone, and fentanyl) and observed a reduction in glomerular filtration rate. The authors found that from these opioids the one presenting the most complaints of constipation and decreased appetite associated with low renal function were presented in patients with serum morphine concentrations above ( $\geq 41.89$  nmol/L). The other two opioids from the research appear to be safer in treating cancer pain. Patients who had serum oxycodone concentrations above ( $> 99.58$  nmol/L) were more likely to report severe fatigue. Fentanyl-treated patients had no complaints.

In contrast, several studies emphasize the use of laxatives in combination with opioids to minimize or treat opioid-induced constipation. In palliative care, the authors<sup>17</sup> highlight the use of laxative Methylnaltrexone. They studied a group of patients ( $n=195$ ) in palliative care in the treatment of opioid pain with emphasis on morphine, where they used methylnaltrexone, and had the effects of laxation as early as 4 hours after use. The authors of this study themselves suggest a randomized placebo study in a larger population. This is what the authors<sup>18</sup> were able to accomplish with 02 groups of patients, one with  $n=301$  and one with  $n=302$ , where they used different dosages of methylnaltrexone in patients using morphine (average dose  $<150$  mg/day vs  $> 150$  mg/day), and concluded that subcutaneous methylnaltrexone provides a fast, robust and consistent response in patients with advanced disease with a favorable dose of  $0.30$  mg/kg in the population studied.

In a study<sup>23</sup> in which prophylactic laxatives were used, it was shown that the experimental opioids showed similar profile and severity of adverse effects. Laxative prophylaxis prevented constipation. In this sense, another group of academics<sup>22</sup> showed that the side effects recorded concerning the use of opioids of 83.4% in the patients and they had some type of side effect, the most frequent being constipation, highlighting the absence of serious effects such as respiratory depression and anaphylaxis. And concludes the study with the statement that it is necessary the prophylactic indication of laxatives, intestinal motility stimulants and antiemetics in pain therapy.

In another clinical trial<sup>13</sup> with 229 cancer patients in palliative care who used opioids and developed constipation and evaluated the effectiveness of methylnaltrexone. And they observed the effect of laxation within 4 hours of use. The authors of this research also used Cochrane Collaboration database reviews to assess the risk of bias in methylnaltrexone randomized trials and concluded that the

use of opioids associated with methylnaltrexone generates quality of life in palliative care.

The same laxation effect was observed in a case study<sup>15</sup> with a male child with moderate to severe pain undergoing morphine therapy who used methylnaltrexone. And the authors suggest that opioid therapy should be done with a laxative. The option for methylnaltrexone is advocated for its antagonistic action to the effects of opioid binding on gut  $\mu$ -receptors, minimizing constipation and not decreasing opioid analgesia. They further suggest that intravenous morphine should be used at  $150$  mcg/kg to minimize constipation and prevent additional distress at this stage. Nonetheless, in the label of this drug, there is an observation that safety and efficacy have not yet been established in pediatric patients. And the use of this methylnaltrexone drug should be discouraged in patients with intestinal obstruction and should be used only with a prescription<sup>13,15,17</sup>. Therefore, regarding the use of medicines, it is up to the physician to observe and prescribe. It is noteworthy that this article is only an integrative review which lists the articles that suggest actions to minimize constipation and should not be used as random prescription criteria without the endorsement of the medicine professional specialized in the field.

Other suggestions to minimize constipation would be to change the route of drug use from being oral, as suggested by the clinical trial<sup>19</sup> conducted with 171 patients using oral morphine ( $60$  mg/day) who developed constipation and suggested replacing opioids with a fentanyl (Lazanda<sup>®</sup>) pectin nasal spray. In this group that made the exchanges observed the most common complaints were insomnia, 9.9%; nausea, 9.4%; vomiting, 9.4%; and peripheral edema, 9.4%, and constipation in only 4.1%, with no apparent dose relationship. Considering this group under study, only ten patients (5.8%) had nasal complaints, most of them either mild or moderate. Concluding the research, the authors suggest that the use of this spray is in a controlled manner by the medical staff as it may lead to addiction, overdose and serious complications due to misuse.

Reports of constipation are also present in another study<sup>4</sup>, where there was a lower prevalence of nausea and vomiting after opioid use and one possible explanation may be that the opioid antagonist naloxone acts at the gastric level through the same mechanism as in bowel dysfunction limitation, thereby reducing the development of nausea and vomiting.

In addition, another study<sup>21</sup> corroborates the possibility of changing the opioid administration route, which showed that continuous subarachnoid drug delivery with an infusion pump provided effective analgesia, reduced the side effects of systemic opioids, and allowed a remarkable improvement in activities of daily living. This technique may be a viable option in palliative care.

In a study with 36 patients in palliative care who compared the efficacy of morphine and ropivacaine use via continuous intrathecal infusion, however, this study is not very successful regarding the results for controlling constipation, since patients who participated in the clinical trial, all used laxatives before the use of opioids, which generated bias

of the results, therefore, masking them. So, it cannot be concluded the efficacy of opioid pathway exchanges to treat constipation through this study. The authors<sup>9</sup> of this trial found that no constipation was observed in the group, which was already expected.

Thus, in a clinical trial<sup>24</sup> of 11 patients undergoing palliative care using morphine to treat severe pain for 05 months, it was observed that the use of venous morphine minimized constipation versus oral administration and suggest studies

with trials with a larger audience to improve the statement. Other authors<sup>16</sup> observed psychological distress in patients (n=168) who used opioids for more than 4 weeks in palliative care and found that depressive changes and anxiety disorder were related to constipation. Often the health team thinks of minimizing pain and forgets that side effects of medication can worsen the emotional of this population. Systematic review articles that presented results on opioid-induced constipation in palliative care are presented in Table 2.

**Table 2** - Systematic review articles with meta-analysis and Cochrane addressing the theme of opioid-induced constipation in palliative care. *Jequié, BA, Brazil, 2018*

Authors	Sample	Objective of the study	Methods	Results
SIEMENS e BECKER <sup>6</sup>	07 studies with 1,860 patients	Evaluating the effectiveness of Methylalntrexone (MNTX) in patients with opioid-induced constipation.	A systematic review with meta-analysis was performed from January 2014 to December 21 <sup>st</sup> , 2015. Dichotomous meta-analyzes with risk indices and 95% confidence intervals were calculated using RevMan 5.3.	The review results indicated that patients on MNTX had higher stool frequency and needed less time for laxation compared with placebo.
CLARK e CURROW <sup>14</sup>	There were found 20 articles. Only 12 of the 20 articles used their cited definitions of constipation as a primary result of the studies and four randomized and controlled blind trials.	Emphasizing issue by systematically examining eligibility measures and primary results in constipation studies in the population of hospices and palliative care.	The survey was performed using the validated care filter developed by CareSearch (www.caresearch.com.au), an online care information resource approved by Flinders University (Australia) and funded by the Australian federal government. Published from 1965 to 2013. The research used articles with randomized controlled trials, cohort studies, or case studies.	There was not a single set of diagnostic criteria for constipation that needed to be included in the study. Since constipation is multifactorial, especially in the population of palliative care and sanatorium, several factors can lead to constipation such as progressive cachexia, increased immobility, poor oral intake, anticholinergic medications (including opioids) and comorbidities that include illness.
CANDY et al. <sup>25</sup>	05 studies involving 370 people in palliative care who used laxatives	Determining the effectiveness of laxatives for treating constipation in people receiving palliative care	Review of the Cochrane Central Controlled Trials (The Cochrane Library), MEDLINE, EMBASE, CINAHL and Web of Science, about the use of laxatives in people with constipation in palliative care until September 2014. The most commonly used laxatives were as follows: lactulose, senna, co-danthramer combined with poloxamer, docusate and magnesium hydroxide combined with liquid paraffin. Misrakasneham has also been rated, this is a traditional Indian medicine.	There was no evidence as to which laxative provided the best treatment. Still, the review was limited as the evidence was only five small trials and patient preference and cost were assessed. Further testing is needed to evaluate the effectiveness of laxatives in palliative care populations. Extrapolating findings on the efficacy of laxatives evaluated in other populations should be done with caution. This is due to the differences inherent in people receiving palliative care.
WIFFEN, DERRY e MOORE <sup>26</sup>	77 studies with 5619 randomized participants with population aged 50 to 70 years old.	Determining the impact of opioid treatment on patient awareness, appetite, and thirst in randomized controlled trials of morphine, fentanyl, oxycodone or codeine to treat cancer pain.	Systematic review with primary data from randomized controlled trials recommended by the UK Ministry of Health included in Cochrane reviews with current data on the use of opioids to treat cancer pain.	For patients using 04 opioid doses together, 1 in 4 people experienced constipation and drowsiness, 1 in 5 with nausea and dry mouth, and 1 in 8 with vomiting complained of loss of appetite and dizziness. The results showed complaints that were affecting the quality of life due to opioid use, with incidence rates of 25% for constipation, 23% drowsiness, 21% nausea, 17% dry mouth and 13% vomiting, anorexia and dizziness. Asthenia, diarrhea, insomnia, hallucinations, and dehydration occurred below 5%.

Source: Review articles published in the Cochrane database from 2013 to 2017 that address the theme proposed in this article.

Given the systematic reviews found here, it was observed in a particular study<sup>26</sup> that, opioids used to treat cancer pain, the incidence rates of adverse reactions were 25% for constipation, 23% for drowsiness, 21% for nausea, 17% for dry mouth, and 13% for vomiting, anorexia, and dizziness. Asthenia, diarrhea, insomnia, mood swings, hallucinations, and dehydration occurred at incidence rates of 5% and below, similar results with other clinical trials<sup>20,22</sup>.

For other authors<sup>14</sup>, constipation remains poorly defined operationally by researchers and clinical trials that take care of this population. Because of this, their study seeks to use a research tool to validate the drug association with the consequent emergence of intestinal constipation, a study similar to a qualitative research<sup>24</sup> already published.

In the research proposed by Siemens and Becker<sup>6</sup>, it was evidenced that the groups that used methylnaltrexone had a better improvement according to the "Assessment of the Patient's Life Quality" questionnaire. Patients in the methylnaltrexone and placebo groups improved by 33%, 27%, and 18%, respectively. According to the results of the Global Clinical Change Impression, no dose-response relationship can be identified for the constipation disorder or the Assessment of the Patient's Life Quality related to Constipation, because of the differences between the groups in which they used methylnaltrexone were no statistical or clinically relevant. Some medical professionals in order to reduce opioid side effects prophylactically prescribe laxatives in the viable route of administration to the patient.

Considering the use of laxative in its most natural form, Candy et al.<sup>25</sup> report that the randomized clinical trials in opioid palliative care patients included in this review showed no differences in the efficacy of three commonly used laxatives; senna, docusate and lactulose, in other words, there was no one laxative that stood out in the treatment of intestinal constipation. Nevertheless, these studies are subject to bias and low reaching. None of the studies have estimated the efficacy of polyethylene glycol in this population.

It was observed in the found studies that little is really addressed about the importance of diet with foods bearing a laxative effect, where the main measure in the face of constipation is the prescription of medicines, which needs further researching.

## FINAL CONSIDERATIONS

It was possible to observe that the articles studied for the elaboration of the present work always brought some measures to treat opioid-induced constipation in some way, either by changing the route of administration of drug use, or by the prophylactic prescription of a laxative drug together with opioids, however, as it is a prescription drug, it is up to medical professionals to make such changes and apply possible suggestions.

It was also noted that little was mentioned about the importance of stimulating food consumption that favors laxative action in this public, such as the use of fiber-rich foods such as oats, papaya, plum, use of foods with probiotic

action, the use of kefir and hydration stimulation for patients who still have a good glomerular filtration rate, as patients still believe in the power of the diet to control bowel constipation and because, naturally, it diminishes the psychological feeling of "using too many medications".

It is also an observation that patients in palliative care face physiological changes intrinsic to treatment such as lack of appetite, weight loss, nausea and vomiting, diarrhea, constipation, xerostomia (dry mouth), among other factors that interfere with nutritional status, which cannot close the diagnosis that constipation by itself was induced by opioids, which made it difficult to perform a meta-analysis in this study.

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Received in: 14/08/2018

Required revisions: 19/12/2018

Approved in: 15/02/2019

Publicado em: 24/08/2020

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**Disclosure:** The authors claim to have no conflict of interest.