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Prescriptions of Strong Opioid Analgesics in Primary Care (PharmacyCare)

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Abstract

Every person experiences pain at some point, and persistent pain is a common symptom of illnesses like cancer. Opioid analgesics have a crucial role in the treatment of persistent cancer pain. This study looked back at VITAE-approved prescriptions for powerful opioid analgesics from January through March of 2015. Adult patients at the Oncology Institute in Kosice were given powerful analgesic prescriptions. All individuals analyzed who were prescribed opioids had a diagnosis of cancer. Retrospective assessments of prescriptions looked at patient demographics, cancer diagnosis, and the generic and brand versions of opioid analgesics provided to treat pain. The research found that throughout the study period, the East-Slovak Oncology Institute in Koice, Slovakia, prescribed 332 doses of powerful opioids to 151 patients (54% male; 46% female) with cancer. Female patients ranged in age from 27 to 88, with 27 being the youngest. Males were most often diagnosed with lung and thoracic cancer, while females were most often diagnosed with breast cancer. The total quantity of packagesFentanyl (44%), buprenorphine (26%), oxycodone (12%), tapentadol (10%), and morphine (7%) accounted for 543 of the powerful opioids. Our data showed that other opioids such as fentanyl, buprenorphine, oxycodone, and the novel chemical tapentadol are given more often than morphine, despite morphine's continued status as the gold standard in oncologic pain management. All of these drugs were recommended to alleviate excruciating pain brought on by various stages of tumor growth.

Keywords: Clinicalpraxis;Oncologicdiseases;Pain;Prescription

1. Introduction

1.1 Painandthecancer

Pain from cancer tends to be chronic or recurrent, with frequent nociceptive stimulation and an emotional component. It's been described as a "total pain" [1, 2] because to its multifaceted nature (involvement of the body, mind, society, and spirit).Age of patient, cancer phase, cancer type, and cancer treatment all have a role in cancer-related discomfort. Oncologic illness and treatment are responsible for around 65% to 85% of all cancer-related discomfort. Tumor and his metastases immediately stimulate cancer pain by, among other things, compressing and infiltrating nerve structures, clogging blood arteries, blocking valvular organs, and obstructing blood flow. After the disease itself, 15–25% of cancer pain is caused by anticancer therapy, including things like surgery, invasive diagnostic and therapeutic procedures, chemotherapy toxicity, and early and late treatment results. Infections, muscular aches in patients who are unable to move, and other types of associated pain account for an estimated 3-10% of all cases of pain [3].

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About 80% of oncologic patients have more than one form of pain, and 34% of patients experience more than four pain types with varying origins. Breast and prostate cancers are the most common primary tumors to metastasize to bones, accounting for 60% and 80% of the pain, respectively [4].Pain is one of the most dreaded signs of cancer. Cancer pain may be debilitating and disheartening for patients, upsetting for loved ones providing care, and challenging for doctors specializing in pain management to alleviate [5]. Approximately 30% of patients report pain during the diagnostic evaluation, and approximately 80% to 90% of patients report pain throughout the terminal stages of cancer [6]. Unchecked pain impairs the immune system and accelerates the development of oncologic disorders, thus effective and regulated treatment of cancer pain is essential. Insomnia, fatigue, and depression are all symptoms of inadequate pain treatment. When a patient is in pain, they may reduce their food and water intake, which may have negative effects on their health and performance. Immediate discomfort, on the one hand, reduces a patient's desire to therapy, worsens his compliance, and reduces the effectiveness of anticancer treatment [2,8].

Findings and clinical experience need for adequate control of the cancer pain. Excessive attenuation of the pain inpatientinvadeshisphysiologicalimmunemechanism andproducesothercomplications[1].Theconsequence ofbothoftheseapproachesisaffliction,aggravationofqu alityoflifeanditisshortening.It isrequiredtodiagnose pain, determine its pathological, psychological, and social characteristics and assess therapy. Conventional medicalmanagement of cancer pain includes prescription of opioids and coadjuvants at doses sufficient to control thesymptomswithoutcausingseveredrug effects [9].

The type of the cancer pain can be acute and chronic. The acute cancer pain is the main symptom of the oncologicdisease.Theeffectivetherapyoftheacutecan cerpainmustbeaggressive,whichcarriessignificantall eviationofthe pain in patients and carries the promise of successful recovery. The chronic cancer pain is very complicateddiagnostic and therapeutic problem, where the important role-plays psychologic factors and a degree of an affliction.The chronic prolonged pain is nameless, foreign and absurd pain. The patients suffer from depression, anxiety, and adisturbance of sleep, an aggravation of concentration, agitation and anger. These symptoms and continuing physicalattenuationofthepatientwithoncologicdiseas esanditstherapycontributetoexacerbatingthepainand requiremoreradical therapy than thetherapyofthepain[8].

1.2 Thetherapy of the pain

The successful treatment of the pain is a challenging task that begins with careful attempts to assess the source andmagnitude of the pain. The amount of pain experienced by the patient is often measured by means of a pain NumericRating Scale or less frequently by marking a line on a Visual

Analog Scale (VAS) with word descriptors rangingfrom no pain (0) to excruciating pain (10). In either case, the values indicate the magnitude of pain as mild (1-3),moderate (4-6), or severe (7-10). A similar scale can be used with children (Face, Legs, Activity, Cry, Consolability[FLACC] or Wong-Baker scales) and with patients who cannot speak, the Wong-Baker scale depicts five facesrangingfromsmiling(nopain)tocrying(maximumpain).

In accordance to World Health Organisation (WHO), the basic strategy of the pain therapy is established by thethree-stepanalgesicladder[2].TheWHOLadderwascreatedin1986topromoteawarenessoftheoptimaltreatment of pain for individuals with cancer and has helped improve pain care for cancer patients worldwide.Researchinthehospicesettinghasalsodemonstratedthatfixed-intervaladministrationofopioidmedication(i.e.,aregulardoseatascheduledtime)is moreeffectiveinachievingpainreliefthandosingondemand[11].

The actual strategy of the pain therapy less differentiates between the causes of the pain, but accentuates to theintensity of the pain and its respond to the therapy [12]. The original WHO analgesic diagram consists of three stepsrepresenting the use of chemical analgesic agents of increasing potency, was revised to integrate advanced treatmentoptions, and which includes the following: step one non-opioids (NSAIDs); step two weak opioids; step three strongopioids,methadone,oral,andtransdermalformulations;andstepfourinterventionaltechniques,pumps, andneuromodulationdevices.Generally,thelowerstepladderlevelsareindicatedforacuteandmilderpainrequirementsandhigherstepsfor chronicand more severepainrequirements[5].

In accordance with new recommendation there is possible to use *the elevator system* - in the therapy of the strongpain and jump over the 2nd degree of the WHO ladder. It means the direct advance from non-opioid analgesics tostrong opioids. Pharmacotherapy of the chronic pain, there are used adjunctive analgesics – co-analgesics, which canattenuate some specific pain aspects, for example, neuropathic pain and implemental drugs assigned for the therapyofanalgesics adverse effects[12].

1.3 Theopioidanalgesics

The pain associated with cancer must be treated aggressively and often requires a multidisciplinary approach for theeffective management. Such conditions may require continuous use of potent opioid analgesics and are associatedwithsomedegreeoftoleranceanddependence.Fora patientinseverepain,administration(oral,parenteral,neuralxial), duration of drug action, ceiling effect (maximal intrinsic activity), duration of therapy, the potential foradverseeffects, andthepatient´spastexperiencewithopioidsallshould beaddressed[13].

The opioids agonists produce analgesia by binding to specific G protein-coupled receptors that are located in thebrain and spinal cord regions involved in the transmission and modulation of the pain. Three major classes of opioidreceptors (μ, δ, κ) have been identified in various nervous system sites and in other tissues. At the molecular level,opioid receptors form a family of protein, that physically couple to G proteins and through this interaction

affect ionchannel gating, modulate intracellular Ca^{2+} disposition, and alter protein phosphorylation. The opioids have twowell-established direct Gi/0 protein-coupled actions on neurons: 1. They close voltage-gated Ca^{2+} channels onpresynaptic nerve terminals and thereby reduce transmitter release, and 2. They open K^{+} channels and hyperpolarizeand thus inhibit postsynaptic neurons. The presynaptic action depressed transmitter release, including glutamate,acetylcholine,norepinephrine, serotonin and substanceP[14].

New dosage forms of opioids that allow slower release of the drug are now available, for example, sustained-releaseforms of morphine (MS Contin) and oxycodone (OxyContin). Their purported advantage is a longer and more stablelevel of the analgesia. However, there is little evidence to support long-term (greater than 6 months) use of sustainedrelease opioid to manage chronic pain in the non-cancer patient. If disturbances of gastrointestinal function, preventthe use of oral sustained-release morphine, then other forms of administration are used, for example, fentanyltransdermal system can be used over long periods, and next buccaltransmucosal fentanyl can be used for shortepisodes of breakthrough pain. Administration of strong opioids by nasal insufflation is also efficacious, and nasalpreparationsarenowavailableinsomecountries.Inaddition,stimulantdrugssuchastheamphetaminescanenhancetheanalgesicactionsofopioidsandthusmaybeveryusefuladjunctsinthepatientwithchronicpain[15].

This publication presents results from retrospective analyses of pharmacotherapy of the pain caused by oncologicdiseasesinSlovakclinicalpraxis.Thisstudy aimedtodescribedthecharacterizationofpatients(ageandgender),the number of the most commonly prescribed strong opioids, the most frequently cancer diagnosis and the favouriteandmost commonly prescribeddrugforms.

2. MaterialsandMethods

This retrospective analysis was conducted from January 2015 to March 2015 using the prescriptions of strong opioidanalgesicsacceptedbypharmacyVITAE.PrescriptionsofstronganalgesicswerewrittenintheEast-SlovakOncology Institute in Košice to adult patients. Opioid prescriptions for all patients in analyses had cancer medicaldiagnosis.

Each prescription contains information about the patient, the gender, the age, the cancer diagnosis, the generic nameofstrongopioid,thedrugformandthedoseandwhotakeupthedrugfromapothecary.Inthisretrospectiveanalysis, we processed this all information. The strong opioid prescriptions were categorized after the cancerdiagnosis, the patients´ demographic data (age) were stratified into seven groups (≤29, 30-39, 40–49, 50-59, 60-69,70-79, 80-89 years old). Utilization measures for the six opioids included number of prescriptions, number ofpatientsandthedrugform.

3. Results

3.1 Characterizationofpatients

This work analyses opioid prescriptions of patients with oncology disease in apothecary shop VITAE, which is nearthe East-Slovak Oncology Institute in Košice, Slovakia from 1.1. 2015 to 31.1. 2015. In total, 332 prescriptions(100%forcancerpain)wereprescribed for151users(number82-54%male;number69-

46%female).

The mean age of men of strong opioids users was 64.3 ± 10.5 (T-test men vs women 0.2) and the mean age ofwomen was 63.2 ± 14.8. There was a higher concentration of patients aged 60 – 69 years old (male 33%; female32%), followed by aged 70-79 years old (male 32%; female 23%) and 50-59 years old (male 21%; female 25%) (seeGraph1).Theyoungestpatient-waswoman27yearsoldandtheoldestpatientwasawoman88yearsold.

3.2 Diagnosesofpatients

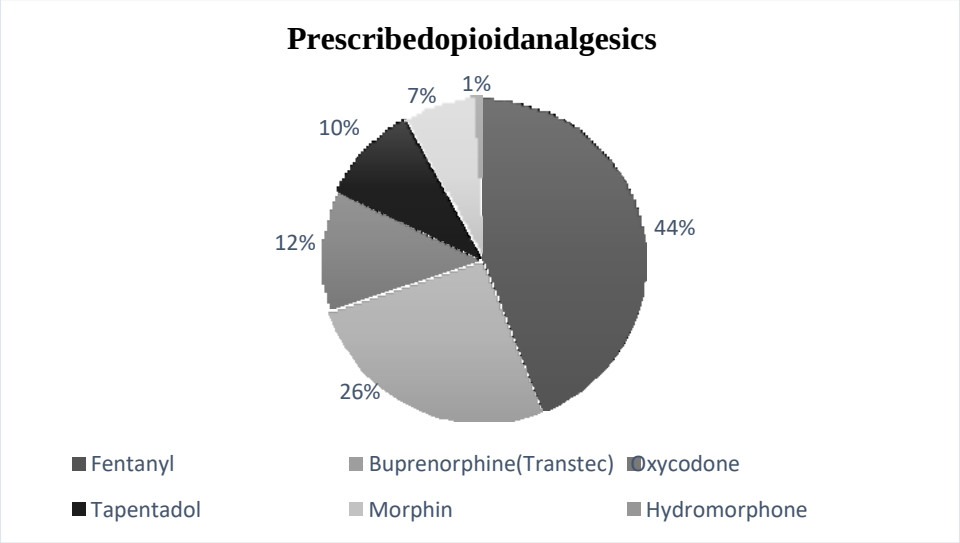
Of all strong opioid users, 151 in our study had cancer diagnoses. The most frequently three diagnoses in male userswere malignanttumoursof respiratoryandthoraxorgans(male32%vsfemale10%),malignanttumoursofgastrointestinal organs (male 22% vs female 22%) and malignant tumours of lip, mouth cavity and pharynges (male18%vsfemale6%).Ontheotherhand,themostcommonthreediagnosesinfemaleuserswere malignanttumoursof breast (female 32% vs male 0%), malignant tumours of woman sex organs (female 22% vs male 0%) andmalignant tumours of gastrointestinal organs (female 22% vs male 22%). The chronic excruciating pain withoutspecific diagnosis was diagnosed in five patients (see Table 1). Ten patients had two diagnosis (6.6 %) and onepatienthad three oncologicdiseases (0.6%).

Diagnose	**Men**	**Women**
Malignanttumoursoflip,mouthcavityandpharynges	15	4
Malignanttumoursofgastrointestinalorgans	18	15
Malignanttumoursofrespiratoryandthoraxorgans	26	7
Melanomaandothermalignanttumoursofskin	3	4
Malignanttumoursofmesotheliumandsofttissue	2	1
Malignanttumoursofbreast	0	22
Malignanttumoursofwomansexorgans	0	15
Malignanttumoursofmansexorgans	12	0
Malignanttumourofurinarysystem	5	1
Non-specificmalignanttumours	5	1
Malignanttumoursoflymphaticandhemopoetictissue	1	1
Chronicexcruciatingpain	0	1
Anotherchronicpain	2	2
Total	163	

Table1: Diagnosesofpatients

3.3 Characterizationofprescribedopioidsanalgesics

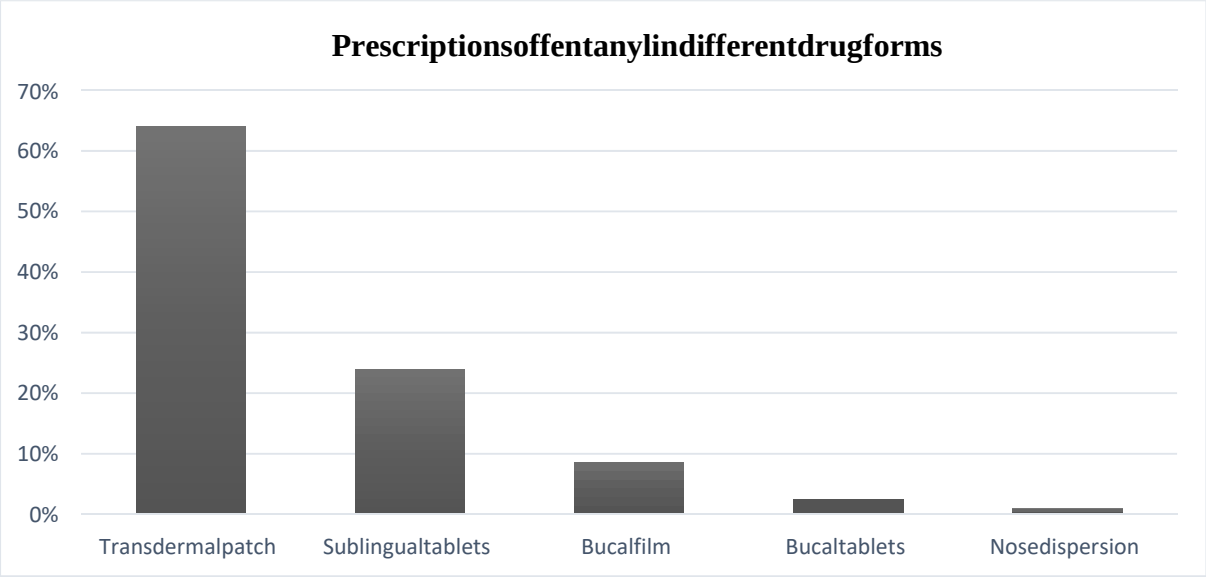
Strong opioids, total 543 in different package of analgesics, were prescribed by 332 prescriptions. The number ofpackage of strong opioids was 543 (fentanyl (44%), buprenorphine (26%), oxycodone (12%), tapentanol (10%),morphine(7%)andhydromorphone(1%))(seeGraph2).Forallpatients,thetotalnumberofstrongopioidswere 3.59packageduringthestudyperiod.



Graph2: Prescribedopioidanalgesics

3.4Drugformsofprescribedmedicament

From mentioned drugs are available buprenorphine (48%) and fentanyl (52%) in transdermal patch. Fentanyl wasprescribed in different drugs forms, the most often was used as transdermal patch (64%), then sublingual tablets(Lunaldin) (24%), buccal film (Breakyl) (8.5%), buccal tablets (Effentora) (2.5%) and nasal dispersion (Instanyl)(1%)(seeGraph3).



Graph3: PrescriptionsofFentanylindifferentdrugforms

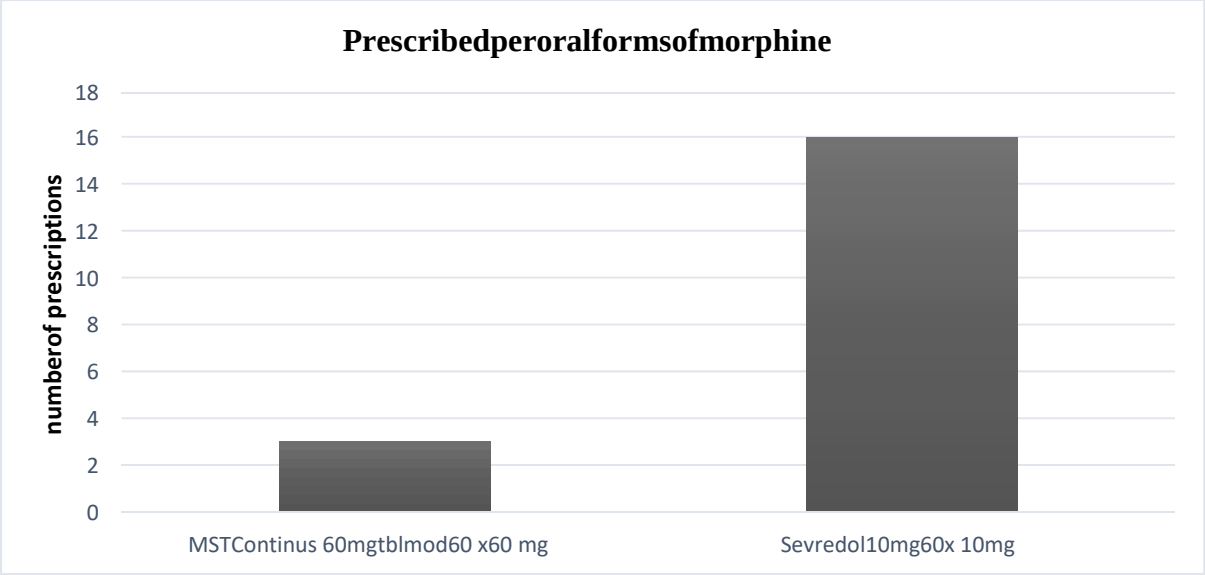
Within of the transdermal patch, fentanyl was prescribed in five different drug form. The most often Fentanyltransdermalpatchwasprescribedwithforce25µg/hand100µg/h.TheleastfrequentwasusedFentanyl

transdermal patch with force 12 µg/h. The sublingual tablets of Fentanyl (Lunaldin) were prescribed in 5 differentforces. The most often sublingual tablets with 100 µg Fentanyl were used. The least frequently was prescribedsublingual tablets with 300 and 800 µg of Fentanyl. Buccal film of Fentanyl constituted additional part of the painpharmacotherapy. Buccal film of fentanyl (Breakyl) was prescribed in force 200 µg of Fentanyl (13 packages) and inforce 400 µg of Fentanyl (7 packages). Besides buccal tablets of Fentanyl (Effentora) were prescribed in forces 100µgFentanyl (4packages) and200µgof Fentanyl (2packages)(Table2).

TypeofFentanylpatch	**Number**
Fentanyl12µg/h EMPTDM5x12µg/h	11
Fentanyl25µg/h EMPTDM5x25µg/h	46
Fentanyl50µg/h EMPTDM5x50µg/h	36
Fentanyl75µg/h EMPTDM5x75µg/h	14
Fentanyl100µg/hEMPTDM5x100µg/h	45
Total	**152**
Sublingualtablets	**Number**
Lunaldin100µgTBLSLG30x100µg	28
Lunaldin200µgTBLSLG30x200µg	11
Lunaldin300µgTBLSLG30x300µg	5
Lunaldin400µgTBLSLG30x400µg	7
Lunaldin800µgTBLSLG30x800µg	6
Total	**57**

Table2: PrescribedFentanylpatchesandFentanylsublingualtablets

Incomparison,morphinewasprescribedintwodrugformsasperoral(46%)andinjectionform(MorphinBiotika1) (54%). Per oral morphine was prescribed in form of drug Sevredol 10 mg in 84% and preparation MST Continus60mg with continualliberationofmorphinein16%(Graph4).



Graph4: Prescribedperoralformsofmorphine

4. Discussion

Patients often seek medical attention due to discomfort since it interferes with daily life. Cancer patients have a natural aversion to and dread of the pain that accompanies their illness [16]. Bone and pancreatic tumors account for a disproportionate share of analgesic prescriptions [12]. Bone metastases from breast cancer account for 60-80% of all breast cancer pain cases [17]. Malignant bone tumors were not identified in our data sets. Pancreatic tumors, which are classified as malignant gastrointestinal neoplasms, affected five men and five women. Malignant tumors of the respiratory and thoracic organs were the leading cause of oncologic pain in males, whereas breast cancer was the leading cause of oncologic pain in women.

Our data showed that just six opioid medicines were prescribed over 332 separate prescriptions for a total of 151 people across 543 individual packages of varying strengths and dosage types. The most often prescribed drugs were those in the opioid family, including fentanyl, buprenorphine, oxycodone, tapentadol, morphine, and hydromorphone.

The most often prescribed transdermal patches were for fentanyl (237 packages) and buprenorphine (139 packages). However, fentanyl was administered in a variety of different pharmacological formulations outside the transdermal patch. Lunaldin sublingual pills, Breakylbuccal film, Effentorabuccal tablets, and Instanyl nasal spray were all forms of fentanyl administration [18]. Twenty-eight packets of fentanyl sublingual tablets containing about 100 g were utilized in our research, whereas only six packages included fentanyl buccal pills. Buprenorphine's advantage is that it doesn't need to be excreted by the kidneys [16]. Buprenorphine, a partial agonist, also has antidepressant potential, which may be helpful for depressed people. Buprenorphine is a narcotic that may be administered in a number of different ways. The transdermal preparation Transtec is the sole source of buprenorphine in Slovakia. According to our data, oxycodone is the third most often prescribed opioid analgesics (66 packages). Chronic non-oncologic pain, neuropathic pain, and sometimes acute pain may all be treated with this potent opioid analgesic. In equianalgesic dosages, oxycodone is twice as potent as morphine. In addition to sustained-release formulations of oxycodone (Oxypro and Contiroxil), a combination of oxycodone and naloxone called Targin has been administered. Patients experiencing constipation may use this combo medication. When given orally, naloxone reverses the effects of opioids while preserving the pain-relieving effects of oxycodone [16]. Among the 53 packages we analyzed, tapentadol was given the fourth most often. Tapentadol represents a novel class of analgesics in the field of pharmacology due to its dual mode of action. Tapentadol is unique in that it has a slight antidepressant effect in addition to relieving physical pain. Inhibitor of noradrenaline reuptake and agonista of the -opioid receptor, tapentadol [19]. According to our findings, there were more tapentadol prescriptions

(53 packages) than morphine prescriptions (44 packages). Tapentadol's lower likelihood of tolerance and physical dependence compared to morphine [20] may have been related to a lower incidence of gastrointestinal side effects. The analgesic effect was shown in the treatment of several forms of pain, including neuropathic pain, visceral pain, and acute nociceptive pain. Tapentadol is available in slow- and rapid-release tablets, so both chronic pain and acute pain may be mitigated [21]. When it comes to treating the pain associated with cancer, morphine is the drug of choice. Its advantage is that it is cheap and available in all possible pharmacologic medication forms. However, our data shows that morphine prescriptions are falling while other opioids are being prescribed more often for oncologic pain management. The fact that morphine alone does not affect all aspects of pain is the leading cause of analgesic treatment failure; morphine also has numerous side effects, most notably in the gastrointestinal system, and may lead to tolerance and physical dependency. Our research showed that both oral (46%) and injectable (MorphinBiotika 1) morphine were given. When dealing with severe, sudden pain, an injectable version of morphine is recommended. For breakthrough pain, doctors often recommend a dose of 10mg of oral morphine like Sevredol (84 percent of prescriptions). Morphine was administered in 16% of cases in a sustained-release per os form (MST Continus 60 mg). These pharmaceutical preparations are used for the treatment of persistent discomfort. Hydromorphone, available solely in slow-release capsules (Palladone), was the least-prescribed opioid in Slovakia, with just seven packets distributed. We also analyzed data on who filled prescriptions for opioid analgesics. Patients personally picked up 171 prescriptions for opioid analgesics, while others did so in 161 instances. The average age of a patient was 64.6, suggesting that either old age or a serious medical condition prevented them from visiting the pharmacy.

5. Conclusion

Our research showed that although morphine is still the gold standard for oncologic pain management, other opioids such as fentanyl, buprenorphine, oxycodone, and the novel compound tapentadol are given more often. This is likely related to the fact that morphine has undesirable side effects and provides inadequate analgesia in the treatment of 10–30% of individuals with oncologic pain.

Long-acting pain relievers for oncology patients, such as transdermal patches containing fentanyl or buprenorphine, are highly sought for. Sublingual pills, buccal film, and buccal tablets are the most often given alternate fentanyl dosage forms. In the treatment of breakthrough pain, these fentanyl medication formulations are superior than morphine. Tapentadol, a novel chemical, has also made significant strides in the treatment of pain. Drugs containing this analgesic chemical are available in both slow- and rapid-acting forms, allowing for more precise control over pain relief and fewer side effects.

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