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Opioid-induced bowel dysfunction: a literature review

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Abstract

Opioid therapy plays a crucial role in the management of acute and chronic pain, with opioids being widely prescribed worldwide. However, alongside the analgesic benefits, the use of opioids is associated with a range of adverse effects, including opioid-induced bowel dysfunction. Opioid-induced bowel dysfunction refers to a constellation of gastrointestinal symptoms caused by the effects of opioids on the gastrointestinal tract. These symptoms primarily manifest as constipation, but can also include abdominal pain, bloating, nausea, and vomiting. Opioid-induced bowel dysfunction poses a significant clinical challenge, as it can severely affect patients' quality of life. Non-pharmacological approaches alone are rarely sufficient to counteract the adverse effects of opioid therapy. The primary pharmacological agents used in opioid-induced bowel dysfunction management are laxatives, which should be chosen according to individual patient needs. Patients with poorly controlled symptoms can benefit from new pharmacological approaches, particularly peripheral mu-opioid receptor antagonists. By better understanding the underlying mechanisms, clinical manifestations,

diagnostic criteria, and management strategies, healthcare professionals can optimize patient care, minimize complications, and improve patients' overall well-being.

Aim of the study

This article aims to provide a comprehensive overview of opioid-induced bowel dysfunction, focusing on its underlying mechanisms, clinical manifestations, and management strategies. By examining the current understanding of opioid-induced bowel dysfunction, this article seeks to enhance knowledge and promote effective management of this prevalent condition. The primary goal is to equip healthcare professionals with up-to-date information to facilitate early recognition, accurate diagnosis, and management of opioid-induced bowel dysfunction. We also want to draw attention to the importance of a multidisciplinary approach in the course of opioid-induced bowel dysfunction management.

Materials and methods

This article presents the current state of knowledge on opioid-induced bowel dysfunction found in various scientific articles. To select them, the literature available in Google Scholar and PubMed databases was reviewed using the keywords *opioid-induced bowel dysfunction, OIBD, opioid-induced constipation, OIC, opioids, adverse effects, gastrointestinal motility, laxatives, PAMORAs, peripherally acting mu-opioid receptor antagonists*. From many available articles, those that best covered the topic were selected. The reviewed literature describes the pharmacology of opioids, the underlying mechanisms of opioid-induced bowel dysfunction, clinical manifestations, as well as various management strategies.

Keywords

opioid-induced bowel dysfunction, OIBD, opioid-induced constipation, OIC, opioids, adverse effects, gastrointestinal motility, laxatives, PAMORAs, peripherally acting mu-opioid receptor antagonists

Introduction

Opioids are drugs commonly used as analgesics to treat severe pain. Despite the fact that opioids were originally meant for usage predominantly for relieving acute severe pain, with their initial intended use cases including post-operative pain and terminal palliative care, they are now also commonly utilized to manage chronic nonmalignant pain. With the number of people who take opioids on the rise, the case numbers of adverse effects reported by patients are increasing simultaneously. Healthcare professionals should therefore seek education on the topic of side effects of opioid therapy in order to provide better care for their patients. The most severe adverse effects of opioids include respiratory depression, sedation, as well as opioid misuse and addiction [1]. Other main adverse effects described by patients in connection with long-term use of opioids, such as sleepiness, nausea, cognitive decline, and bowel dysfunction, are less dangerous, but all the same challenging for the patients and damaging to their health [2].

Opioids and their mechanism of action

To comprehend the role of opioids in the development of opioid-induced bowel dysfunction, it is essential to understand their pharmacology. Opioid pharmaceuticals deliver pharmacological effects, such as pain relief, by binding to receptors on neuronal cell membranes in the central nervous system. There are 3 primary opioid receptor subtypes: mu (μ), delta (δ), and kappa (κ). However, while the opioid receptors are found predominantly throughout the central nervous system, they are also distributed throughout the peripheral nervous system, albeit to a lesser extent. Sites in the peripheral nervous system occupied by opioid receptors include the vas deferens, knee joint, gastrointestinal tract, heart, and immune system [3]. Therefore, in addition to the receptors located in the central nervous system, opioids also bind to peripherally-acting opioid receptors.

It is worth noting that the activation of different opioid receptors can produce a wide range of effects, which are frequently dependent upon the location of the receptor. Agonists binding to mu-opioid receptors may cause analgesia, but also respiratory depression, bradycardia, sedation, nausea and vomiting, as well as a reduction in gastric motility. Activation of delta-opioid receptors can cause spinal and supraspinal analgesia, but also reduce gastric motility [4].

Effects on the gastrointestinal tract

Opioid drugs binding to opioid receptors in the myenteric and submucosal plexuses of the whole wall of the gastrointestinal tract affect several aspects of gastrointestinal function, leading to the development of opioid-induced bowel dysfunction. One of the primary effects is delayed gastric emptying. Opioids inhibit the release of neurotransmitters involved in the coordination and regulation of gastric contractions. This inhibition leads to reduced peristaltic contractions and impaired gastric emptying, resulting in the retention of ingested food and liquids in the stomach for longer durations [5]. Delayed gastric emptying can contribute to feelings of early satiety, bloating, and upper abdominal discomfort in individuals receiving opioids.

In addition to delayed gastric emptying, opioids also decrease gastrointestinal motility, particularly in the small intestine and colon. The myenteric plexus is responsible for controlling gastrointestinal motility. Neurotransmitters are released from the enteric neurons, causing coordinated excitation-contraction movements of the circular smooth muscles. Those neurotransmitters include acetylcholine, serotonin, vasoactive intestinal peptide, and nitric oxide. The coordination of the contractile and propulsive gut movements is dependent on a balance in the release of neurotransmitters [6,7]. Opioid drugs inhibit the release of those neurotransmitters, therefore causing abnormal coordination of motility. As a result, peristaltic contractions and the propulsive movements required for normal bowel movements are suppressed. The decreased motility leads to prolonged transit time and increased fluid absorption, resulting in the formation of hard, dry stools, and ultimately, the development of constipation in individuals on chronic opioid therapy [8].

Opioids further influence gastrointestinal function by increasing sphincter tone [9]. Increased sphincter tone can affect the lower esophageal sphincter, leading to gastroesophageal reflux disease characterized by heartburn, regurgitation, and chest discomfort [10]. Additionally, increased sphincter tone in the anal region can result in difficulty with defecation, contributing to constipation and straining during bowel movements.

Understanding the effects of opioids on the gastrointestinal tract is crucial in comprehending the pathophysiology of opioid-induced bowel dysfunction. By targeting specific aspects of gastrointestinal function, opioids disrupt normal bowel function and contribute to the constellation of symptoms experienced by individuals receiving opioid therapy. These insights into the pharmacological effects of opioids lay the foundation for developing effective management strategies for opioid-induced bowel dysfunction.

Clinical manifestations of opioid-induced bowel dysfunction

Constipation is the most common and prominent clinical manifestation of opioid-induced bowel dysfunction. It is characterized by infrequent bowel movements, difficulty passing stools, and a sense of incomplete evacuation. Opioids contribute to constipation through their effects on gastrointestinal motility, increased fluid absorption, and alterations in sphincter tone [11]. The severity of constipation can vary, ranging from mild discomfort to severe cases requiring medical intervention. Chronic constipation can significantly impact patients' quality of life, leading to physical discomfort, psychological distress, and reduced adherence to opioid therapy [12].

In addition to constipation, individuals with opioid-induced bowel dysfunction often experience abdominal pain and distension. The impaired gastrointestinal motility caused by opioids can lead to the accumulation of gas and stool, resulting in bloating and abdominal distension. The distension can cause discomfort, pain, and a feeling of fullness. The pain may be further intensified in some patients by hyperalgesia caused by narcotic bowel syndrome (NBS) [13]. The abdominal pain associated with opioid-induced bowel dysfunction can vary in intensity and may be described as crampy, colicky, or generalized. This pain can significantly impact daily activities and overall well-being [14].

Opioid-induced bowel dysfunction can also manifest as gastroesophageal reflux. Increased sphincter tone, particularly at the lower esophageal sphincter, can result in the backward flow of stomach acid into the esophagus, leading to symptoms such as heartburn, regurgitation, and chest discomfort. Gastroesophageal reflux can further contribute to a decline in patients' quality of life, affecting their ability to eat, sleep, and engage in daily activities [15].

It is worth noting that the clinical manifestations of opioid-induced bowel dysfunction extend beyond constipation, encompassing a range of gastrointestinal symptoms that can

significantly impact patients' quality of life [16]. Recognizing and addressing these symptoms is crucial for effective management and improved patient outcomes. Healthcare professionals should assess the severity and impact of these symptoms on patients' daily lives, tailoring treatment approaches to individual needs and considering their overall opioid therapy regimen.

Diagnosis and assessment of opioid-induced bowel dysfunction

Diagnosing opioid-induced bowel dysfunction requires a comprehensive evaluation of the patient's clinical presentation, medical history, and the exclusion of other potential causes of gastrointestinal symptoms. The assessment of individuals with suspected opioid-induced bowel dysfunction involves a thorough patient history and physical examination. The healthcare professional should inquire about the duration and pattern of opioid use, the specific opioid agent and dosage, and the presence of any concurrent medications or comorbidities that may contribute to gastrointestinal symptoms. It is essential to assess the severity and impact of the symptoms on the patient's quality of life, including the frequency of bowel movements, stool consistency, abdominal pain, distension, and other associated symptoms.

To further evaluate the symptoms, standardized questionnaires and scoring systems can be utilized. These tools help assess the frequency and severity of symptoms and provide objective measures for monitoring treatment effectiveness. Examples include the Bowel Function Index (BFI) [17], Patient Assessment of Constipation-Symptoms (PAC-SYM), Stool Symptom Screener (SSS) and Patient Assessment of Constipation-Quality of Life (PAC-QOL) [18]. These instruments allow for consistent symptom evaluation, comparison of treatment outcomes, and monitoring disease progression.

It is crucial to consider the differential diagnosis of opioid-induced bowel dysfunction, as many other gastrointestinal disorders can present with similar symptoms. Conditions such as irritable bowel syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis) [19], mechanical bowel obstruction, and functional gastrointestinal disorders should be ruled out through appropriate investigations and evaluation. Diagnostic tests, including imaging studies, blood tests, and endoscopic procedures, may be necessary to exclude other potential causes and confirm the diagnosis of opioid-induced bowel dysfunction.

In some cases, objective assessments may be warranted to evaluate gastrointestinal function and assess the severity of opioid-induced bowel dysfunction. These assessments can include radiological studies such as abdominal X-rays, transit studies using radiopaque markers, radionuclide scintigraphy, or wireless motility capsules. Colonic manometry can be performed to assess sphincter function and motor patterns. These objective assessments can provide valuable information to guide treatment decisions and monitor treatment response [20].

Accurate diagnosis and assessment of opioid-induced bowel dysfunction are essential for appropriate management and improved patient outcomes. A comprehensive evaluation of symptoms, consideration of opioid therapy, and exclusion of other gastrointestinal disorders are key components of the diagnostic process. Utilizing standardized questionnaires and objective assessments can aid in evaluating symptom severity, monitoring treatment response, and optimizing patient care.

Prevention strategies

Prevention of opioid-induced bowel dysfunction is an important aspect of patient care, particularly in individuals anticipated to require long-term opioid therapy. Healthcare professionals should educate patients and caregivers about the potential gastrointestinal side effects of opioids and the importance of proactive management. Starting prophylactic laxative therapy concurrently with opioid initiation and titrating the dose based on individual response can help prevent the development of severe constipation. Regular monitoring, patient education, and early intervention are key components of successful prevention strategies.

Non-pharmacological interventions

Non-pharmacological interventions form an essential component of the management of opioid-induced bowel dysfunction. These interventions focus on lifestyle modifications and behavioral changes to alleviate symptoms and improve bowel function. Strategies include dietary modifications, increasing fluid intake, regular physical activity, and establishing a consistent bowel routine. Patients should be advised to maintain consistent meal times, ensure an adequate intake of fluids and dietary fiber, and engage in regular physical activity if possible. Healthcare professionals should provide dietary guidance, emphasizing the importance of a balanced diet. Encouraging patients to establish a regular time for bowel

movements, such as after meals, can help stimulate bowel motility [21]. Patient education and counseling play a crucial role in ensuring adherence to these interventions. However, such interventions are rarely sufficient to prevent or treat opioid-induced bowel dysfunction, and therefore additional pharmacological treatment is often necessary in patients who take opioid drugs [22].

Pharmacological interventions

Pharmacological interventions are often necessary for managing opioid-induced bowel dysfunction, particularly when non-pharmacological interventions are insufficient. The primary pharmacological agents used in opioid-induced bowel dysfunction management are laxatives. They can be classified into different categories, including osmotic laxatives (magnesium and sulfate salts, lactulose, polyethylene glycol), stimulant laxatives (senna, bisacodyl), stool softeners (anionic surfactants), and lubricants (mineral oil). These medications help improve stool consistency, promote bowel movement, and relieve constipation. It is important to tailor the choice of laxative and its dosage to the individual patient, considering factors such as the severity of symptoms, response to treatment, and potential side effects [23,24].

Research is ongoing to explore emerging therapeutic options for the management of opioid-induced bowel dysfunction. Novel pharmacological agents, such as peripheral mu-opioid receptor antagonists [25], prokinetic agents, and secretagogues, are being investigated for their potential to improve gastrointestinal motility and relieve symptoms.

Naldemedine, a peripheral mu-opioid receptor antagonists taken orally, has been shown to improve bowel function in patients suffering from opioid-induced bowel dysfunction without reducing opioid-mediated analgesia [26-28].

Methylnaltrexone, a peripheral mu-opioid receptor antagonists taken as a subcutaneous injection, can also be used to improve bowel function without significant changes in the analgesia [29-31].

Combined opiate/naloxone medications have been shown to reduce the risk of opioid-induced bowel dysfunction [32]. An opioid receptor agonist combined with its antagonist, particularly prolonged-release oxycodone with prolonged-release naloxone tablets at a fixed ratio of 2:1, are well tolerated and associated with patient convenience and potential improved

compliance[33,34]. Oxycodone provides analgesia, while naloxone prevents binding or displaces it from opioid receptors located in the gastrointestinal tract [35].

Unlike other commonly used pharmacological treatments, peripheral mu-opioid receptor antagonists address underlying causes of opioid-induced bowel dysfunction, namely the effects of opioid drugs on peripheral opioid receptors located in the gastrointestinal tract. As these emerging therapies continue to advance, they hold promise for more effective management of opioid-induced bowel dysfunction in the future.

Multidisciplinary approach

The management of opioid-induced bowel dysfunction benefits from a multidisciplinary approach, involving various healthcare professionals. A team consisting of physicians, nurses, pharmacists, dietitians, physiotherapists and psychologists can provide comprehensive care and address the diverse aspects of opioid-induced bowel dysfunction. Collaborative efforts ensure a holistic assessment of patients, individualized treatment plans, and ongoing monitoring of treatment effectiveness. Each healthcare professional contributes their expertise to optimize symptom management, address medication-related concerns, provide dietary guidance, manage pain, improve mobility and motor function, as well as support psychological well-being [36].

Patient education

Patient education is crucial in managing opioid-induced bowel dysfunction. Healthcare professionals should educate patients and their caregivers about the potential gastrointestinal side effects of opioids and the importance of proactive management. Patients should be informed about the expected bowel changes, symptoms of opioid-induced bowel dysfunction, and the significance of reporting any new or worsening symptoms promptly. Clear communication regarding the need for adherence to prescribed medications, lifestyle modifications, and the appropriate use of over-the-counter laxatives is vital. Education about the most common adverse effects and various ways to prevent or counteract them can be crucial in ensuring that patients do not discontinue opioid treatment.

Promoting patient adherence to the recommended management strategies is essential for effective outcomes in opioid-induced bowel dysfunction. Healthcare professionals should

provide clear instructions on medication use, potential side effects, and the importance of regular follow-up appointments. Monitoring treatment response and adjusting interventions based on individual needs and preferences is crucial to optimize symptom relief. Regular assessments, symptom tracking, and communication with the healthcare team help ensure that patients receive the necessary support and interventions.

Shared decision-making empowers patients to actively participate in their opioid-induced bowel dysfunction management. Healthcare professionals should engage patients in discussions about treatment options, potential risks and benefits, and their individual preferences and goals. By involving patients in the decision-making process, healthcare professionals can ensure that treatment plans align with patients' values and enhance treatment adherence and satisfaction. This collaborative approach fosters a sense of partnership, trust, and shared responsibility for managing symptoms effectively [37,38].

Conclusion

Opioid-induced bowel dysfunction is a prevalent and challenging condition that significantly impacts patients receiving opioid therapy. It encompasses a range of gastrointestinal symptoms, with constipation being the most prominent manifestation. The clinical manifestations of opioid-induced bowel dysfunction extend beyond constipation and include abdominal pain, distension, nausea, vomiting, and gastroesophageal reflux. Accurate diagnosis and assessment are crucial for effective management, considering the impact on patients' quality of life and tailoring treatment approaches to individual needs.

The management of opioid-induced bowel dysfunction requires a comprehensive approach that includes non-pharmacological interventions as well as pharmacological agents. Non-pharmacological interventions focus on lifestyle modifications, dietary changes, and establishing a consistent bowel routine. Pharmacological approaches involve the use of laxatives tailored to individual patient needs.

Prevention strategies play a vital role in managing opioid-induced bowel dysfunction, emphasizing the importance of patient education and proactive management. Initiating prophylactic laxative therapy concurrently with opioid initiation and regular monitoring help prevent severe constipation.

Emerging therapies and ongoing research offer promise for more effective treatment options in the future. The development of novel pharmacological agents and targeted therapies holds the potential for improving gastrointestinal motility and symptom relief. Peripheral mu-opioid receptor antagonists such as naldemedine and methylnaltrexone address underlying causes of OIBD, which enables better outcomes for patients with symptoms poorly controlled by other pharmacological approaches. Fixed-dose, prolonged-release oxycodone/naloxone tablets offer good pain management and reduced risk of adverse effects, as well as convenience for patients.

A multidisciplinary approach involving healthcare professionals from various disciplines ensures comprehensive care and individualized treatment plans. Patient education plays a critical role in promoting adherence to treatment strategies, understanding symptom management, and seeking timely medical attention. Psychosocial support, shared decision-making, and ongoing communication between healthcare professionals and patients are essential for optimizing outcomes and improving patients' overall well-being.

Author's contribution

Conceptualization, U.Ž.; writing, review and editing, U.Ž., M.M., I.T., Z.L., J.F., D.S., Z.K., K.A., K.D., A.Š., D.M., H.C.K., E.S., K.S.. All authors have read and agreed with the published version of the manuscript.

Disclosures

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