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Transdermal buprenorphine in the treatment of cancer and non-cancer pain – the results of multicenter studies in Poland

Anna Przeklasa-Muszyńska, Jan Dobrogowski

Department of Pain Research and Treatment, Chair of Anesthesiology and Intensive Therapy, Medical College, Jagiellonian University, Śniadeckich 10, PL 31-531 Kraków, Poland

Correspondence: Anna Przeklasa-Muszyńska, e-mail: aprzemusz@wp.pl

Abstract:
This was a multicenter, non-interventional, post-marketing study that aimed to evaluate the analgesic activity, safety of use, safety profile and adverse drug reactions of transdermal buprenorphine (Transtec® 35, 52.5 and 70 μg/h) during the treatment of moderate to severe chronic cancer and non-cancer pain. The study was performed in Poland by 339 doctors. The study involved 4,030 general practice outpatients (managed by primary care physicians), pain therapy center patients, specialist outpatient clinic patients as well as patients treated in inpatients units The recruitment process began in September of 2007, and the study was completed in October of 2008. The study has been reported to the Central Register of Clinical Trials in Poland; it was also in accordance with the requirements of the Polish Pharmaceutical Law in force. The objective of the study was to evaluate the efficacy, safety of use and application of transdermal buprenorphine in patients with moderate to severe cancer pain and in patients with severe, non-malignant pain in the course of other diseases. Patients were enrolled if their pain was not well-controlled after using non-opioid analgesics. Another objective of the study was to monitor adverse drug reactions of transdermal buprenorphine reported by patients or noted by the doctors during the study visits. This first such multicenter study in Poland has confirmed high efficacy and good tolerability of buprenorphine and, therefore, confirmed its usefulness in the treatment of moderate to severe cancer pain as well as in the treatment of severe pain in patients with non-cancer pain that cannot be effectively treated with non-opioid analgesics.

Key words:
transdermal buprenorphine, Transtec®, cancer pain, non-cancer pain, safety

Abbreviations: ATC – Anatomical Therapeutic Chemical Classification, CIOMS – Council for International Organizations of Medical Sciences, C_{max} – maximum concentration, CRF – Case Report Form, CYP – cytochrome P450, MAO – monoaminooxydase, NON-SADR – non-serious adverse drug reaction, ORL – opioid-like receptor, SADR – serious adverse drug reaction, $T_{1/2}$ – half-life of the medication, T_{max} – time to maximum plasma concentration, WHO – World Health Organization, VAS – visual analogue scale

Introduction

The treatment of chronic pain remains a serious problem and is often a challenge for doctors in a variety of fields. The number of patients experiencing severe pain increases with age. With advancing age, both the number of cancer patients and the number of people

experiencing severe, non-cancer pain in the course of other diseases (e.g., osteoarthrosis) that is not controlled using non-opioid medication is known to increase [30, 31]. The primary therapeutic treatment modality in controlling pain is pharmacotherapy. Chronic, severe pain should always be effectively and appropriately treated, even if the patient cannot describe his/her experiences and can only show signs suggesting that he/she feels pain. This situation may occur in patients who are unable to verbalize their pain experience or those who hide their suffering, whether consciously or unconsciously [6].

Chronic moderate to severe pain is an indication for using strong opioid drugs (Degree III of the WHO analgesic ladder). The decision to select a strong opioid is made in various clinical situations: when opioid-naive patients suffer pain requiring the use of strong opioids, when non-opioid analgesics are ineffective, when patients receive opioids in the setting of pain exacerbation due to disease progression, when patients experience other types of acute pain, or when patients have severe pain that requires immediate analgesic treatment [18]. Recommendations are to maintain efficient analgesia by keeping the serum opioid drug levels relatively stable and preventing fluctuations of this concentration, thereby reducing the risk of adverse drug reactions [8, 31].

Buprenorphine is a thebaine derivative and a member of the pharmacotherapeutic group of opioids (ATC code N 02 AE 01). It was first synthesised in the 1960s, and it was introduced in clinical practice in 1978 as a parenteral drug; in 1981, buprenorphine sublingual tablets were introduced on the market, and in 2001, the transdermal system was introduced in some countries, with final marketing authorization in Poland on 5 December 2002. The analgesic activity of buprenorphine results from its agonistic effect on the μ opioid receptor, for which its affinity is high. The drug shows strong receptor binding, low internal activity and a slow dissociation curve. Buprenorphine is also an antagonist of κ opioid receptors and an agonist of the opioid-like receptor (ORL)1 [2, 14]. Buprenorphine is about 96% bound to plasma proteins. Nearly two-thirds of the drug is not metabolized, and the remaining part is metabolized in the liver by a P-450 cytochrome isoenzyme, CYP3A4, into three main metabolites: norbuprenorphine, buprenorphine-3-glucuronide, and norbuprenorphine-glucuronide. Nearly two-thirds of the product is eliminated *via* the feces. The remaining metabolites are excreted *via* the kidneys. Renal exposure to buprenorphine metabolites is low. The half-life ($T_{1/2}$) of buprenorphine is 20–70 h, with an average of 37 h [2, 5]. In patients with liver failure, the $T_{1/2}$ of the drug is extended [15].

The physicochemical properties of buprenorphine, especially its low molecular weight, high lipophilicity, and its chemical structure, contribute to a good distribution of the drug throughout the tissues; therefore, it is suited for use in a transdermal system. This drug preparation guarantees slow release and a stable serum concentration after having achieved the steady state [9]. Transdermal buprenorphine is available in Poland in three doses: 35, 52.5 and 70 μg/h, corresponding to 0.8, 1.2, 1.6 mg of buprenorphine/day, respectively [29]. Following the first use of buprenorphine in transdermal form, serum concentrations gradually increase. After 12–24 h, the minimum effective concentration is 100 pg/ml. In a study involving healthy volunteers, the following results were obtained for the 35 μg/h dose: a mean C_{max} of 200–300 pg/ml and a mean T_{max} of 60–80 h. After removing the transdermal system, the serum buprenorphine concentration constantly decreases; the drug is eliminated with a mean half-life of 30 h (22–36 h) [29].

The objectives of the study were to evaluate the use of buprenorphine in a transdermal system (Transtec®) in clinical practice, with a special emphasis on dosage, indications, and therapeutic efficacy in patients with chronic cancer and non-cancer pain. We also assessed the patient's quality of life and monitored the occurrence of adverse drug reactions reported during the treatment by the patients or noted by the doctor at follow-up visits. We sought to determine the optimal method of administration, the analgesic efficacy, the changes in sleep patterns related to the use of transdermal buprenorphine, patient satisfaction with the treatment (the ease of use) and the presence of issues related to drug dose modifications and treatment switching. Another objective of this study was to evaluate supportive treatments.

Materials and Methods

Study type and plan

The study was performed in Poland by 339 doctors. The recruitment began in September 2007 and the study was completed in October of 2008. The study was reported to the Central Register of Clinical Trials

in Poland, and it also met all of the requirements of the Pharmaceutical Law. Each study protocol contained Council for International Organizations of Medical Sciences (CIOMS) forms. Documentation for 4,030 patients was collected during the study: 4,030 – baseline visit; 3,996 – first follow-up visit 1 month after starting treatment; 3,644 – second follow-up visit 2 months after starting treatment; 3,283 – third follow-up visit 3 month after starting treatment; 3,934 – summary of follow-up.

This was a prospective, non-randomized, uncontrolled, open-label, single-arm, post-marketing study of the efficacy and safety of the drug. The visits were as follows: Baseline visit (day 0) – starting treatment with transdermal buprenorphine; visit 1, 2, 3 – follow-up visits 1, 2 and 3 month after starting treatment with transdermal buprenorphine.

Demographic data

The patient's demographic data were recorded at the baseline visit. The following parameters were recorded: age (the study was carried out on adult patients 18 years of age and older), sex, disease type, pain type, pain duration, previous pain therapy, previous adjuvant therapy, and medications for other diseases.

Evaluated medicinal product

The evaluated medicinal product was a transdermal system containing buprenorphine (Transtec®) used in Poland at doses of 35, 52.5 and 70 μg/h. The transdermal system was changed twice weekly. The drug dose was selected individually for each patient at the baseline visit and was verified as necessary or during the subsequent visits.

Study course

A patient was included in the study if the doctor found indications for using transdermal buprenorphine based on medical history, physical examination and additional tests. The data obtained in this study were prospective. The documentation of the follow-up period contains data from three months after starting transdermal buprenorphine therapy, even if the therapy with the drug was continued. On study inclusion, the demographic data were completed, and the cause of symptoms and clinical diagnosis, as well as previous treatments and their efficacy, were recorded. The documentation from follow-up was divided into several parts: medical history, three follow-up visits during treatment with transdermal buprenorphine, and finally, summary documentation. An important objective of the follow-up was to record adverse drug reactions.

Patient information and consent for participation in the study

The doctor or a designated person informed the patient of the purpose of the clinical study and obtained oral consent from each patient for the anonymous use of their study-related data. The study doctor and the persons authorized by the doctor had access to the patient's complete medical records. The data were also made available to the study monitor assigned by the sponsor.

Study inclusion criteria

- Chronic moderate to severe cancer pain.
- Chronic severe non-cancer pain in the course of other diseases (musculoskeletal, low back pain, osteoarthritis, neuropathic pain or other types of chronic pain) if not controlled by non-opioid drugs.

Study exclusion criteria, contraindications for transdermal buprenorphine

- Known hypersensitivity to buprenorphine or to any excipient.
- Use of opioids in the treatment of patients with opioid dependence or withdrawal syndrome.
- Conditions in which the respiratory centre and function are severely impaired or may become impaired.
- Patients treated with MAO inhibitors within two weeks of initiating transdermal buprenorphine.
- Myasthenia gravis, delirium tremens, pregnancy.

Post-study patient follow-up – withdrawal from the study

A patient could withdraw from the study at any time at his/her own request; he/she could also be withdrawn from the study by the study doctor. All cases of withdrawal were recorded in the documentation. Withdrawn patients were not replaced. If withdrawal from

the study was caused by adverse drug reactions, the appropriate form: non-serious adverse drug reaction report form (NON-SADR) or serious adverse drug reaction (SADR) report form was filled out, and the withdrawal was reported to the coordinating study site.

Ethical aspects

The study was non-invasive. Transdermal buprenorphine is a drug approved in Poland (decision of the Minister of Health, Drug Policy and Pharmacy Department on 05 December 2002), and it can be prescribed by doctors to patients with chronic moderate to severe cancer pain as well as to patients with chronic severe non-cancer pain in the course of other diseases that cannot be effectively treated with non-opioid drugs.

In this study, the patient's data recorded in the study protocol were kept unknown for the sponsor and were anonymous; only the patient's initials were used. The patient gave his/her oral consent for participation in the study, and the information was recorded in the patient's records. Participation in the study did not affect the patient's further therapy. The study sponsor only had access to the patient's initials recorded in the assigned number on the Case Report Form (CRF). The other data for the patient were contained in the patient's medical records, which were independent of the clinical study file.

Parameters evaluated

• The frequency of transdermal buprenorphine patch changes.
• The dose of transdermal buprenorphine.
• The change in the dose of transdermal buprenorphine (during follow-up).
• The person who changed the patch; whether the medication change was difficult for the patient.
• The analgesic efficacy of the patch, assessed using a five-degree scale (very good, good, satisfactory, poor, none).
• The pain intensity measured using a visual analogue scale (VAS) of 0–100 (mm).
• Any change in the patient's sleep duration and quality since starting treatment with transdermal buprenorphine.
• Adverse drug reactions (serious and non-serious).
• Changes to the analgesic and adjuvant treatment.
• The use of antiemetic and anti-constipation prophylaxis.
• Continuation or discontinuation (with an associated reason) of therapy with transdermal buprenorphine.

Additional analgesic treatment

At the baseline visit, previous analgesic therapy during the last two months, drug type, dose, and route of administration were recorded. Additional analgesic treatment during therapy with transdermal buprenorphine was allowed. In the study protocol, the following data were recorded: drug type, dose, start of treatment and end of treatment.

Adjuvant therapy

The adjuvant treatment, consisting of co-analgesics (antiepileptics, antidepressants), was recorded in the CRF with the specification of the drug type and the dose, both at the initiation of transdermal buprenorphine therapy and at subsequent visits. At each visit, the use of antiemetic and laxative treatments was also recorded with specification of the drug type and dose.

Efficacy and safety

Treatment efficacy was assessed at three consecutive visits after starting transdermal buprenorphine therapy. The following parameters were evaluated:
• the current pain intensity measured using a visual analogue scale (VAS);
• the analgesic efficacy of transdermal buprenorphine, measured on a five-degree scale (very good, good, satisfactory, poor, none);
• any changes in the quality of sleep, measured on a five-degree scale (significant improvement, improvement, slight worsening, worsening, no effect);
• the continuation or discontinuation of the previous additional analgesic therapy;
• the continuation or discontinuation of the previous adjuvant treatment;
• the continuation or discontinuation of the previous antiemetic/laxative treatment;
• the continuation or discontinuation of treatment with transdermal buprenorphine;
• a change in the dose of transdermal buprenorphine;
• the ease of use of transdermal buprenorphine;
• the person who changed the patch, if changed;
• the occurrence of non-serious and serious adverse drug reactions with the use of transdermal buprenorphine.

Statistical methods

The collected data were presented from the VAS scale as the mean ± SEM of 3,188 to 3,959 the study patients during the follow-up visits. The results were evaluated by a one-way analysis of variance (ANOVA). The differences between groups were further analyzed by Bonferroni's *post-hoc* test. *** $p < 0.001$ *vs.* baseline visit; ### $p < 0.001$ 1st *vs.* 2nd visit and 2nd *vs.* 3rd visit. The collected data were presented using standard methods of descriptive statistics. For continuous variables, the following parameters were specified: sample size, range (minimum and maximum values), median, and mean with standard deviation. For categorical variables, the absolute and relative numbers were given for each class; in the case of relative numbers, they were given both in relation to the entire sample size and as a percentage in the subgroup without missing data.

Results

Demographic data

In total, data from 4,030 patients (1,923 women, 2,024 men) were collected in the study; the mean patient age was 62.8 years. Patients had been treated in the following settings: family physicians, 927 (23%); pain therapy clinics, 600 (14.9%); specialist outpatient clinics, 1,669 (41.4%) and hospital departments, 834 (20.7%). The indication for inclusion in the study was cancer pain in 3,254 (80.7%) of the patients and non-cancer pain in 757 (18.8%) of the patients (musculoskeletal, 323 (8%); neuropathic, 371 (9.2%); other pain types, 88 (2.2%)); there was no specified cause of pain in 19 (0.5%) of the patients (Tab. 1).

Course of study, number of patients who completed the study

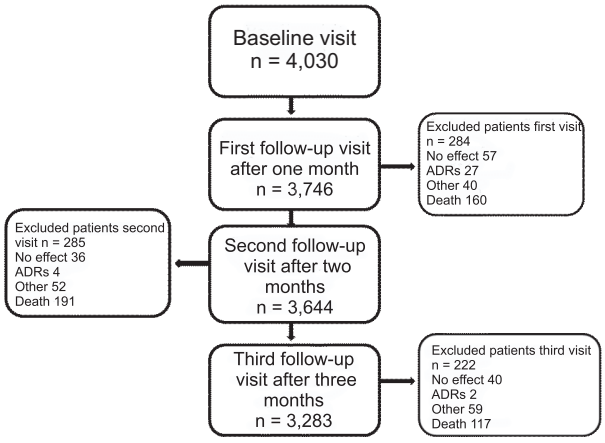
Four thousand and thirty patients were included in the study. At the first follow-up visit, one month after starting study drug therapy, complete data for 3,996 patients were collected. At the first visit, therapy was discontinued in 284 patients. The causes included no effect, non-serious adverse drug reactions, patient's death (not related to the study medication), patient lost during follow-up, and other causes (Scheme 1, Tab. 2, Tab. 3).

At the second follow-up visit, data were collected for 3,644 patients. At the second visit, therapy was discontinued in 285 patients; the causes were similar to those from the first visit (Scheme 1, Tab. 2).

At the third follow-up visit, data were collected for 3,283 patients. Transdermal buprenorphine therapy was discontinued in 222 patients. The causes of discontinuation were similar to the causes at the first visit (Scheme 1, Tab. 2, Tab. 3). In total, during the follow-up period, data for 3,934 patients were collected.

Tab. 1. Diagnoses in patients included in the study

Diagnosis	Percentage (number of patients)
Cancer	81 (n = 3,266)
Neuralgia	5.5 (n = 222)
Other	3.6 (n = 146)
Osteoarthritis of the spine	3.4 (n = 137)
Osteoarthritis of the joints	2.1 (n = 86)
Neuropathy	1.9 (n = 78)
Radicular syndrome	1.6 (n = 66)
Tumor (non-cancer)	0.4 (n = 18)
N/A	0.3 (n = 11)
Total	100.0 (n = 4,030)



Scheme 1. Discontinuation of treatment with the drug and its cause at each follow-up visit

Tab. 2. The percentage (number of patients) of discontinuation of drug treatment at each follow-up visit

Therapy discontinuation	1st	2nd	3rd
YES	7.1% (n = 284)	7.8% (n = 285)	6.8% (n = 222)
NO	92.4% (n = 3,692)	91.7% (n = 3,340)	92.9% (n = 3,051)
N/A	0.5% (n = 20)	0.5% (n = 19)	0.3% (n = 10)

Tab. 3. The percentage (number of patients) of causes of withdrawal from treatment with transdermal buprenorphine over the entire follow-up period

Reason for discontinuation	1st	2nd	3rd
No effect	20.1% n = 57	12.6% n = 36	18.0% n = 40
Adverse drug reaction	9.5% n = 27	1.4% n = 4	0.9% n = 2
Other	14.1% n = 40	18.2% n = 52	26.6% n = 59
Death	56.3% n = 160	67.0% n = 191	52.7% n = 117

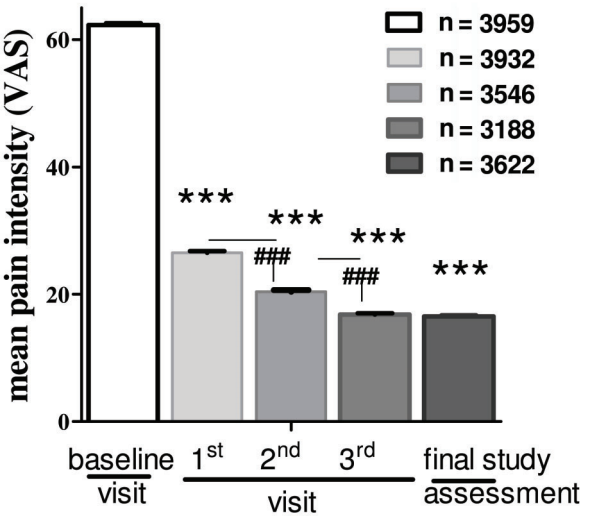


Fig. 1. Mean pain intensity (VAS scale) during follow-up: pain intensity recorded at the baseline visit; pain intensity recorded at the first, second and third follow-up visits and pain intensity recorded at the final study assessment. The collected data are presented on the VAS scale as the mean ± SEM (mm) of 3,188 to 3,959 during the follow-up visits. The results were evaluated by a one-way analysis of variance (ANOVA). The differences between groups were further analyzed by Bonferroni's *post-hoc* test. *** $p < 0.001$ *vs.* baseline visit; ### $p < 0.001$ 1st *vs.* 2nd visit and 2nd *vs.* 3rd visit

Transdermal buprenorphine efficacy assessment – change in pain intensity

During the study, the mean pain intensity assessed using a visual analogue scale (VAS 0–100 mm) gradually decreased from a mean value of 62.5 mm at the baseline visit to the value of 16.5 mm at the final study assessment (Fig. 1). Documentation from 4,030 patients was collected during this study; however, the Case Report Forms contained complete data for pain intensity in only 3,959 patients at the baseline visit and for 3,622 patients at the final study assessment. The pain decrease observed during the first, second and third follow-up visits compared to baseline was statistically significant ($p < 0.001$). The beneficial effect of transdermal buprenorphine on pain intensity also improved with time, and comparisons between visit 1 *vs.* visit 2 and visit 2 *vs.* visit 3 revealed a statistically significant decrease in pain ($p < 0.001$) (Fig. 1).

Pain intensity reduction was assessed at each visit using a five-degree relief assessment scale: very good, good, satisfactory, poor, and no relief. Compared to baseline at the first follow-up visit, very good efficacy of the study drug used in a transdermal system was reported by 1,120 patients (28.0%), good efficacy by 1,920 patients (48%), satisfactory by 720 (18%) and poor or no relief by 195 (4.9%) patients (Fig. 2A). At the second follow-up visit, very good efficacy of the transdermal buprenorphine treatment was recorded in 1,345 (36.9%), good in 1740 (47.7%) and satisfactory in 370 (10.2%) patients compared to baseline (Fig. 2A). At the third follow-up visit, very good efficacy for the transdermal buprenorphine treatment was recorded in 1,454 (44,3%), good in 1,459 (44.4%), satisfactory in 239 (7.3%) and low or none in 45 (1.3%) patients compared to baseline (Fig. 2A). The general analgesic efficacy of transdermal buprenorphine in the entire follow-up period was as follows: very good efficacy – 1630 patients (41.4%), good – 1749 (44.5%), satisfactory – 250 (6.4), poor – 64 (1.6%), and none –10 (0.2%) (Fig. 2B).

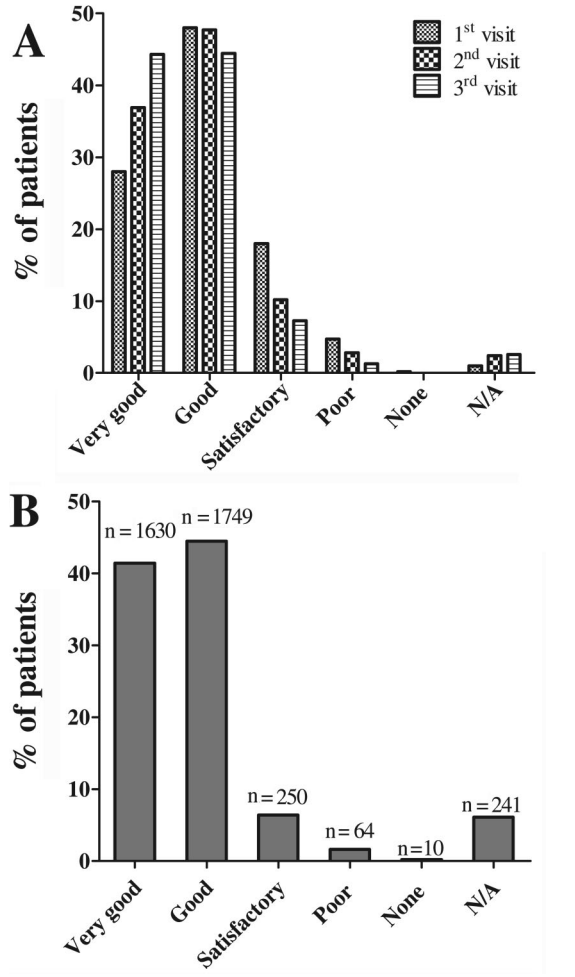


Fig. 2. Analgesic efficacy (percent of patients) of the buprenorphine used in a transdermal system, assessed at the third follow-up visit (**A**). Mean analgesic efficacy of the drug used in a transdermal system in the entire follow-up period (**B**)

Change in sleep quality related to transdermal buprenorphine

The effect of transdermal buprenorphine on the patient's sleep quality was assessed in the study. Changes in the quality of sleep were assessed using a five-degree Verbal Sleep Quality scale, based on Quality of Life Scale: significant improvement, improvement, slight worsening, worsening, or no effect on sleep quality [19]. Compared with the baseline visit, at the first follow-up visit, significant improvement in sleep quality was seen in 737 patients (18.5%), improvement in 1,709 (42.8%) and no improvement in 1,426 (35.7%) (Fig. 3A). Compared with the baseline visit, at the second follow-up visit, significant improvement in sleep quality was seen in 891 patients (24.5%), improvement was seen in 1,279 (35.1%), a slight worsening was seen in 70 (1.9%) and no improvement was seen in 1,301 (35.7%) patients (Fig. 3A). Compared with the baseline visit, at the third follow-up visit, significant improvement in sleep quality was seen in 918 patients (28.0%), improvement in sleep quality was seen in 1,035 (31.5%), slight worsening was seen in 47 (1.4%) and no improvement was seen in 1,187 (36.2%) patients (Fig. 3A).

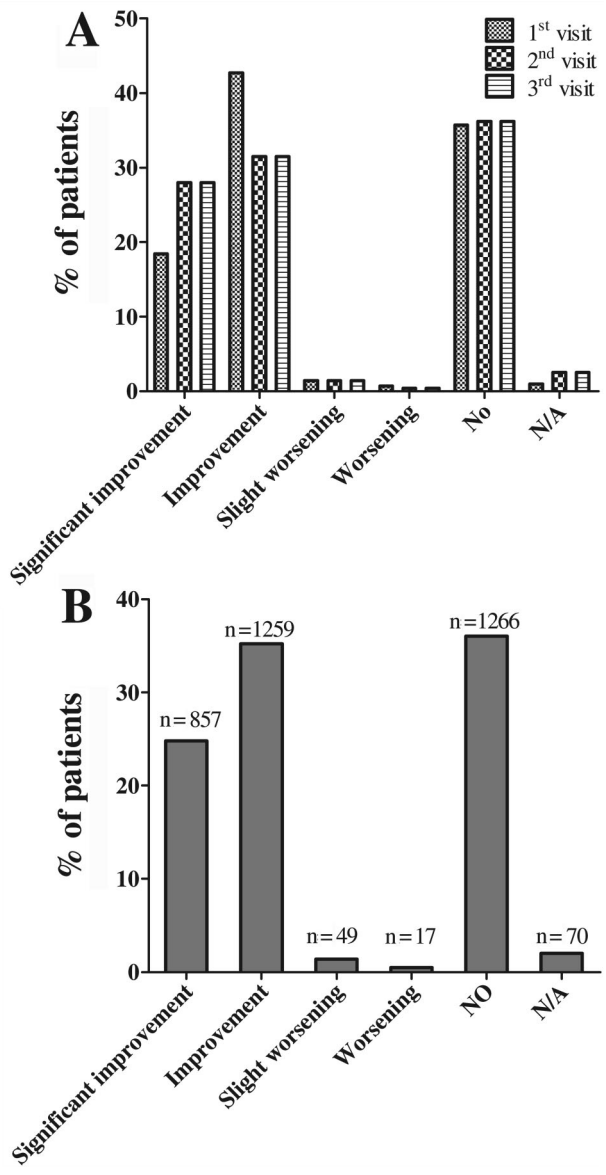


Fig. 3. Change in sleep quality (per cent of patients) at each visit: first, second and third follow-up visit (**A**). Mean change in sleep quality throughout the follow-up period (**B**)

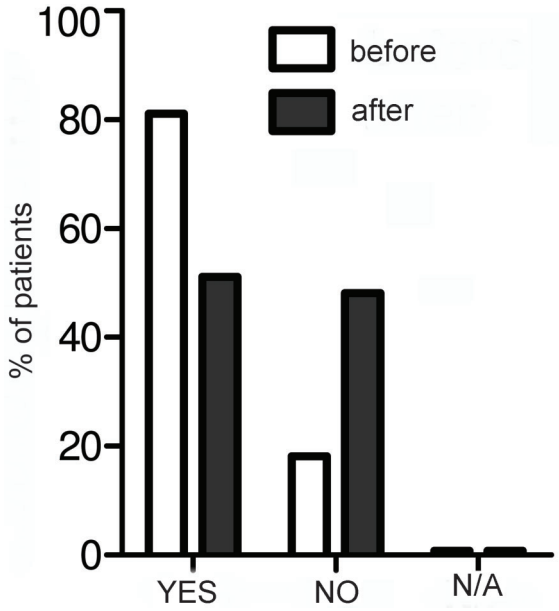


Fig. 4. General analysis of additional analgesic treatment before and after using transdermal buprenorphine

Mean change in sleep quality compared to baseline visit yielded the following results: significant improvement in sleep quality was seen in 857 patients (24.8%), improvement in sleep quality was seen in 1,259 (35.2%), slight worsening was seen in 49 (1.4%), and no improvement was seen in 1,266 (36%) patients (Fig. 3B).

The use of analgesics before and after starting transdermal buprenorphine treatment

Before starting treatment with transdermal buprenorphine, 758 (18.8%) out of 4,030 patients included in the study received no analgesic treatment over the last two months. The remaining patients (81.1%) did receive analgesic treatment over the last two months (Fig. 4). The various analgesic treatments used before transdermal buprenorphine included the following non-opioid analgesics: diclofenac – 6.8%, ibuprofen – 3.4%, ketoprofen – 34.1%, nimesulide – 1.1%, meloxicam – 3.4%, metamizole – 4.5%, paracetamol – 3.4%; they also included the following opioid analgesics: morphine – 2.2%, paracetamol/codeine – 2.2%, and tramadol – 38.6% (Fig. 5). The most commonly used non-opioid drug was ketoprofen, whereas among the opioid drugs, tramadol was the most commonly used. After the inclusion of transdermal buprenorphine in the treatment, 1,937 (48.1%) out of the 4,030 patients included in the study received no additional analgesic treatment. The other 2,059 patients (51.1%) received additional analgesic treatments (Fig. 4).

Additional analgesic drugs used after starting therapy with transdermal buprenorphine included the following non-opioid analgesics: diclofenac – 8.7%, ibuprofen – 6.5%, ketoprofen – 41.3%, meloxicam – 2.2%, metamizole – 4.4%, paracetamol – 8.7%; they also included the following opioid analgesics: buprenorphine – 2.2%, morphine – 2.2%, paracetamol/codeine – 6.5%, paracetamol/tramadol – 2.2%, and tramadol – 15.2%

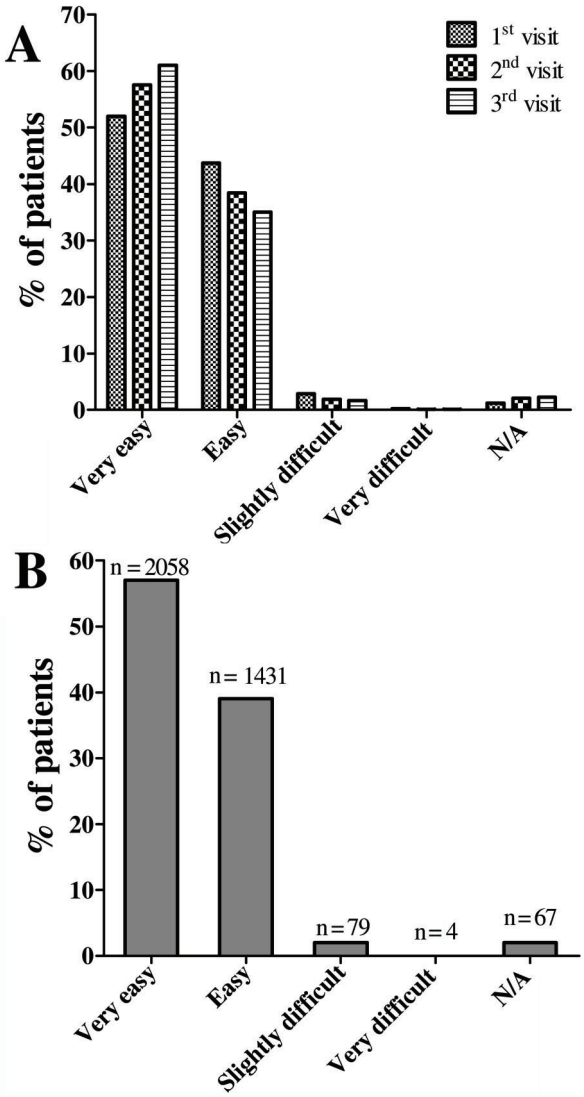


Fig. 5. The ease of change of the transdermal system in patient assessment at first, second and third follow-up visit (**A**). Analysis of ease of use of transdermal system change (**B**)

Tab. 4. The percentage (number of patients) of the analysis of drug dose modifications at each follow-up visit

Transdermal buprenorphine	1st	2nd	3rd
35 µg/h	1.5% (n = 14)	3.2% (n = 18)	6.3% (n = 20)
52.5 µg/h	66.3% (n = 612)	45.9% (n = 259)	35.2% (n = 112)
70 µg/h	24.3% (n = 224)	37.5% (n = 210)	38.4% (n = 122)
Other doses (higher)	7.6% (n = 70)	12.8% (n = 72)	18.6% (n = 59)
N/A	0.3% (n = 3)	0.9% (n = 5)	1.6% (n = 5)

Tab. 6. Detailed analysis of the additional analgesic treatment before and after starting transdermal buprenorphine treatment

Drug	Before	After
Diclofenac	6.80%	8.69%
Ibuprofen	3.40%	6.52%
Ketoprofen	34.10%	41.30%
Meloxicam	3.40%	2.20%
Metamizole	4.50%	4.35%
Paracetamol	3.40%	8.69%
Buprenorphine	–	2.20%
Morphine	2.20%	2.20%
Paracetamol/codeine	2.20%	6.52%
Paracetamol/tramadol	–	2.20%
Tramadol	38.60%	15.21%

(Tab. 6). After starting therapy with buprenorphine, the most commonly used non-opioid drug was ketoprofen, whereas among the opioid drugs, tramadol was the most commonly used. In most cases, after starting treatment with transdermal buprenorphine, the drugs used previously as additional analgesic treatments were maintained in 86.1% of patients at the baseline visit, in 95.5% of patients at the first follow-up visit, in 88.4% patients at the second visit and in 90.8% of patients at the third visit. The additional analgesic treatment was changed in 9.7% of patients at the baseline visit, in 2.3% of patients at the first follow-up visit, in 6% patients at the second visit and in 4.4% of patients at the third follow-up visit.

Tab. 5. List of non-serious adverse drug reactions (NON-SADR)

Symptom	No. of cases	Percentage (of all NON-SADR)	Percentage (Total group)
Constipation	1	2.94%	0.025%
Local skin reactions (itching, edema, rash, reddening)	17	50%	0.42%
Generalized erythema	1	2.94%	0.025%
Excessive sweating	3	8.25%	0.074%
Nausea	2	5.88%	0.049%
Vomiting	5	14.7%	0.12%
Dizziness	3	8.25%	0.074%
Somnolence, confusion	2	5.88%	0.049%

Adjuvant therapy

Before using transdermal buprenorphine, adjuvant treatment was used by 881 patients in the study groups (i.e., 21.9% of subjects). Three thousand and forty-four patients (75.5%) had not used adjuvant treatment before starting therapy with transdermal buprenorphine. After starting therapy with the drug, no adjuvant treatment was used by 1,937 patients (48.1%). Adjuvant drugs were used by 2,059 patients (51.1%). The adjuvant drugs used before starting treatment with transdermal buprenorphine were as follows: lamotrigine – 8.3%, gabapentin – 8.3%, sodium clodronate – 8.3%, tianeptine – 16.6%, carbamazepine – 8.3%, amitriptyline – 33.3%, lorazepam – 8.3%, and dexamethazone – 8.3%. The most commonly used drug was amitriptyline.

The adjuvant drugs used after starting treatment with transdermal buprenorphine were as follows: carbamazepine – 12.5%, alprazolam – 6.25%, lamotrigine – 6.25%, gabapentin – 18.5%, amitriptyline – 25.0%, dexamethazone – 12.5%, tianeptine – 12.5% and lorazepam – 6.25%. The most commonly used drug was amitriptyline; the use of gabapentin increased as compared with its use before starting treatment with transdermal buprenorphine.

Antiemetic and laxative treatment before and after using transdermal buprenorphine

Antiemetic/laxative drugs had been used by 825 (20.5%) patients before starting therapy. These drugs had not been used by 3,149 (79.3%) patients. At the first follow-up visit after starting treatment with transdermal buprenorphine, the use of antiemetic/laxative agents was reported by 992 (24.8%) patients; at the second follow-up visit, 744 (20.4%) patients were using these agents, and at the third follow-up visit, 626 (19.1%) patients were using these agents. The drugs most commonly used before using the medicinal product under study were as follows: lactulose, Alax, and metoclopramide (with similar frequency). After starting treatment with transdermal buprenorphine, the most commonly used drugs were the following: metoclopramide – 51.8%, lactulose – 22.2%, duphalac – 11.1%, Alax – 7.4%, and docusate sodium – 7.4%.

Ease of use of transdermal buprenorphine

During the entire follow-up period, the ease of changing the transdermal system was assessed using a four-degree scale: very easy, easy, slightly difficult, and very difficult. At each follow-up visit, the change of the transdermal system was assessed as very easy or easy by most patients (96.7%) at the first follow-up visit, by 95.9% at the second follow-up visit and by 95% at the third follow-up visit (Fig. 5A). The 3,485 of patients assessed change of transdermal system as very easy or easy (Fig. 5B).

Change of the transdermal system

The mean number of patients who changed their transdermal system by themselves during the entire follow-up period was 1,690 (46%); the mean number of patients for whom the relatives changed the transdermal system was 1,563 (42.9%) patients. In the other cases, the changes were performed more often by the nurses 324 (8.4%) than by the doctors 7 (0.4%) patients.

Doses of transdermal buprenorphine used during study

At the baseline visit, at which the patient's treatment with transdermal buprenorphine was started, the most commonly prescribed dose was 35.5 μg/h, which was given to 73.4% of the patients, followed by the dose of 52.5 μg/h, which was given in 21.5% of patients, and the 70 μg/h or higher doses which was given to 4.8% of patients (Fig. 6A). During the follow-up visits, about 80% of the patients had no need to change their transdermal system doses (Fig. 6B)

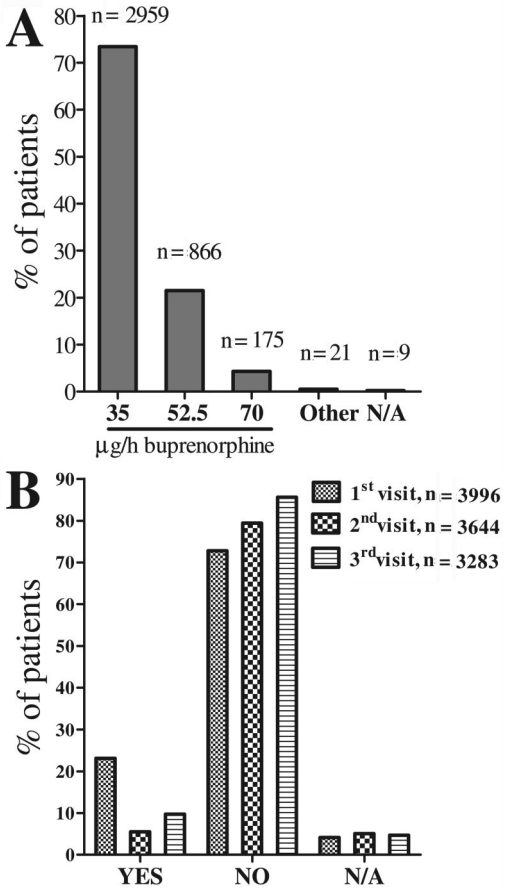


Fig. 6. Transdermal buprenorphine doses prescribed at the baseline visit; number of patients, 4030 (**A**). Changes in the transdermal buprenorphine doses during follow-up (**B**)

At the first follow-up visit, the drug doses were changed in 920 patients. The dose most commonly recommended at the first visit was 52.5 μg/h. At the second follow-up visit, the drug doses were changed in 564 patients; at the third follow-up visit, the drug doses were changed in 318 patients (Tab. 4).

Continuation or withdrawal from treatment with transdermal buprenorphine

After the third follow-up visit, continuation of treatment with transdermal buprenorphine was planned in 2,756 (70.1%) patients, and the drug was discontin-

ued in 1,111 (25.7%) patients included in the study at the baseline visit. Over the entire follow-up period, treatment with transdermal buprenorphine was discontinued at the first follow-up visit in 284 (7.1%) patients, at the second follow-up visit in 285 (7.8%) patients and at the third follow-up visit in 222 (6.8%) patients (Scheme 1, Tab. 2, Tab. 3).

The most common cause of withdrawal from treatment with transdermal buprenorphine was patient death, which was not related with the study product but was the result of disease progression (468 patients). The second-most common cause of withdrawal from treatment was the lack of analgesic efficacy of the product in 133 patients. Another cause of withdrawal of medication was the occurrence of non-serious adverse drug reactions that occurred in 33 subjects (Tab. 3).

Safety and tolerability of adverse drug reactions related to the use of transdermal buprenorphine

In total, 34 cases of non-serious adverse drug reactions were reported; this figure corresponds to 0.84% of the patients included in the study. The most commonly reported adverse drug reactions were local skin reactions, representing 50% of the non-serious adverse drug reactions reported. The second most common adverse drug reaction was vomiting, a reaction that represented 14.7% of the adverse drug reactions reported (Tab. 5).

Discussion

Transdermal buprenorphine is a promising treatment option in chronic cancer pain because of its efficacy as well as its good safety and tolerability profile, including a low risk of respiratory depression, a lack of immunosuppression and a lack of accumulation in patients with impaired renal function [1, 3, 10, 11, 21, 26–28]. Less is known about the efficacy and safety of transdermal buprenorphine in non-cancer pain [3, 28]; therefore, in our study, we examined patients not only with cancer pain, but also 757 patients with chronic severe non-cancer pain (osteoarthritis, neuropathic pain). Transdermal buprenorphine represents a new treatment option for initial opioid therapy in patients with severe non-cancer pain [12, 22, 25]. Randomized, placebo-controlled studies have shown drug efficacy (pain decrease), an extension of the sleep duration without interruption by pain and a reduction in rescue medication doses after using transdermal buprenorphine as compared to placebo in patients with chronic pain or neuropathic pain. The efficacy of buprenorphine in the treatment of neuropathic pain can be explained by the ability of this substance to prevent hyperalgesia, a state that can be caused by several other opioids [12, 22, 23, 25]. The use of transdermal buprenorphine shows a dose-dependent analgesic effect without the ceiling effect if used at therapeutic doses [13, 22].

The present open-label, post-marketing, multicentre study involved at total of 4,030 patients (1,923 women, 2,024 men). This number included 3,254 (81%) patients with cancer pain and 757 (18.1%) patients with non-cancer pain (musculoskeletal, neuropathic, other pain); the mean patient age was 62.8 years.

The efficacy of transdermal buprenorphine was demonstrated in this study by a decrease in the intensity of pain compared to the previous analgesic treatment in most patients. The efficacy was assessed as very good in 1,630 (41.4%) patients and good in 1,749 (44.5%) patients. A significant decrease in pain intensity measured in the VAS was also seen over the follow-up. Pain intensity was reduced by 73.6% of patients *versus* baseline. The pain decrease observed during the first, second and third follow-up visits compared to baseline was statistically significant ($p < 0.001$). The pain decrease was statistically significant ($p < 0.001$) when comparing the 1st *vs.* 2nd and 2nd *vs.* 3rd visits. It should be emphasised that over the entire follow-up period, few patients were withdrawn from the study due to the lack of efficacy (133 patients, 3.3%). The analgesic activity of the transdermal buprenorphine in this study was comparable to the results reported previously by other authors. In the study by Griessinger et al., good or very good efficacy was reported in 84% of patients; Muriel et al. reported good or very good efficacy in 65.3% of patients in a prospective study and Likar et al. found similar efficacy in 86.6% of patients [17, 19, 20].

This high efficacy of the transdermal buprenorphine at the end of the study depending on the selection of an appropriate effective dose. At the baseline visit, the most commonly used dose was 35 μg/h (73.4% of patients); at subsequent visits, the product doses were modified and individually changed for each patient. The dose of buprenorphine was changed in 44.7% of

patients and was usually increased, but many patients were able to continue a constant dose of transdermal buprenorphine over the follow-up period.

Before starting treatment with transdermal buprenorphine, 758 (18.8%) patients in the study group received no analgesic treatment over the last two months. The remaining patients (81.1%) received analgesic treatment, usually non-opioid or weak opioid analgesics. The most commonly used non-opioid analgesic was ketoprofen (34.1%), and opioid analgesic was tramadol (38.6%). Strong opioids (morphine) were used by only 2.2% of enrolled patients. After the inclusion of transdermal buprenorphine, 48.1% of patients required no additional analgesic treatment other than the study drug. In the study by Schmitz et al., after starting transdermal buprenorphine, 65.5% of patients received additional analgesic treatment; however, it should be emphasised that most patients in this study (95.6%) received analgesic treatment before using buprenorphine with both non-opioid and weak or strong opioids – 26.5% [25]. The data from the study by Griessinger et al. are similar; in that study, 91% of patients included in the study received analgesics, and 19% received strong opioids [13].

Before transdermal buprenorphine, adjuvant treatment was used by 21.9% of patients; after inclusion, adjuvant drugs were used by 51.1% of patients. The most commonly used drugs were amitriptyline and gabapentin. In the study by Schmitz et al., the use of adjuvant drugs was reported in 40.4% of patients, and the most commonly used were antidepressants. The study population for this investigation mainly consisted of patients with cancer-related pain [25]. Before transdermal buprenorphine, antiemetic/laxative drugs had been used by 20.5% of patients as a prophylaxis. During the study, these drugs were used in 21.4% of patients on average. In the Likar et al. study, antiemetic/laxatives were used in 38.9% patients as prophylaxis [17].

Sleep quality is a good marker of the analgesic quality in patients with chronic pain [1, 25]. In our follow-up, over 60% of patients in the study reported an improvement or a significant improvement in sleep quality after using the study product. Our results are similar to the data recently presented by Muriel et al., which observed an improvement in the quality of sleep in 63.2% of patients [19].

The change of the transdermal system was assessed as very easy or easy by most of the study patients (95%). The transdermal system could be used by the patient alone by 46% of the study subjects, whereas in about 42% of patients, the system was changed by family members. In the study by Likar et al., 74.5% of the patients changed their transdermal system on their own [17]. The differences could result from the fact that in the study by Likar et al., 56.1% were patients with cancer pain and 43.9% had non-cancer pain, whereas among our patients, most (80.7%) had cancer pain and often significant disability due to advanced underlying disease.

All of used to pain treatment opioids can cause side effects such as nausea, vomiting, constipation, dry mouth, pruritus, drowsiness, somnolence confusion and respiratory depression [16].

In the study total, adverse drug reactions were the cause for withdrawal of 33 (0.8%) patients from the study. In total, 34 adverse drug reactions were reported, of which 33 (97.05%) were NON-SADR and 1 (2.9%) was SADR, although the analysis of this case showed that it was not related to the study drug and thus, cannot be classified as SADR. In the study by Grissinger et al., the incidence of adverse drug reactions was estimated to be 1% of patients. In this group, the most common adverse drug reactions were vomiting (18), nausea (11), somnolence (7), confusion (6), constipation (7) and respiratory problems (1) [13]. In our follow-up, local skin reactions were the most common adverse drug reactions reported; they represented 50% of all adverse drug reactions reported (0.42% of the study population); the other NON-SADR included the following: vomiting and nausea, 20.5% of the adverse drug reactions (0.17% of the study population); hyperhidrosis and dizziness, each constituting 8.25% of symptoms (0.07% of the study population each); confusion, 5.88% of symptoms (0.04% of the study population); and constipation, only 2.94% of symptoms (0.02% of the study population). In our follow-up, we have not seen respiratory depression, a side effect that is the most significant concern for doctors prescribing opioids. In the study by Likar et al., adverse events that required discontinuation of transdermal buprenorphine were experienced by 42 patients; the most common cause was skin reactions in 24/42 patients and the next was nausea and vomiting, which occurred in 12/42 patients [17]. Previous studies have shown that the long-term use of transdermal buprenorphine is associated with a low incidence of constipation; this low frequency was confirmed in our follow-up, where constipation was not a significant clinical problem. The use of

laxatives during treatment with transdermal buprenorphine did not differ significantly from the use of these agents by the patients before starting treatment with the study drug. We did not observe ADRs. In our study, there were no cases of respiratory depression. The low incidence of adverse drug reactions associated with the central nervous system, reactions which are typical for opioids, may result from the antagonist effect of buprenorphine on the κ receptor [2, 29]. Studies have shown that respiratory depression after using buprenorphine is much less common than after morphine, hydromorphone, methadone, fentanyl [7, 24]. Our clinical observations have been confirmed in the study by Dahan that showed, in both a clinical model and in volunteer experiments, that increasing buprenorphine doses allow for a better analgesic effect with limited respiratory depression compared with fentanyl, a drug that often causes dose-dependent respiratory depression [6].

Our multidirectional studies have confirmed the high efficacy and good tolerability of buprenorphine and, therefore, its utility in the treatment of moderate to severe cancer pain as well as in severe pain in patients with non-cancer pain that cannot be effectively treated with non-opioid analgesics. Previously published data in the Polish population focused on the use of buprenorphine in cancer pain patients alone [4]. It should be noted that our study is the first in Poland to involve such a large group of patients with cancer and non-cancer pain.

Conclusions

Based on the present study, transdermal buprenorphine can be considered an efficient, safe, well-tolerated drug in patients with moderate to severe cancer pain as well as in patients with severe non-malignant pain that cannot be effectively treated with non-opioid drugs. Transdermal buprenorphine was an efficient drug in the assessed population of patients. As shown in our follow-up, consistent with previous studies, transdermal buprenorphine used by both patients with cancer pain and patients with non-cancer pain is a drug of a significant analgesic efficacy in these two groups of patients. At the same time, its safety profile is favorable; as was also noted by some authors; this profile may be due to the mechanism of action of this drug. Transdermal buprenorphine is associated with a low incidence of adverse drug reactions. It is a safe drug that is easy to use for most subjects, and its application methods caused no problems for most patients included in the study.

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