Agnieszka Sękowska[1, 2], Hanna Kucia[1, 2], *Małgorzata Malec-Milewska[1]

The use of oxycodone in the treatment of different chronic pain syndromes – preliminary findings

Zastosowanie oksykodonu w terapii różnych zespołów bólu przewlekłego – ustalenia wstępne

[1]Department of Anesthesiology and Intensive Care, Medical Centre of Postgraduate Education, Warszawa
Head of Department, a.i.: Małgorzata Malec-Milewska, MD, PhD
[2]2-nd Department of Obstetric and Gynecology, Medical Centre of Postgraduate Education, Warszawa
Head of Department: prof. Romuald Dębski, MD, PhD

Key words

oxycodone, postherpetic neuralgia, osteoarthritis, pelvic pain syndrome, cancer pain

Słowa kluczowe

oksykodon, neuralgia popółpaścowa, choroba nowotworowa, choroba zwyrodnieniowa stawów, zespół bólowy miednicy mniejszej

S u m m a r y

Introduction. Chronic pain is a serious clinical problem. The therapy consists of paracetamol, anty-inflammatory non steroidal drugs and opoids combined with co-analgesics and invasive methods. Oxycodone is a strong opioid drug with proved efficacy in neuropathic, visceral, cancer and persistent non-cancer pain.

Aim. The aim of the study was to assess the effectiveness and safety of control-released oxycodone in a combined therapy of selected chronic pain syndromes.

Material and methods. The study was conducted among 32 out-patients (10 male, 22 female), aged between 46-76 years, with strong chronic pain as a consequence of: postherpetic neuralgy (group I), cancer disease (group II), osteoarthritis (group III), pelvic pain syndrome (group IV). The initial dose of oxycodone was 10 mg/24h with paracetamol and co-analgesics. The intensity of pain in numeric rating scale (NRS > 7) and incidence of adverse effects were assessed at the moment of starting the therapy and on the 7th,14th and 28th day of the treatment.

Results. The initial intensity of pain in the whole examined group was 7-9 points. After one month of treatment, most effective pain relief was achieved in group I (1-2 points). Nausea was observed among 31% of the patients, vomiting among 13%, vertigos among 33%, somnolence among 31%, constipations among 38% of the patients.

Conclusions. Oxycodone appears to be an efficacious and well tolerated opioid in the management of chronic pain in four groups of patients. Using relatively small doses assure good pain control for patients in group I, II and IV. We did not observe any serious adverse effects in any of the examined groups.

S t r e s z c z e n i e

Wstęp. Ból przewlekły jest istotnym problemem klinicznym. Podstawą jego leczenia są leki przeciwbólowe: paracetamol, niesteroidowe leki przeciwzapalne (NLPZ) i opioidy, uzupełniane o koanalgetyki i inwazyjne metody leczenia. Oksykodon należy do grupy silnych opioidów o potwierdzonej skuteczności w leczeniu bólu: neuropatycznego, trzewnego i somatycznego, zarówno pochodzenia nowotworowego jak i nienowotworowego.

Cel pracy. Celem pracy była ocena skuteczności przeciwbólowej i bezpieczeństwa stosowania oksykodonu w terapii złożonej w wybranych zespołach bólu przewlekłego.

Materiał i metody. W badaniu wzięło udział 32 chorych (22 kobiety, 10 mężczyzn), w wieku 46-76 lat, u których rozpoznano ból przewlekły o dużym natężeniu (NRS > 7). Grupę I stanowili chorzy z neuralgią popółpaścową, grupę II pacjenci chorobą nowotworową, grupę III pacjenci z chorobą zwyrodnieniową stawów, grupę IV chorzy z zespołem bólowym miednicy mniejszej. Wstępna dawka oksykodonu wynosiła 10mg/24h w skojarzeniu z paracetamolem i koanalgetykami. Oceniano natężenie bólu w skali numerycznej NRS oraz występowanie objawów niepożądanych w chwili rozpoczęcia leczenia, a następnie w 7, 14 i 28 dniu terapii.

Wyniki. Wyjściowe natężenie bólu w całej badanej grupie wynosiło 7-9 punktów w skali NRS. W ciągu miesięcznej terapii największe złagodzenie dolegliwości bólowych uzyskano w grupie I (1-2 pkt.). Najwyższe natężenie bólu utrzymywało się w grupie III (4-5pkt.). W całej badanej grupie nudności zaobserwowano u 31% chorych, wymioty u 13%, zawroty głowy u 33%, senność u 31%, zaparcia u 38% chorych. U żadnego chorego nie zanotowano poważnych działań niepożądanych.

Address/adres:

*Małgorzata Malec-Milewska
Department of Anesthesiology and Intensive Care
Medical Centre of Postgraduate Education
ul. Czerniakowska 231, 00-416 Warszawa
tel. +48 (22) 584-12-20
kl.anestezjologii@szpital-orlowskiego.pl

Wnioski. Oksykodon wydaje się być skutecznym i dobrze tolerowanym opioidem w leczeniu zespołów bólu przewlekłego w wybranych czterech grupach chorych. Przy zastosowaniu stosunkowo niskich dawek leku, oksykodon zapewnia dobrą kontrolę bólu u chorych w grupie I, III i IV. U żadnego chorego nie obserwowano poważnych działań niepożądanych.

INTRODUCTION

Chronic pain affects a significant proportion of the adult population. In Poland, its incidence amounts to 27% (1). The treatment is based on analgesic drugs: paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. The treatment may be supplemented at every rung of the analgesic ladder by the so-called co-analgesics and/or invasive treatment. This scheme can effectively alleviate pain in over 85% of patients (2). Oxycodone belongs to a group of strong opioids. It is a semi-synthetic derivative of thebaine and an agonist of opioid receptors μ and κ. It shows a stronger analgesic effect than morphine. Its intrinsic activity towards μ receptors is lesser than that of morphine, but it shows 8-fold better penetration to the central nervous system (CNS) through the blood brain barrier and has much higher bioavailability than morphine. Oxycodone causes less respiratory depression and fewer symptoms from the gastrointestinal tract than selective agonists of μ receptors (3). In Poland, oxycodone was registered in 2009.

The indication for use of oxycodone is acute and chronic pain of moderate to severe intensity. Many studies have documented its high efficacy in relieving various types of chronic pain: somatic, visceral, and neuropathic (3, 4).

Postherpetic neuralgia (PHN)

The incidence of postherpetic neuralgia is estimated at 9-34% depending on the age of the patients (3). Postherpetic neuralgia is diagnosed in cases when chronic pain syndrome persists or reappear, is of neuropathic origin, and usually is one-sided, limited to one or more dermatomes or branches of the trigeminal nerve (5). Clinically significant PHN was defined as average, everyday pain in the past 48 hours, amounting to ≥ 3 points in the 11-point NRS scale, where 0 represents no pain and 10 the worst pain imaginable, at 3 months after rash onset (6). This pain is difficult to treat. In the treatment of neuropathic pain in PHN, the following drugs are used: antidepressants, antiepileptics, opioids and locally acting drugs (5% lidocaine and 8% capsaicin patches).

Oxycodone is now considered the first-line opioid for the treatment of neuropathic pain syndromes and, in the opinion of many authors, its effectiveness is comparable to gabapentin and pregabalin (3, 5, 7). For oxycodone, the therapeutic index NNT (number needed to treat) specifying the number of patients who should be given the drug in order to get a favorable therapeutic effect in one is 2.6 (1.9-4.1), the NNT for tricyclic antidepressants (TCAs) is 2.6 (2.1-3.5), for gabapentin – 4.4 (3.3-6.1) and for pregabalin – 4.2 (3.7-7.6) (8).

Pain associated with cancer

The prevalence of pain in cancer patients exceeds 50% of the total population of oncological patients. Pain associated with cancer is a complex process and may be a consequence of the presence of the tumor, cachexia, anti-cancer treatment, and comorbidities. This complex mechanism is responsible for pain of many different origins – somatic, visceral, and neuropathic (9). Oxycodone is widely used in the treatment of pain associated with cancer. It belongs to the group of three opioids of first choice (together with morphine and hydromorphone), recommended by the European Association for Palliative Care (EAPC) for the treatment of cancer pain (3).

Pain in osteoarthritis

Osteoarthritis (OA) affects 60% of men and 70% of women aged 65 years. Pain in the OA is caused by imbalance between the formation and degradation of articular cartilage and subchondral bone parts, which eventually affects all joint tissue causing permanent damage to the structure. The principles of treatment are based on the recommendations of the WHO, the three-rung analgesic ladder, which includes the initial use of non-opioid analgesics. If they are found to be ineffective, a weak opioid is added, and at the third level, after the withdrawal of the weak opioid, a potent opioid is introduced. When a component of neuropathic pain is present, it is advisable to include TCAs and AEDs (10).

Chronic pelvic pain syndrome (CPP)

Chronic pelvic pain syndrome affects up to 15% of the population. The CPP has a complex and unclear mechanism. The ailments have the characteristics of somatic, neuropathic and visceral pain. The reasons for the CPP could be associated with several systems: genitourinary, digestive, nervous and musculoskeletal. The treatment of pain in the course of the CPP should be causal. On the other hand, the pharmacological treatment has a supporting role in relation to the causal treatment or a primary role when the causative agent of symptoms is not known (11).

AIM

The aim of the study was to evaluate the effectiveness and safety of the use of controlled-release oxycodone in a combination therapy for various types of chronic pain of high intensity assessed as > 7 in NRS.

MATERIAL AND METHODS

The observational study was conducted among patients of the Outpatient Pain Clinic, Department of Anesthesiology and Intensive Therapy, Centre

of Postgraduate Education in Warsaw, who were diagnosed with chronic pain of high intensity in one of the following pain syndromes: postherpetic neuralgia (group I – 17 patients), cancer (group II – 7 patients), osteoarthritis (group III – 5 patients), chronic pelvic pain syndrome (group IV – 3 patients). The treatment started with the daily dose of 10 mg of oxycodone (Oxycontin made by Mundipharma). The oxycodone dose was altered depending on the analgesic efficacy and tolerability of adverse effects. As a rescue medication, we used: in group I – acetaminophen (paracetamol made by Polfa Łódź SA) at a dose of up to 3g/24 h; in group II – acetaminophen (paracetamol made by Polfa Łódź SA) at a dose of up to 4 g/24 h and tramadol (Tramal made by Grünenthal) at a dose of up to 200 mg/24 h (50 mg capsules); in group III – acetaminophen (paracetamol made by Polfa Łódź SA) at a dose of up to 4 g/24 h; and in group IV – acetaminophen (paracetamol made by Polfa Łódź SA) at a dose of up to 4 g/24 h. Depending on the type and cause of pain, we used co-analgesics. In the case of neuropathic pain, we included: in group I – gabapentin (Gabapentin TEVA made by Teva Pharmaceuticals Poland) 300 mg/24 h, amitriptyline (Amitryptylinum VP made by ICN Polfa Rzeszów/Valeant) 25 mg/24 h; we used additionally infiltration anesthesia and/or anesthesia of intercostal nerves; in group II – gabapentin (Gabapentin TEVA made by Teva Pharmaceuticals Poland) 300 mg/24 h, amitriptyline (Amitryptylinum VP made by ICN Polfa Rzeszow/Valeant) 25 mg/24 h; in group III – gabapentin (gabapentin TEVA made by Teva Pharmaceuticals Poland) 200 mg/24 h, amitriptyline (Amitryptylinum VP made by ICN Polfa Rzeszow/Valeant) 10 mg/24 h; and in group IV – gabapentin (Gabapentin TEVA made by Teva Pharmaceuticals Poland) 300 mg/24 h, amitriptyline (Amitryptylinum VP made by ICN Polfa Rzeszow/Valeant) 25 mg/24 h. We assessed pain intensity in NRS (Numeric Rating Scale, where 0 means no pain, and 10 – worst pain imaginable) and the occurrence of adverse effects such as nausea, vomiting, drowsiness, dizziness, disorientation, confusion, seizures and constipation at selected time points: at the start of the treatment (baseline) and then on the 7th, 14th and 28th day of therapy.

RESULTS

In the period from February to June 2011, we treated 32 patients (22 women, 10 men) aged 46-76. The observed results are shown at figures 1-4.

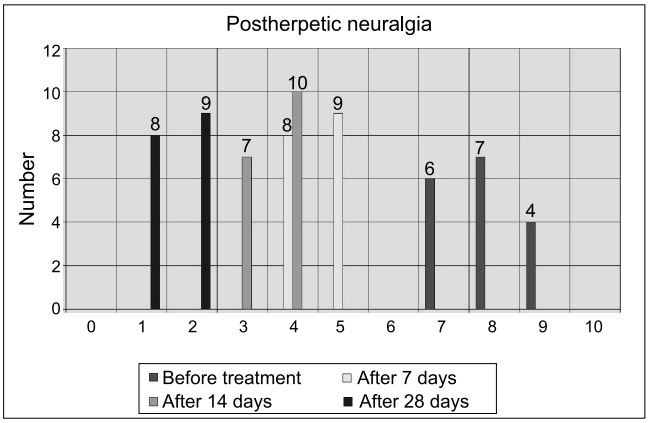

Fig. 1. The intensity of pain in NRS in the group of patients with postherpetic neuralgia was assessed at baseline and on the 7th, 14th and 28th day of the treatment.

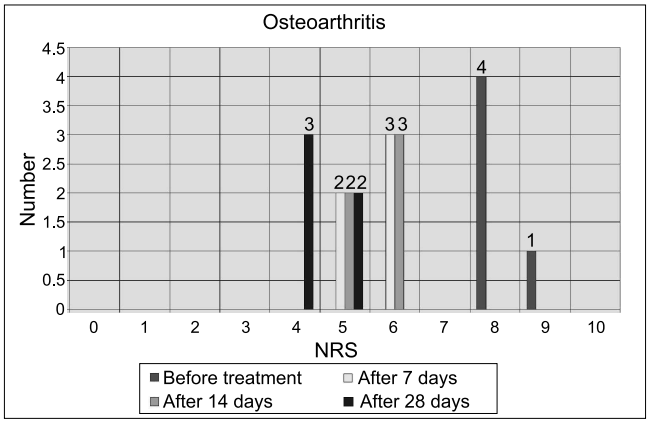

Fig. 3. The intensity of pain in NRS in the group of patients with osteoarthritis was assessed at baseline and on the 7th, 14th and 28th day of the treatment.

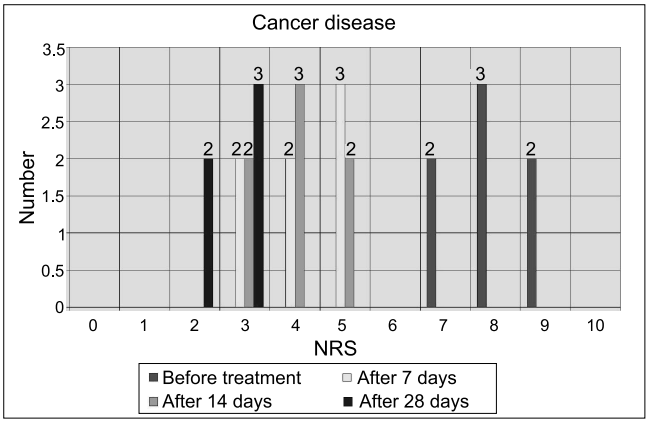

Fig. 2. The intensity of pain in NRS in the group of patients with pain associated with cancer was assessed at baseline and on the 7th, 14th and 28th day of the treatment.

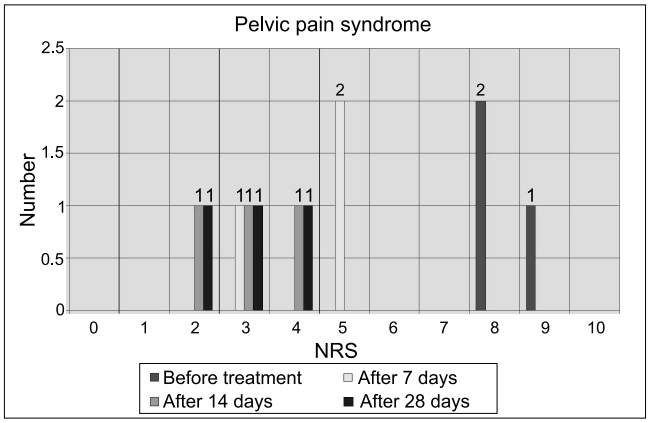

Fig. 4. The intensity of pain in NRS in the group of patients with chronic pelvic pain syndrome was assessed at baseline and on the 7th, 14th and 28th day of the treatment.

The baseline pain intensity in all groups of patients was equal to 7-9 points in NRS and, subsequently, after 7 days: in group I (postherpetic neuralgia) – 4-5, in group II (cancer) – 3-5, in group III (osteoarthritis) – 5-6, and in group IV (chronic pelvic pain syndrome) – 3-5; after 14 days: in group I – 3-4, in group II – 3-5, in group III – 5-6, in group IV – 2-4; and after 28 days: in group I – 1-2, in group II – 2-3, in group III – 4-5, and in group IV – 2-4. The maximum daily dose of oxycodone was: in group I – 40 mg/24 h, in group II – 100 mg/24 h, in group III – 40 mg/24 h, and in group IV – 40 mg/24 h. Transient adverse effects in the whole study group were noted in the following numbers of patients: nausea – 10/32 (31%), vomiting – 4/32 (13%), dizziness – 11/32 (33%), somnolence – 10/32 (31%), and constipation – 12/32 (38%). The incidence and type of the adverse effects that were observed are shown in figure 5. In group II, 2 out of 32 patients (6%) experienced severe nausea, vomiting, or dizziness, which required using another opioid instead of oxycodone. There were no serious adverse events in any group, such as apnoea, loss of consciousness, or convulsions.

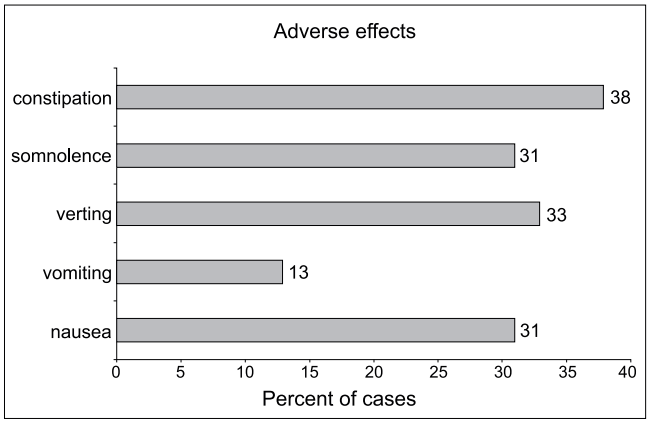

Fig. 5. Adverse events recorded in the entire studied group of patients.

DISCUSSION

Postherpetic neuralgia (PHN)

The predisposing factors for developing the PHN are age of the patient, herpes zoster of the first branch of the trigeminal nerve, severe pain felt before the appearance of skin lesions, severe course of the disease, diabetes, cancer, and coexistence of other diseases impairing the body's immunity (5). 17 patients were observed in the postherpetic neuralgia group. According to the latest guidelines concerning chronic neuropathic pain in the PHN, we used a combination therapy, with TCA – amitriptyline, antiepileptic drug – gabapentin and oxycodone – an opioid recommended as first-line drug, in the form of a controlled release drug. Combination of co-analgesics with opioid in the treatment of chronic pain can improve the efficiency of the treatment and enhance its safety profile (8, 12). In the studied group of patients we achieved a very good analgesic effect and a reduction of the NRS score from 7-9 to 1-2 on the 28th day of the therapy. The maximum used dose of oxycodone was 40 mg/24 h.

Pain associated with cancer

In accordance with the latest guidelines concerning treatment of chronic cancer pain, we selected oxycodone – one of the three opioid of first choice for this kind of pain (9). The study group included 7 patients over 65 years of age, with an aggravating history pertaining to internal medicine (coexistence of multiple comorbidities), decrease in the degree of efficiency of the organs, and problems associated with an opioid that has been used previously (dependence, hyperalgesia). The patients in this group were also given a lot of different medications that could enter into mutual interactions, which increased the likelihood of adverse effects and reduced the chances of success of the treatment. The use of oxycodone, an agonist of both the μ and the κ receptor, is appropriate in the presented group of patients, since it is less likely to cause respiratory depression and symptoms of the gastrointestinal tract than selective agonists of μ receptors. It is a safe opioid for elderly patients and there is no need to modify its dose. In patients with impaired hepatic or renal function, the initial dose should be reduced by half. In cases of severe hepatic and renal impairment, the drug is not recommended. Further characteristics of oxycodone that are beneficial in the treatment of patients with neoplastic disease are metabolism to inactive metabolites, low risk of interactions with other concomitantly administered drugs due to double-track metabolism, and lack of immunosuppressive activity. Even in case of opioid dependence (associated with prior treatment of malignancy with a strong opioid) oxycodone appears to be the right choice, since due to acting primarily through κ receptors it causes dysphoria states rather than mental satisfaction and, as a result, the risk of addiction is reduced (3, 13, 14). In the studied group of patients we obtained a very good analgesic effect and a reduction of the NRS score from 7-9 points to 2-3 points on day 28 of the treatment. The maximum used dose of oxycodone was 100 mg/24 h.

Pain in osteoarthritis

Pain in osteoarthritis usually affects hip joints, knee joints, joints in the hands, joints of the spine, and, less frequently, shoulder, elbow, ankle, and wrist joints. The principles of treatment are based on the use of the three-rung WHO analgesic ladder. The use of strong opioids in the treatment of chronic non-malignant pain (CNMP) raises doubts and controversy in many countries, including Poland, because of existing prejudices and fear of the occurrence of adverse effects, such as tolerance, psychological dependence, and nausea (14). Strong opioids may be used alone or in combination with paracetamol and NSAIDs. Therapy should be consistent with the recommendations concerning the use of strong opioids in patients with

non-malignant pain (10). In the studied group, a strong opioid – oxycodone – was recommended to 5 patients due to pain of high intensity. It was used at a maximum dose of 40 mg/24 h, yielding a reduction of pain intensity in NRS from 8-9 points to 4-points. These not fully satisfactory analgesic effects can be explained by the fact that patients in the study group had very advanced degenerative changes, which in several cases qualified them for surgery. Also, the very short period of observation (28 days) was not sufficient to determine the need for oxycodone in these patients.

Chronic pelvic pain syndrome

In 30-40% of cases of patients with the CPP the cause of the pain is unknown, or the pain does not decrease after the application of the causal therapy. This is an indication to include drug therapy. The standard procedure is a strategy consistent with the three-rung WHO ladder. Due to the complex mechanism of pain in the CPP, it is recommended to include analgesics, TCAs, and AEDs (11). In the studied group of patients with the CPP, we achieved a very good analgesic effect – pain relief – a decrease in the NRS score from 8-9 to 2-4 on day 28 of the therapy. The maximum used dose of oxycodone was 40 mg/24 h. A significantly better analgesic effect was observed in patients with the visceral pain component in the course of the CPP. This can be explained by the fact that opioid receptors κ (KOR – κ-opioid receptor), localized in the peripheral nerves are considered important for the conduction of visceral pain. The main mechanism of action of oxycodone is associated with stimulation of the peripheral and central opioid receptors, type μ and κ. Therefore, this drug has a high therapeutic efficacy precisely in pain of visceral origin (3, 15).

We want to emphasize the noteworthy fact of achieving good pain control in three of the four groups of patients (I, III and IV) using relatively low doses of oxycodone. In the entire group we observed no serious side effects in the form of respiratory depression, seizures, or significant cognitive impairment. The higher incidence of adverse events throughout the study group of patients, compared to that reported in the literature, could be associated with the simultaneous use of both co-analgesics and the short – monthly – period of observation. It seems that both the short period of follow-up and the small size of the group require further research.

CONCLUSIONS

1. Oxycodone has proven to be effective in combination therapy of somatic, visceral and neuropathic pain in the whole studied group of patients.
2. There were no serious adverse events in the entire group of patients, which confirms the high degree of safety of the administered treatment.
3. Controlled-release oxycodone provides good pain control, with relatively low doses of the drug, in patients of groups I, III and IV.

BIBLIOGRAPHY

1. Kocot-Kępska M, Dobrogowski J: Evaluation of epidemiological studies on chronic pain conducted in Europe in 2002. Ból 2004; 5(3): 18-24.
2. Wordliczek J, Dobrogowski J: (eds.): Pain treatment. Wydawnictwo Lekarskie PZWL, Warszawa 2011.
3. Misiołek H, Woroń J, Zajączkowska R: Oxycodone in pain treatment. Wydawnictwo Lekarskie PZWL, Warszawa 2012: 7-13, 25-44.
4. Waldmann SD (ed. I. Smreka): Atlas of pain syndromes. Elsevier Urban & Partner, Wrocław 2009: 214-216.
5. Dobrogowski J, Zajączkowska R, Wordliczek J: Neuropatic pain syndromes. [In:] Wordliczek J, Dobrogowski J (eds.): Pain treatment. Wydawnictwo Lekarskie PZWL, Warszawa 2011: 356-363.
6. Coplan PM, Schmader A, Nikas A: Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials: adaptation of the brief pain inventory. J Pain 2004; 5: 344-356.
7. Dworkin RH, Barbano RL, Tyring SK: A randomized placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster. Pain 2009; 142: 209-217.
8. Recommendations concerning the management of herpes zoster. Medycyna Praktyczna 2008/04, WS-2008/05, elaborated on the basis of: Dworki RH, Johnson RW, Breuer J et al.: Recommendations for the management of herpes zoster. Clin Inf Diseases 2007; 44 (suppl. 1): 1-26.
9. Krajnik M: Pain in cancer. [In]: Malec-Milewska M, Woroń J (eds.): Pain treatment compendium. Medical Education, Warszawa 2012: 283-295.
10. Istrati J, Dobrogowski J: Pain in the locomotor system. [In]: Malec-Milewska M, Woroń J (eds.): Pain treatment compendium. Medical Education, Warszawa 2012: 283-295.
11. Sękowska A, Malec-Milewska M: Pain in pelvis minor and perineum pain in women. [In:] Malec-Milewska M, Woroń J (eds.): Pain treatment compendium. Medical Education, Warszawa 2012: 11-228.
12. Kocot-Kępska M, Przeklasa-Muszyńska A, Dobrogowski J: Treatment of neuropatic pain. [In:] Malec-Milewska M, Woroń J (eds.): Pain treatment compendium. Medical Education, Warszawa 2012: 75-86.
13. Dzierżanowski T, Ciałkowska-Rysz A: Oxycodone – first choice drug in treatment of strong cancer pain. Medycyna paliatywna 2010; 3: 123-131.
14. Malec-Milewska M, Zajączkowska R: Principles of use of opioids in chronic non-cancer pain. [In:] Malec-Milewska M, Woroń J (eds.): Pain treatment compendium. Medical Education, Warszawa 2012: 65-74.
15. International Association for the Study of Pain. Visceral pain. Pain Clinical Updates 2005 Dec; 13(6).

received/otrzymano: 19.02.2014
accepted/zaakceptowano: 26.03.2014