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Constipation Management in Patients with Cancer: Systematic Review

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Abstract: **Constipation is a common complication in patients with cancer. Whilst the standardized clinical guidelines are established to be implemented in the different settings, still the implementation of these guidelines are unclear and scanty researches were conducted.**

Aim: Summarize evidences related to constipation management in adult patients with cancer. Method: A systematic review search of Cumulative Index of Nursing and Allied Health Literature (CINAHL), PubMed, Scopus and Web of Science was conducted. English language articles about the prevalence, risk factors, non-pharmacologic and pharmacologic measures for constipation in cancer patients were included.

Results: Initial search retrieved a total of 157 articles. After screening 88 were refined. Another screening was done to include only articles meet the inclusion criteria. A total of 29 full text articles were identified as eligible articles. A final list of 20 articles was decided to be included in the analysis.

Conclusion: Extraordinary prevalence of constipation remained observed among patients with cancer. Subcutaneous injection of Methylnaltrexone is effective in management of constipation for cancer patients and enema is contraindicated for certain conditions.Advanced practitioners such as specialist nurses and clinicians should establish a standardized bowel protocol including preventive and non-pharmacological guidelines to be implemented in the practice settings.

Keywords: **Cancer, Constipation, pharmacological, non-pharmacological, management.**

1. INTORDUCTION

Constipation is a condition in which patients may have fewer than three bowel movements a week, stools are hard and difficult to pass, a feeling of incomplete emptying (Bharucha, Pemberton& Locke, 2013 ; NICE, 2018). It occurs in almost 60% of patients with cancer (Wickham,2017). Despite the availability of various classes of laxatives, constipation remains quite common among cancer patients (McQuade, Stojanovska, Abalo, Bornstein & Nurgali , 2016). If constipation left untreated, it will cause very distressing life threatening symptoms especially during cancer therapies.

Constipation occurs in patients with cancer due to many causes such as organic, functional, and drug-related effects (Clemens et al., 2013; Costilla & Foxx-Orenstein, 2014).In patients with advanced cancer, unmanaged constipation can lead to fecal impaction as a consequences of poor oral and fluid intake , lack dietary fiber and low physical activity (Hussain, Whitehead & Lacy, 2014). Fecal impaction impairs patients' life and increases health-care economic affliction due to referral, cost of laboratory investigations and medications.

Since discontinuation of opioid analgesics or medications with anticholinergic properties is often not feasible in oncology patients, enhancing preventive measures for constipation is essential role for advanced nurse practitioners and other clinicians.So, advanced practitioners such as specialist nurses and clinicians should establish bowel protocol to be implemented in the practice settings for minimizing the consequences of unmanaged constipation in cancer patient.

The bowel protocol should be established in collaboration of a multidisciplinary team and should be based on whether the patient is already reported constipation or the patient is liable to it because of opioid therapy or drug with anticholinergic properties. Nurses should encourage patients to adhere to bowel protocol in order to avoid the consequences of such condition(Brick, 2013; Pitlick& Fritz, 2013; Camilleri et al., 2014;McQuade , Stojanovska V, Abalo R, Bornstein , Nurgali K,2016).

National Health System (NHS), 2017 established guidelines for management of constipation in palliative care and highlighted factors such as reduced mobility,poor food intake ,weakness and dehydration should always be addressed as far as is practical. Also added that increase fluid intake at least 1.5 liter daily because patients with cancer always struggles to meet fluid requirements. In addition, cancer patients often require to be referred to a dietetic service. Key risk factors for development of constipation in cancer patients are receiving opioids therapy, poor appetite and no information given on constipation.

Recently, National Comprehensive Cancer Network (NCCN), 2019 and American Cancer Society (2020) published clinical guidelines on management of constipation in cancer patient. However, there still lack of research studied testing and establishing such guidelines. Therefore the aim of the current systematic review is to identify, evaluate and summarize the evidences of current practices related to constipation management in cancer patient.

2. METHODS

Systematic review of literature related to management of constipation in cancer patient was conducted guided by Aveyard's (2014) Search Strategy: Cumulative Index of Nursing and Allied Health Literature (CINAHL),PubMed, MEDLINE, Scopus and Web of Science were searched in March 2021. Also reference lists of related studies were searched. Key search terms included the following: Cancer Patient OR Cancer Care OR cancer management; Constipation OR Constipat*; pharmacological OR nonpharmcological; and Manag* OR Assess* OR Symptom management. Only articles published after 1 January 2008 were included (Table 1).

Table (1): Inclusion criteria for selection of articles

1-	Research based articles
2-	Descriptive, correlational, randomized controlled studies, as well review articles
3-	Target: Cancer patient with constipation
4-	Setting in oncology and palliative care units
5-	Include constipation management in cancer patient
6-	Study period from 2008 – 2020
7-	Articles in English language

Data extraction and analysis

No software has been utilized to analyze the data. The data was extracted based on a specific form that contains (Author's name, year of publication, aim, study design and setting and conclusion for management of patients with cancer). These data were reviewed by the researchers to determine its initial findings. Two authors separately screened the titles and ruled out irrelevant articles .The researchers selected paper met inclusion criteria and screened the full texts.A double revision of each researcher was applied to ensure the validity and minimize the mistakes.

3. RESULTS

Initial search retrieved a total of 157 articles. Afterward screening of these 157 articles the researchers excluded non English and duplicate articles as well included only full text research reports. The remaining articles were 88. Another screening was done to include only articles meet the inclusion criteria. A total of 29 articles were identified. Another screening was conducted and final list of 20 articles were decided to be included in the analysis

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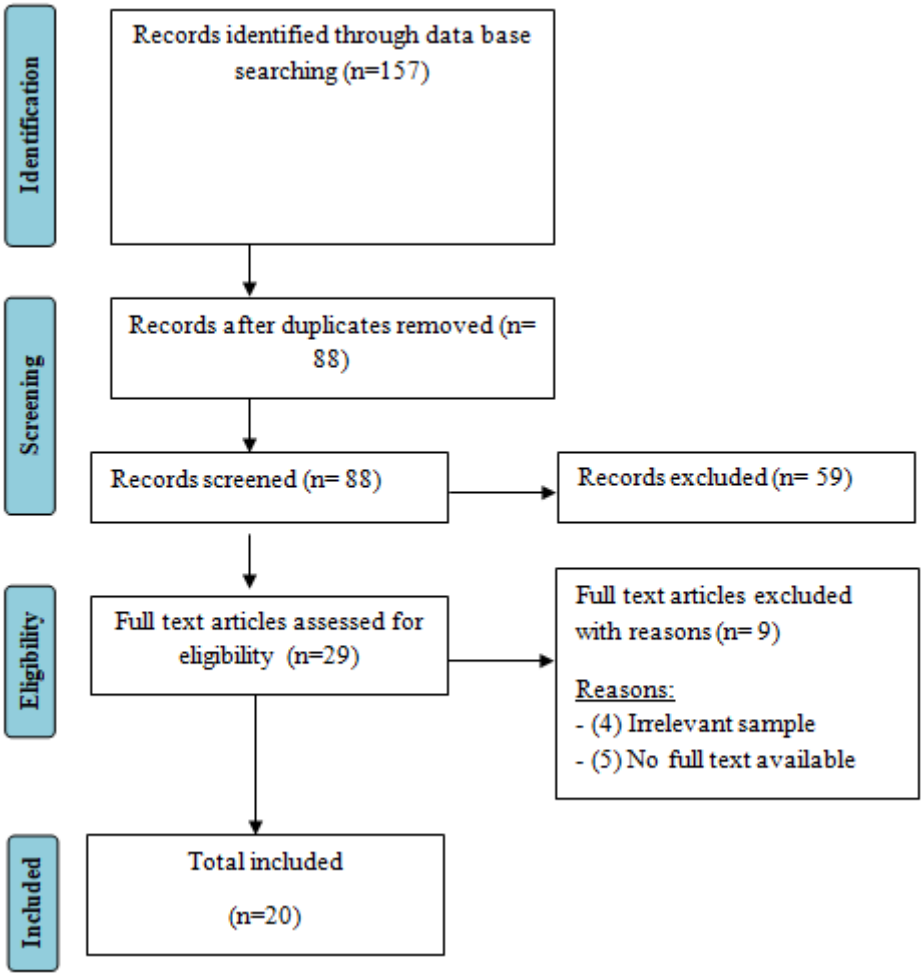

Figure (1) PRISMA flow diagram of study selection process

Studies were reviewed by two authors for quality inclusion. Overall, based on the limited scope of high-quality trials and meta-analyses in cancer care, the expert group considered the quality of evidence for the management of constipation in patients with cancer to be low and largely based on expert opinion, pharmacological reviews and clinical case reports.

Table (2) Results of the study

No.	Author, Year of publication	Design and sample size	Country/ Setting	Study aims	Conclusion
1	Wickham (2017)	Review Article	Chicago	The main aims is to: - Explore the incidence of and risk factors for constipation in patients with cancer. - Explore the non-pharmacologic and pharmacologic measures for constipation and fecal impaction. - Synthesize a laxative management.	-Advanced practitioners have important roles in recognizing risk factors, screening for constipation and developing logical implementation plans that center on oral laxatives. - They can disseminate this information and collaborate with physician and nurse colleagues to focus on close patient follow-up to avoid adverse effects which can occur with any laxative.

2	Arnall & Hamadeh (2018)	Review Article	USA	The primary aim is to provide clinicians with a practical or a real-world approach for managing constipation.	-Despite the availability of various classes of laxatives, constipation remains quite common among cancer patients due to lack of guidelines that help select the most appropriate agents. -Stimulant laxatives should be avoided in patients with suspected intestinal obstruction. -Stool softeners is useful for patients with anal fissure.
3	Mc Fee, Pawasauskas & Sera (2015)	Review Article	USA	Provide overview of treatment options for opioid induced constipation(OIC)	In patients experiencing severe constipation due to the chronic use of opioids, there are novel options to consider subcutaneous injection of Methylnaltrexone bromide every other day as needed which peripherally acting as a μ-opioid receptor antagonist .
4	Nezar, Abdallah & Nusairat (2016)	Review article	Jordan	The evidence-based review was conducted to examine the effect of methylnaltrexone on the management of OIC compared with laxatives (C) within 24 hours after administration.	Subcutaneous methylnaltrexone is effective in inducing laxation in advanced cancer patients with OIC and where conventional laxatives have failed.
5	Slatkin, Thomas, Lipman, Wilson, Boatwright et al., (2009)	Double-blind, randomized, placebo-controlled study (154 patients)	USA	The aim is to examine the effect of Methyl naltrexone for treatment of OIC in advanced illness patients.	Methyl naltrexone was rapidly effective and well tolerated in patients with advanced cancer who are receiving opoid induced analgesics.
6	Thompson ,Romito & Bark (2020)	Review article	USA	The aim is to provide an overview of cancer home treatment for constipation.	- Laxative not recommended for patients with sodium restriction and kidney problem - Stimulant laxative prevent vitamin D and calcium absorption so must be used with doctor consultation. -Stool softener is more recommended for patients with cancer
7	Neefjes et al., (2019)	Prospective observational study (39 patients)	Amsterdam	Evaluate the development and treatment of OIC and resolving	With increase dose of opoid for cancer patients, prophylactic laxative treatment is

				effect of methylnaltrexone for different opioid subtypes in daily clinical practice.	recommended with intensifying dose , to prevent OIC . -Methylnaltrexone is recommended for OIC requires as a laxative regimen.
8	Connolly & Larkin (2012)	Review	UK	Provide nurses and doctors with cause impact and management of constipation in cancer patients	Enemas are used only if oral treatment fails after several days and in order to prevent fecal impaction. -Enema not recommended for neutropaenia or thrombocytopaenia, paralytic ileus or intestinal obstruction, gynaecological surgery, severe colitis….ect. The management of constipation for cancer patients should be undertaken with early intervention and careful assessment to improve patients comfort .
9	Larkin, Sykes, Centeno, Ellershaw, Elsner, Eugene, et al.,(2008)	Review	Switzerland	Raise awareness of constipation in palliative care and provide clear as well practical guidance on management.	The combination of softener and stimulant laxative (choice for laxative based on individual circumstances).
10	Wirz et al., (2012)	A controlled Prospective open-label trial study (348 patients)	Germany	To evaluate whether the effectiveness of Polyethylene Glycol, Sodium Picosulphate or Lactulose varied with the respect to opioid induced constipation Explore the incidence and severity of constipation and the consumption of laxatives in cancer pain outpatients undergoing opiod therapy.	For prevention of constipation in early disease stage ,Laxative Polyethylene Glycol and Sodium Picosulphate are recommended instead of Lactulose.
11	McIlfatrick et al.,(2019)	A multi-site retrospective case-notes review (150 patients)	UK	To examine clinical practices for the assessment and management of constipation for patients with advanced cancer within inpatient.	-Lack of standardized documentation and follow up of constipation in patients with cancer . -Education on constipation management is needed for the staff nurses on knowledge and skills related to assessment and appropriate non-pharmacological and preventative intervention.

12	Andrews & Morgan (2012)	Review article	UK	Examine the potential of independent nurse prescriber for constipation management in the UK. Provide a simple algorithm to assist in the constipation management process.	-Thorough and frequent holistic bowel assessment for patients with cancer is the priority including plan to initiate prophylactic treatment. -Nurses should receive the necessary support and training of constipation management in the clinical setting with case scenario help.
13	Katakami, Harada & Murata (2017)	Randomized double blind placebo controlled study (193 Patients)	Japan	Investigate the efficacy and safety of a peripherally acting u-opoid receptor anatagonist ,Naldemedine for OIC in patients with cancer.	Once daily oral Naldemedine 0.2mg effectively treated OIC and generally well tolerated.
14	Brown Keshvani, Gupta et al.,(2020)	Retrospective cohort study (130,990 patients)	USA	Evaluating pattern of prescription of laxative agents in patients with lung cancer initiating opioids.	Rate of OIC prophylactic in newly diagnosed Veterans with cancer was low and not consistent with published guidelines. -Ongoing study is needed on quality oncology practice initiative guidelines address OIC in patients with cancer . Efforts to educate physicians and patients to promote appropriate OIC prophylaxis in combination with system level changes are warranted in USA.
15	Mori, Ji,Kumar ,Ashikaga & Ades (2017)	Single dose phase II Clinical trial (12 patients)	Japan	Evaluate the efficacy of Methylnaltrexone over 48 hours in cancer patients who were not terminally ill.	Methylnaltrexone may relive sever OIC in cancer patients who are not terminally ill and patients tolerated it without opoid withdrawal.
16	Chamberlain, Rhiner, Slatkin ,Stambler& Israel (2020)	Post hoc analysis comprises two Phase III, multicenter, double blind, randomized ,placebo controlled studies (287 patients)	USA	Evaluate Methylnaltrexone for OIC in patients with and without cancer.	Methylnaltrexone provides significant improvement in patient with and without cancer.
17	Hanai et al., (2016)	A randomized controlled clinical trial (30 patients)	Japan	To evaluate the effectiveness of a self management program on antiemetic-induced constipation in cancer patients	-Self management program is effective for mitigating the symptoms of antiemetic-induced constipation during chemotherapy.

					-The self management program consisted of abdominal massage, abdominal muscle stretching, and education on proper defecation position.
18	Portenoy et al.,(2008)	Multicenter Randomized parallel group (33 patients)	USA	To assess the efficacy and safety of methylnaltrexone in a population of patients with advanced illness and OIC.	Methylnaltrexone relieved OIC at doses > or = 5mg in patients with advanced illness and did not cause opioid withdrawal symptoms.
19	Thomas et al.,(2008)	Randomized Controlled Trial (133 patients)	UK	To investigate the safety and efficacy of subcutenous methylnaltrexone for treating OIC in patients with advanced illness.	Subcutaneous methylnaltrexone rapidly induced taxation in patients with advanced illness and OIC.
20	Bull et al., 2015	Randomized placebo controlled study and Open-Label Extension (230 patients)	USA	To assess safety and efficacy of fixed dose of methylnaltrexone in two phase 4 trials.	Fixed dose of methylnaltrexone was effective and well tolerated in treating OIC in patients with advanced cancer.

4. DISCUSSION

Constipation is a common condition, with higher -impact on patients with cancer. Professional nurses have a crucial role inidentifying those at risk for developing constipation and formulating nursing care plans that are based on appropriate assessment and effective management. There are essential factors that nurses should consider when formulating management plan for cancer patients who suffer from or at risk for constipation. These factors includes disease prognosis, starting opioid therapy for pain control, receiving more than one drug with anticholinergic properties and other risk factors.

Patients with OIC generally need higher doses of laxative than patients who are constipated secondary to other causes (Wickham , 2017). Nurses in collaboration with a multidisciplinary team should find appropriate regimen for cancer patients who are suffering from constipation (Keller, Jusufagic & Spiegel ,2019) in a qualitatively studied patients with OIC and they highlighted that patients reported that the health team did not discuss with them adequate information about treating constipation and other side effects. In-addition, patients have embarrassed feeling to bring up issues such as constipation.Also added that clinicians reported that moderate to severe constipation considered as a nursing problem and should be handled by nursing staff.

Therefore, it is very important to address symptoms of constipation through effective and standardized assessment method such as the one developed by NIH (Patient Reported Outcomes Measurement Information System (PROMIS), GI questionnaires) patients did not report the issue (Spiegel, 2014). In-addition, a lack of standardized documentation may result in the identification and subsequent management of constipation being missed for some patients within oncology settings. So, effective assessment and management of constipation following standardized guidelines along with good documentation of all aspects may assist in minimizing the burden to both staff and patients.

Dhingra et al., (2013) conducted a study to determine OIC in cancer patients with advanced disease and found that patients closely associate their constipation symptoms with diet and modified dietary habits, such as adding supplemental fiber and fiber-rich foods, to alleviate constipation .Additionally the study reported that patients with advanced cancer do not perceive constipation as a factor to deteriorate their health. So it is suggested that nurses should provide patients with instruction to increase fiber in their diet. Also clinicians should prescribe appropriate μ-opioid receptor antagonist according to patients' condition.

Subcutaneous injection of methylnaltrexone acting μ-opioid receptor antagonist is effective for management of constipation in cancer patients (McFee, Pawasauskas & Sera 2015; Arnall & Hamadeh ,2018). Consensus of researches reported that methylnaltrexone antagonizes opioids bound to peripheral mu receptors in the GI tract and does not cross the blood-brain barrier, provides significant improvement in patient with and without cancer (Mori , Ji ,Kumar, Ashikaga, Ades , 2017; Chamberlain , Rhiner , Slatkin ,Stambler ,Israel , 2020 ;Neefjes et al., 2019). Research studies had a consensus about the effectiveness of initiating the SC injection of methylnaltrexone as an intensive laxative regimen for OIC in cancer patients. This was even emphasized by previous studies (Argoff et al., 2015; Wald, 2016 ; Wickham,2017 ; Siemens & Becker ,2016). As a consensus recommendations on initiating prescription therapies for opioid-induced constipation suggested that subcutaneous methylnaltrexone is an alternative when standard laxatives have not been effective and improved patients' outcomes.

In spite of all the various classes of laxatives, constipation still common problem among cancer patients. This may be due to failure to prescribe laxatives before the condition arises and lack of standardized guidelines (Arnall & Hamadeh ,2018). In UK, the researchers call for a greater awareness of a comprehensive approach prevention and management of constipation in palliative care. The focus was on the preventative and non-pharmacological strategies. The researcher highlighted that the issue is equal relevance to pharmacological care and should be discussed by health care providers and recorded alongside the pharmacological interventions (McIlfatrick, 2019).

Another non-pharmacological intervention used for prevention and management of constipation is the administration of enema. Enemas can be used to manage constipation when other interventions such as laxatives are ineffective. When it comes for cancer patient, enema might be of contrivers. Enema is a rectal invasive procedure and usually associated with pain, discomfort, embarrassment, and health care burdens. It is risky for patients suffering thrombocytopenia and receiving anticoagulation therapy because rectal bleeding and bowel perforation may occur (Vilke, DeMers, Patel, Castillo, Charles et al., 2015). McIlfatrick et al., (2019) concluded that enema not recommended for neutropaenia or thrombocytopaenia, paralytic ileus or intestinal obstruction, recent colorectal orgynaecological surgery, recent anal or rectal trauma, severe colitis, inflammation or infection of the abdomen, toxic megacolon and undiagnosed abdominal pain or recent radiotherapy to the pelvic area. Enema administration consumes the bedside care givers time and effort more than was most of other tasks related to the management of constipation (e.g., oral laxative administration and discussions of bowel care (Wee, Adams, Thompson et al., 2010). Therefore, enema administration is not recommended for cancer patients.

Collaboration of multidisciplinary team should be enhanced to achieve optimal quality health care and good professional practice in the management of constipation and reducing staff time required to manage constipation. A recent meta-synthesis of qualitative evidence indicated the key coordinating role of the nurse in managing constipation between the patient, family, and other health care providers as a fundamental aspect of their overall role (Sekse, Hunskår, Ellingsen S,2018). Moreover, McIlfatrick (2019) added that the nurse had a significant role in the assessment and management of constipation, with variable involvement from other members of the multidisciplinary team as appropriate and when required.

5. CONCLUSION

Constipation is a major management issue in cancer patients. Application of pharmacological interventions appeared to adhere to clinical guidelines, but prevention and non-pharmacological interventions requires further attention. Subcutaneous injection of Methylnaltrexone is effective in management of constipation for cancer patients. Enema is not recommended for certain conditions of cancer if necessary prescribed should be continuously used. Accurate documentation is essential not only for identifying areas of practice that require improvement, but also for preventive measures .Further education is needed to equip health care providers with the knowledge and skills to perform not only a full assessment, but also to use appropriate non-pharmacological and preventative strategies. Establishing standardized preventive and non-pharmacological guidelines is imperative for this group of patients. The lack of clinical studies and over-reliance on research reviews and consensus means that this area needs further clinical research investigation.

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