A patient with pain associated with metastatic colon cancer: considerations for analgesic therapy selection

Nevzorova D. V. [1], Sidorov A. V. [1,2], Osetrova O. V. [3], Krakauer E. L.[4], Chwistek M[5], Connor S.[6], Konson C.[7], Michaelson S.[8], Ustinova A. I.[1]

[1] Federal State Autonomous Educational Institution of Higher Education I. M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University)
[2] Federal State Budgetary Educational Institution of Higher Education "Yaroslavl State Medical University" of the Ministry of Healthcare of the Russian Federation
[3] Autonomous non-profit organization Samara Hospice
[4] Harvard Medical School, Boston, USA
[5] Fox Chase Cancer Center, Pennsylvania, USA
[6] Worldwide Hospice Palliative Care Alliance, London, WC1X 9JG, United Kingdom of Great Britain and Northern Ireland
[7] International Medical Cluster Foundation, Moscow, Russia
[8] American Eurasian Cancer Alliance, Fox Chase Cancer Center, Philadelphia, USA

Abstract

The article analyzes the clinical case of an 80-year-old patient with pain associated with a malignant neoplasm of the large intestine with multiple metastases. The intensity of the pain syndrome required prescription of strong opioid analgesics to the patient. The case demonstrates the individuality of patient's response to opioid therapy. Pain intensity and the analgesic potential of the opioid must be taken into account in drug selection and dose selection; condition of the intestines, liver, kidneys; the presence of additional factors – fever, concomitant diseases and concomitantly received medications.

Key words: chronic pain, colorectal cancer, opioid rotation, pain management, palliative care.

Introduction

Colorectal cancer was estimated to be the fourth leading cause of death in the world in 2019, causing about 900,000 deaths each year [1]. Analysis of morbidity and mortality databases from 39 countries in Asia and Europe revealed that the incidence of colon and rectal cancer continues to increase in countries with medium and high levels of development, including among younger populations [2]. According to the American Cancer Society, colorectal cancer is the third most common cancer [3]. In Russia, according to the Herzen Institute data, one of the leading oncological pathologies among the population of both sexes are malignant neoplasms of the colon – the incidence is 7.1%, and of the rectum – 5.0% [4]. Pain is a symptom reported by more than 70% of patients with colorectal cancer [5]. Its origin is associated with the primary tumor, metastases, and cancer treatment. About a third of cancer patients require opioid rotation to treat uncontrolled pain or opioid-induced neurotoxicity [6].

Clinical case description

On June 2, 2021, the relatives of female patient N., 80 years old, contacted the home care service of autonomous non-profit organization Samara Hospice with a request for pain management. The patient lived in the Stavropol Territory, and at the time of deterioration of condition she was visiting her relatives in Samara – she came to her granddaughter to see her newborn great-grandson. She had a daughter, three grandchildren, a great-grandson, and was widowed a year ago (husband died of COVID-19). Disability of 2nd class.

The patient was treated at home by a palliative home care team.

Complaints

At the time of initial contact with the Samara Hospice palliative service, the patient complained of dull diffuse abdominal pain which increased periodically, periodic disturbances in the clarity of consciousness, sleep disturbances, periodic nausea and vomiting, constipation for 72 hours or more, hiccoughs for 3–5 hours a day, jumps in blood pressure, and decreased appetite.

Anamnesis

Cancer was diagnosed in March 2019. In November 2019, the patient underwent exploratory laparotomy with resection of an obstructed sigmoid colon and

diverting colostomy. Progression of the disease was noted in 2020 in the form of metastases to liver the retroperitoneal space and abdominal cavity, with spread to the small intestine. Tumor growth continued despite 6 cycles of chemotherapy and 3 cycles of targeted therapy (Aflibercept + Bevacizumab). After that, curative therapy was discontinued at the request of the patient on April 30, 2021.

On May 15, 2021, the patient's condition worsened – pain increased to 7–8 points on Numeric Rating Scale (NRS0–10) with radiation to the right thigh, her weakness worsened. She was unable to return home to Stavropol. Her pain treatment at that time of tramadol 100 mg orally every 6 hours did not relieve the pain. A fentanyl patch was added.

Data from the initial examination on June 3

The patient's height was 160 cm, weight 70 kg, BMI = 27.3 kg/m2. The general condition was severe, more than 60% of the time she spends in bed. Sedated, answers questions in monosyllables. There is a cyclical disturbance of consciousness (the daughter associates with the weather), but during the examination, it was found that the fentanyl transdermal patch (Russian manufacture) 25 mcg/h acts only 36–48 hours instead of 72 hours, during the day intensity of the pain depends on body temperature. Miosis, the temperature is 37.3^{0}C for 3 weeks with fluctuations from 37.2^{0}C to 38.20^{0}C, insufficiently responsive to antipyretics. Hyperkinesis of the upper and lower extremities, the patient refuses to take pregabalin due to a side effect – dizziness. Vesicular breathing, no wheezing, respiratory rate 18–20 per minute. BP 140/65 mm Hg., pulse 74 per minute, heart sounds are muffled, rhythmic. PCR for SARS-CoV-2 – negative (5 days). Subcutaneous fat is developed satisfactorily. Hygiene of the skin and mucous membranes is sustained well, the tongue is lined with a white coating. The abdomen is slightly tense, painful on palpation in all sections. Appetite is reduced slightly, the bowel movement was 30 hours ago. There are no open wounds and bedsores. Urination is painless, and urine output is adequate for hydration. Edema: pastosity of the legs and feet. PPS 30–40%, ECOG 3.

Psychosocial status – according to the daughter (impossible to assess at the time of examination), the patient understands the severity of the disease and accepts the terminal prognosis. A day ago, the patient called her sister in Ukraine, saying that they needed to see each other in the summer since she might not live until the fall.

Diagnosis

C18.7 Cancer of the sigmoid colon pT3N0M1, stage 2, dispensary observation group 3.

Concomitant diseases: Stable coronary artery disease. Atherosclerosis of the aorta. CHF. Chronic iron deficiency anemia of mild degree.

Previous therapy

- Fentanyl 50 mcg/h every 72 hours (4th patch)
- Metamizole sodium 1.0 g + Drotaverine 40 mg + Dexamethasone 4 mg – intramuscularly if pain worsens (administer periodically from 0 to 3 times a day, on average 2 times)
- Metoclopramide 10 mg IM for vomiting (used occasionally).

Therapy under the supervision of palliative care team

Taking into account hyperthermia, which led to an uneven analgesic effect of TTS Fentanyl, the narcotic analgesic was rotated

- Basic analgesic – combination of Oxycodone + Naloxone prolonged release (10 mg + 5 mg) PO (12 hours after the removal of Fentanyl patch (which reduced the effect of the Fentanyl)) 2 times a day – 8 AM and 8 PM.
- Morphine 10 mg PO for worsening/breakthrough pain up to 4 times a day. The prescription of additional oral short forms allows, on the one hand, to manage breakthrough pain, on the other hand, it serves as a criterion/indicator for increasing the dosage of the basic analgesic.
- Pancreatin 10.000 units PO regularly
- Dexamethasone 12 mg IM once a day, with a gradual decrease in dosage. Dosage reduction – by 2–2.5 mg every four days; upon reaching a dose of 10 mg – switching to oral forms with a subsequent decrease in dose, respectively – 7.5 mg; 5 mg; 2.5 mg., cancellation
- Omeprazole 20 mg PO once a day
- Metoclopramide 10 mg PO 0.5 hour before meals, morning and afternoon
- Sodium picosulfate 7–10–13–15 drops PO at 9 PM (titration to a comfortable dosage)
- Baclofen 5 mg PO 3 times a day
- Saline 400 ml SC drip No. 3 (to relieve symptoms of fentanyl intoxication)
- +Throat spray with lidocaine + lysozyme + cetylpyridinium chloride regularly for 1 week
- + enteral nutrition – sipping 150 ml between meals
- Since the family was in a difficult psychological condition, the patient and her relatives were consulted by a medical psychologist.

Physician visits – once in 2 weeks, nurse visits – once in 2–3 days.

Status dynamics

Consciousness on current treatment cleared up, the pain decreased to 1–2 points according to NRS0–10, periodic, relieved by an additional intake of short-acting morphine. During the observation period, 2 cycles of dexamethasone therapy (10 mg; 7.5 mg; 5 mg; 2.5 mg) were conducted.

Therapy on the deterioration of the condition

By August 4, the clinical condition had deteriorated further, the patient spends about 90% of the time in bed, so the family received an anti-decubitus mattress. There are no bedsores, but small areas of diaper rash under the breasts and on the buttocks (1–2 degrees with slight damage to the skin). Due to the increase in pain (up to 8 tablets of Morphine 10 mg per day), the dosage of Oxycodone + Naloxone (20 mg + 10 mg) combination was increased at 10 AM and 10 PM.

- Morphine PO 10 mg for pain intensification/breakouts up to 4 times a day (4 tablets per day beginning on August 18)
- Baclofen 10 mg PO 3 times a day
- Dexamethasone 7.5 mg PO
- Omeprazole 20 mg PO
- Metoclopramide 10 mg PO bid
- Pancreatin 10,000 units PO regularly
- Liquid paraffin (Vaseline oil) 20 ml per day in 2 doses + Sodium Picosulfate 20 drops per day PO (diaper rash treatment (cleansing, treatment with chlorhexidine, protective cream with zinc oxide)

Dynamics of the condition on August 24

Despite the increase in the dosage of Oxycodone + Naloxone combination to 40 mg + 20 mg x 2 times a day, no enhancement of the analgesic effect was achieved. The analgesic effect of morphine is maintained.

The condition is severe, patient spends 100% of the time in bed. Swallowing is intact, periodic nausea. The stool is regular, the appetite is significantly reduced (20% of the usual intake), drinks about 1.2 liters of fluid per day. BP is unstable for 2–3 days. Rapid fatigue, sleeps 12–14 hours a day.

Opioid rotation (25% reduction of estimated dose)

- Long-acting morphine 60 mg at 10 AM and 10 PM
- Morphine 20 mg PO (oral solution 2 x 10) – for pain intensification/breakthroughs up to 4 times a day (takes 2–4 monodoses/day)
- Dexamethasone 5 mg PO daily
- Omeprazole 20 mg PO
- Haloperidol 2.5 mg SC twice a day
- Liquid paraffin (Vaseline oil) (40 ml per day PO in 2 doses) + sodium picosulfate 20 drops per day (in the evening)

Discussion of prognosis. Decision making

The patient's daughter, seeing her condition worsen, hopes that hospitalization will bring back a stable state. The patient is upset by this prospect, believing that hospitalization means that the family abandons her, and refuses hospitalization.

The family had a joint discussion with the PC team about the benefits and disadvantages of at-home and inpatient supervision. A joint decision was made to continue with home care for the rest of the time.

Therapy: administration of drugs in case of swallowing disorders prioritized as follows: morphine (oral solution), haloperidol, dexamethasone. Also recommended to timely receive prescription solution of morphine for injections.

Dynamics of the state on September 3

The clinical status continued to worsen. Dysphagia for about 14 hours in the last 24 hours. Consciousness is confused, clears up from time to time. Shallow breathing, respiratory rate 22–26 per minute. BP 87/65 mm Hg.; heart rate 104 per minute. Pronounced marbling of the skin. Life expectancy – up to 72 hours.

Due tothe end-stage condition, all oral medications were discontinued. Syringe driver for 24 hours installed. In the syringe – a solution of morphine 60 mg and haloperidol 10 mg.

Also prescribed: dexamethasone 4 mg IM, saline 400 SC No. 2. Recommendations for skin and mucous membranes care are given.

Death on September 4th. Pain and nausea are relieved.

Discussion

In the presented clinical case, the patient suffered from chronic pain syndrome due to a malignant neoplasm of the large intestine with multiple metastases. The intensity of the pain syndrome required prescription of strong opioid analgesics. However, it was not immediately possible to find adequate pain management therapy.

Therapy with tramadol at maximum doses of 300–400 mg/day was insufficient, apparently due to the high intensity of the pain syndrome.

Sequential applications of three transdermal fentanyl patches 25 mcg/h followed by an increase in dosage to 50 mcg/h did not result in adequate pain relief. The drug's effect lasted only for 36–48 hours instead of the 72 hours expected when reaching steady-state plasma fentanyl concentration (usually occurs by the second application of the patch). Also, during the periods of the analgesic effect of the patch, the patient developed signs of opioid intoxication – impaired clarity of consciousness, delirium, hyperkinesia of the limbs, and hypotension in addition to constipation and miosis.

The action profile of the fentanyl patch in this case may be related to the patient's persistent fever. Model experiments in vitro demonstrate a double increase in the absorption of fentanyl from the patch with a temperature increase of 5 °C [7]. There are a number of reports of cases of acute toxicity of fentanyl due to increased absorption of the substance from the patch with an increase in body temperature, as well as under the influence of heat sources (heating pads, heated blankets) [7–9]. Thus, we can assume an accelerated and increased absorption of fentanyl from the patch against the background of fever in this patient, which

ultimately led to an excessive, but shorter duration of drug action.

The insufficient effect of high doses of the second opioid, oxycodone, seems to be associated not so much with oxycodone itself, but with the second component of the drug, naloxone. In Russia, oxycodone is only available as a fixed combination with naloxone in the form of extended release tablets. The maximum daily dose of the drug oxycodone/naloxone is 160 mg/80 mg and is due to the presence of naloxone in the composition of the drug. This combination was conceived to contain abuse of oxycodone by parenteral route, as well as to reduce the risk of opioid-induced constipation. Naloxone, as an opioid receptor antagonist with a higher affinity for opioid receptors than agonists, prevents the development of all the effects of oxycodone. Therefore, with parenteral (inhalation, injection) administration of the oxycodone/naloxone combination, typical opioid effects, including euphoria and analgesia, do not develop. When taken orally, naloxone binds to μ-opioid receptors on the neurons of the musculo-intestinal plexus in the intestinal wall and prevents the development of the obstipation effect of oxycodone [10]. At the same time, naloxone has a very low systemic bioavailability – on average, only 2–3% of the substance reaches the systemic circulation after oral administration of therapeutic doses and practically does not interfere with the systemic effects of oxycodone [11, 12]. The low systemic bioavailability of naloxone when taken orally is a consequence of the almost complete metabolism of the substance to inactive metabolites in the cells of the intestine and liver, mainly by glucuronidation (see Fig. 1) [13].

However, with intestinal damage and/or impaired liver function, the systemic bioavailability of naloxone, especially in high doses, may increase, which will lead to a decrease in the analgesic effect of oxycodone [14]. Prescription drug information contains a contraindication for the use of the oxycodone + naloxone combination in moderate and severe liver failure, since the systemic exposure of naloxone in such patients increases by 11518 and 10666%, respectively, and disproportionately to the increase in the bioavailability of oxycodone – by 319 and 310%, respectively [15]. There is also a recommendation to take precautions when prescribing the drug to patients with mild hepatic insufficiency (bioavailability of naloxone increases by 411%) and to refrain from using the drug in patients with complications of malignant tumors in the form of peritoneal carcinomatosis or with partial occlusion syndrome in advanced tumors of the gastrointestinal tract or small pelvis area due to the lack of clinical experience [15].

The literature describes a case of ineffectiveness of the combination of oxycodone + naloxone at a high dose (240 mg + 120 mg) and preservation of the effectiveness of oxycodone at the same dose (240 mg) in a patient with a malignant neoplasm of the lungs and metastases to the soft tissues of the chest [16]. Another report describes an opioid withdrawal syndrome following administration

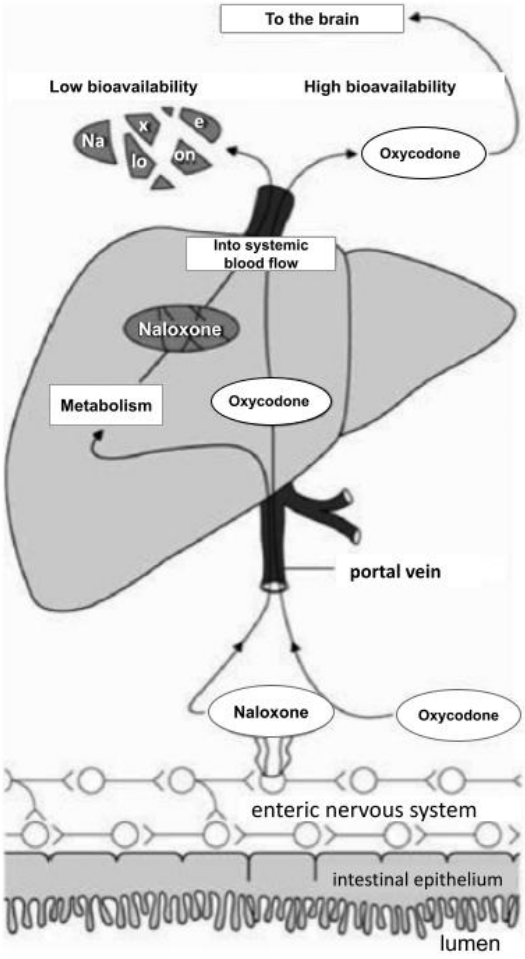

Figure 1. The principle of action of the combination oxycodone + naloxone when taken orally [18].

of a combination of oxycodone + naloxone at a low dose (10 mg + 5 mg) to a patient with gastric cancer, peritoneal carcinomatosis, and extensive portal vein thrombosis who previously received long-acting oxycodone at a daily dose of 20 mg [17]. Finally, a small randomized, double-blind, placebo-controlled trial specifically examined the effects of low-dose oral naloxone on bowel function and opioid analgesic efficacy [11]. It was demonstrated that at a dose of 2–4 mg 3 times a day, oral naloxone, which improved intestinal motility in all patients, nevertheless, reduced the analgesic effect of the opioid in three of them, and in one patient the analgesic effect disappeared completely. The authors concluded that patients receiving high doses of the opioid are most susceptible to the risk of weakening analgesic effect of the opioid against the background of oral intake of naloxone.

Thus, the lack of response to an increase in the dose of oxycodone + naloxone may be associated with the high dose of naloxone, damage to the intestines and liver by progressive malignant process that contributed to an increase in the bioavailability of naloxone and, accordingly, a decrease in the effect of oxycodone. However, this reason, apparently, is not the only one, since the analgesic effect of morphine seemed to persist. Perhaps, against the background of liver damage,

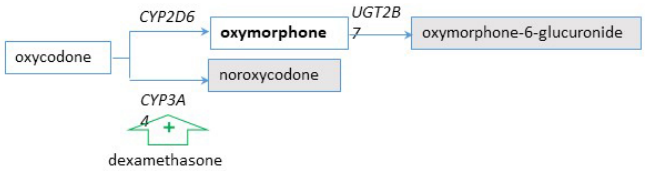

Figure 2. Simplified scheme of oxycodone metabolism [18].
Notes: CYP, cytochrome P450; UGT, UDP-glucuronosyltransferase; noroxycodone and oxymorphone-6-glucuronide are inactive metabolites; dexamethasone is an inducer of CYP3A4.

the formation of the active metabolite of oxycodone, oxymorphone, was disrupted. In addition, the induction of CYP3A4 during repeated courses of dexamethasone therapy could play a certain role, which theoretically could accelerate the metabolism of oxycodone through the formation of the inactive metabolite noroxycodone (see Fig. 2).

Initially, oral morphine in immediate release tablets was prescribed to the patient for the relief of episodes of increase/breakthrough of pain. It can be assumed that the maximum plasma concentration of morphine in this case was reached by the time the concentration of naloxone decreased – the half-life of naloxone is 30–80 minutes versus 2–3 hours for morphine. In this case, morphine occupied the opioid receptors released from the bond with naloxone. These circumstances, together with the above considerations regarding the likely causes of the reduced response to an increased dose of the combination of oxycodone + naloxone, may explain the persistence of the analgesic effect of morphine in the patient.

Dexamethasone has been used as an adjuvant to opioid therapy for visceral pain. Glucocorticosteroids help reduce peritumoral edema and associated pain due to stretching of the walls of hollow organs, liver capsule, etc. [18]. There are other known effects of glucocorticosteroids that are relevant for palliative practice: reducing nausea, improving mood, and increasing overall tonus. However, it is necessary to remember the dose-dependent adverse reactions of these drugs, incl. neuropsychiatric – provocation or increased anxiety, psychosis [20]. In this case, relatively high doses of dexamethasone were used.

In current clinical practice in Russia, intramuscular injections are often used, although non-invasive forms of opioids in immediate and extended release dosage forms are available in many regions. Yet, primary care physicians do not use them often, preferring large doses of tramadol and NSAIDs. Special attention should be called to the use of drug combinations – the so-called 'triple analgesic combination" and other lytic mixtures. In our case, before being taken under observation by palliative care service, the patient was receiving a combination of metamizole sodium 1.0 g + drotaverine 40 mg + dexamethasone 4 mg in intramusc ular injections when pain was increasing while she was on the basic therapy with transdermal fentanyl. The frequency of administration of this combination averaged 2 times a day. In general, as an ambulance tool, such a combination is rational, provided that concomitant diseases and contraindications for use in a particular patient are taken into account. However, the use of this and similar combinations administered intramuscularly on an ongoing basis is the least appropriate method of pain relief in palliative practice, especially given the availability of oral morphine in our country. First, intramuscular injections are painful and least preferred. Secondly, the course (more than 5 days) use of metamizole sodium is unacceptable according to the instructions for the use of drugs; in addition, with the introduction of the combination more than 2 times a day, the maximum allowable daily dose of metamizole sodium, which is 2 g, was exceeded. Thirdly, a rather high total dose of glucocorticosteroid was administered, which increased the risk of systemic adverse reactions.

In this case, careful work on the selection of analgesic therapy was carried out taking into account many factors – treating the patient at home, patient living in another region, the need to register, and sign to the local polyclinic. However, the receiving of both prescriptions and medications was organized in a timely manner. The case demonstrates that the problem of receiving proper pain relief in another region of the country is absolutely solvable.

From a decision-making point of view, it can be noted that the patient had sufficient clarity regarding the goals of care: curative treatment was terminated at her initiative. When the patient has a good understanding of the prognosis of the disease, this circumstance can be used when discussing the treatment strategy with relatives: to remember the decisions the patient made herself and find comfort in the fact that such treatment strategy corresponds to her desires.

Conclusion

The case under consideration presents common problems in palliative care, both in Russia and abroad. The selection and difficulties of pain relief at home, taking into account the associated medical, psychological and social aspects, the need to make a decision whether to stay at home or go to the hospital – all these are issues of daily practice. This case illustrates the individuality of a patient's response to opioid therapy. Pain intensity and the analgesic potential of the opioid must be taken into account in drug selection and dose selection; condition of the intestines, liver, kidneys; the presence of additional factors – fever, concomitant diseases and concomitantly received medications. Fentanyl transdermal patch should be avoided in a patient with fever/hyperthermia, and it is not suited to titration of opioid (dose-finding) because of the long time needed to reach steady state blood levels. The combination of oxycodone with naloxone should be avoided in a patient with widespread bowel damage and

hepatic dysfunction. Dexamethasone can be used as an adjuvant to opioid therapy to reduce visceral pain. The use of combinations of drugs ("triple") is rational mainly as an emergency remedy, subject to consideration of concomitant diseases and contraindications for use in a particular patient. However, the pain of intramuscular administration of such combinations on a permanent basis makes them the least appropriate method of pain relief in palliative practice.

Universal and "the best" drugs do not exist. Each patient needs his own, the most optimal analgesic, the dose and route of administration of which should provide adequate pain relief and good tolerability of therapy.

Bibliography

1. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. colorectal cancer. Lancet. 2019 Oct 19;394 (10207):1467–1480. doi: 10.1016/S0140–6736 (19)32319–0. PMID: 31631858.

2. Wong MCS, Huang J, Lok V, Wang J, Fung F, Ding H, Zheng ZJ. Differences in Incidence and Mortality Trends of Colorectal Cancer Worldwide Based on Sex, Age, and Anatomic Location. Clin Gastroenterol Hepatol. 2021 May;19 (5):955–966.e61. doi: 10.1016/j.cgh.2020.02.026. Epub 2020 Feb 21. PMID: 32088300.

3. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021 Jan;71 (1):7–33. doi: 10.3322/caac.21654. Epub 2021 Jan 12. Erratum in: CA Cancer J Clin. 2021 Jul;71 (4):359. PMID: 33433946.

4. Malignant neoplasms in Russia in 2019 (morbidity and mortality). Edited by A.D. Kaprina, V.V. Starinsky, A.O. Shakhzadova – Moscow, 2020

5. Zielińska A, Włodarczyk M, Makaro A, Sałaga M, Fichna J. Management of pain in colorectal cancer patients. Crit Rev Oncol Hematol. Jan 2021;157:103122. doi: 10.1016/j.critrevonc.2020.103122. Epub 2020 Oct 19. PMID: 33171427.

6. Akhila Reddy, Sriram Yennurajalingam, Suresh Reddy, Jimin Wu, Diane Liu, Rony Dev, Eduardo Bruera, The Opioid Rotation Ratio From Transdermal Fentanyl to "Strong" Opioids in Patients With Cancer Pain, Journal of Pain and Symptom Management, Volume 51, Issue 6, 2016, Pages 1040–1045, ISSN 0885–3924, https://doi.org/10.1016/j.jpainsymman.2015.12.312.

7. Gupta SK, Southam M., Gale R. et al. System functionality and physicochemical model of fentanyl transdermal system. J Pain Symptom Manage. 1992; 7: S17-S26.

8. Rose PG, Macfee MS, Boswell MV. Fentanyl transdermal system overdose secondary to cutaneous hyperthermia. Anesth Analg. 1993 Aug;77 (2):390–1. doi: 10.1213/00000539–199308000–00029. PMID: 834684

9. Southam M.A. Transdermal fentanyl therapy: system design, pharmacokinetics and efficacy. Anticancer Drugs 1995 Apr; 6:29–342.

10. Brock C., Olesen SS, Olesen AE et al. Opioid-induced bowel dysfunction: pathophysiology and management//Drugs. 2012; 72 (14): 1847–65.

11. Liu M., Wittbrodt E. Low-dose oral naloxone reverses opioid-induced constipation and analgesia. J Pain Symptom Manage. 2002; 23 (1): 48–53.

12. Dupoiron D, Stachowiak A, Loewenstein O, Ellery A, Kremers W, Bosse B, Hopp M. Long-term efficacy and safety of oxycodone-naloxone discontinued-release formulation (up to 180/90 mg daily) – results of the open- label extension phase of a phase III multicenter, multiple-dose, randomized, controlled study. Eur J Pain. 2017;21 (9):1485–94.

13. Cubitt HE, Houston JB, Galetin A. Relative importance of intestinal and hepatic glucuronidation-impact on the prediction of drug clearance. PharmRes. 2009;26 (5):1073–83.

14. Snyder B. Revisiting old friends: update on opioid pharmacology. AustPrescr 2014;37:56–60.

15. Instructions for the medical use of the drug Targin. Available on the website of the State Register of Medicines of the Ministry of Health of the Russian Federation: https://grls.rosminzdrav.ru.

16. Mercadante S., Ferrera P., Adile C. High doses of oxycodonenaloxone combination may provide poor analgesia. Support Care Cancer. 2011; 19:1471–2

17. Kang JH, Lee GW, Shin SH, Bruera E. Opioid withdrawal syndrome after treatment with low-dose extended-release oxycodone and naloxone in a gastric cancer patient with portal vein thrombosis. J Pain Symptom Manag. 2013; 46: e15–e17

18. Schenk M. Controlled-release oxycodone/naloxone: analgesic effect of the drug in the treatment of chronic pain and counteracting effect on opioid-induced constipation – a review. manage pain; 2017; 2

19. Fundamentals of palliative care/ed. R. Twycross, E. Wilcock/trans. from English: Vera Charitable Foundation for Hospices – V.V. Erokhin, G. Sh. Yunusova. – M.: Charity fund for helping hospices "Vera", 2020. – 456 p.

20. Akid I, Nesbit S, Nanavati J, Bienvenu OJ, Smith TJ. Prevention of Steroid-Induced Neuropsychiatric Complications With Neuroleptic Drugs: A Review. Am J Hosp Palliat Care. 2021 Aug 13:10499091211034771. doi: 10.1177/10499091211034771. Epub ahead of print. PMID: 34387114.