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Pain Management and Costs of a Combination of Oxycodone + Naloxone in Low Back Pain Patients

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1. Introduction

In industrial nations, low back pain (lbp) is one of the leading causes of physical limitation. It is also a main source of incapacitation, suffering and expense. According to the national institute of neurological disorders and stroke in the US, LBP accounts for more sick leave and disability than any other medical condition. In Germany, life time prevalence of LBP reaches up to 84 %, with the highest rate for people aged between 35 and 55. According to the German Health Report of the year 2002, the costs of rehabilitation and early retirement amounted to more than 15 billion € , and direct and indirect cost of illness up to 26 billion EURO. Thus the effective management of low back pain is a major health and economic concern.

In a minority of patients presenting for evaluation in a primary care setting, lbp can be reliably attributed to a specific underlying pathology, such as malignancy, vertebral compression fracture or inflammatory/infectious processes. The majority, 80-90%, of patients present primary or non-specific lbp. There is little documented knowledge of possible causes of non-specific lbp. Risk factors are probably related to genetic predisposition, lifestyle (e.g., overweight, lack of physical activity), physical strain and psychological distress.

Opioid analgesics are well established in the treatment of severe pain conditions and have internationally gained a strong position as a potent daily pain treatment option. Many physicians are still apprehensive about the administration of opioids within a continuous therapy, due to potential drug abuse and possible adverse effects, such as impaired gastrointestinal functioning.

To achieve a satisfactory balance between analgesia and side effects, the assessment and treatment of opioid side effects are fundamental aspects of the therapy. This may increase the likelihood of a favourable treatment outcome, potentially allow higher and more efficacious opioid doses, and improve quality of life by reducing other discomforting symptoms. Economic consequences of insufficiently treated chronic lbp and treatment of potential adverse drug effects also play a significant role from the society's point of view. Additional expenses may include costs that emerge from additional obligatory treatments, hospitalization and work incapacity.

2. Primary objective

The primary objective of this health services research study was to assess the health-related quality of life and the total costs (direct and indirect) of patients in Germany suffering from chronic back pain. Therapy with oxycodone + naloxone¹ was compared to therapy with other strong opioids (WHO-step III opioids).

Main aims are:

- Health related quality of life over a period of one year – patients on therapy with oxycodone + naloxone compared to therapy with other WHO-step III opioids.
- Costs for the pain therapy and therapy of AE/ ADR in in- and out-patients.
- Patients' inability to work, days off work compared between both cohorts.
- The incidence of early retirement due to chronic back pain and the average age of these patients.

3. Secondary objective

The secondary objective of the study was to evaluate the data for effectiveness under daily routine conditions of the therapy with oxycodone + naloxone or other WHO-step III opioids (strong opioids).

Main issues were:

- The long-term effectiveness of treatment of chronic back pain under daily routine conditions with oxycodone + naloxone or other strong opioids (WHO-step III opioids).
- Frequency of the administration of rescue-medication (drugs additionally taken once only, as an emergency treatment of pain) under therapy with oxycodone + naloxone compared to other strong opioids (WHO-step III opioids).

4. Methods

In order to portray the actual costs ("true costs") incurred for patients suffering from chronic back pain, data had to be documented under daily routine conditions ("real-world-design"). Therefore, a cohort study design was chosen. Two cohorts were observed: Patients in the first cohort were treated with oxycodone + naloxone (cohort 1). Patients in the second cohort were treated with another WHO-step III opioid (cohort 2). In accordance with the statistical analysis plan, each participating physician was asked to document five patients per cohort. Because of the non-interventional study design, individual site-specific imbalances due to the cohort recruitment will be discussed from a statistical point of view.

4.1 Patient population

Opioid-naïve and opioid-pretreated female and male adults (> 18 years) who suffered from chronic back pain below the costal arch and above the gluteal groove, who require a round-a-clock-treatment with WHO-step III opioids, were considered. Patients with cancer pain, herniated vertebral disks, or pain caused by an accident, were excluded. Patients who recently started therapy with oxycodone + naloxone or another WHO-step III opioid were also considered, as well as patients, who were switched from a WHO-step

¹ Targin®

II to a WHO-step III opioid or from one WHO-step III opioid to another WHO. The change of therapy was not allowed to be correlated to the study. Consequently, patients treated with oxycodone + naloxone or other WHO-step III opioids were eligible for the study.

For all patients, the summary of product characteristics (SPC) was considered with regard to patient's safety and need to perform daily activities.

Patients not treated according to the SPC were excluded from the study.

4.2 Inclusion and exclusion criteria

- Therapy with oxycodone + naloxone or another WHO-step III opioid was documented for all patients over an observation period of approximately twelve months, including prescription and administration of the medication (regular daily administration, period of administration).
- Patients were informed about the study and agreed to participate by signing and dating the informed consent form.
- Patients were able to comprehend the language as well as the contents of the study materials (patient information, informed consent form and patient questionnaires).
- Patients suffered from chronic back pain below the costal arch and above the gluteal groove.
- Patients with tumor pain, herniated vertebral disks, or pain caused by an accident, were excluded.
- Patients were more than 18 years old.
- oxycodone + naloxone or another WHO-step III opioids were not contraindicated.
- Female patients were neither pregnant nor breastfeeding.

Patients were excluded from the study if any of the following applied:

- A contraindication to the planned treatment regime occurred.
- The patient withdrew his/her consent to participate in the study.
- Newly diagnosed pregnancy.
- Administration of oxycodone + naloxone or another WHO-step III opioid was not in accordance with the specifications of the SPC.

4.3 Duration and conduct of the study

4.3.1 Study sites and number of patients

200 general practitioners and orthopedics, some of them specializing in pain therapy, should be achieved to participate at in this nation-wide, multi-center, non-interventional study. As stated in the observational plan, the enrolment of 2,000 patients (10 patients per physician, 5 patients per cohort) with chronic back pain was required to document patients at baseline (V1), after one week (V2), four weeks (V3), six months (V4) and after 12 months.

4.3.2 Time schedule

Screening and recruitment of the participating physicians were conducted by the Institute of Empirical Health Economics (IfEG) prior to the start of the study. IfEG CRAs started to visit the physicians' medical centers in September 2008. Patients were enrolled by the physicians and observed for one year. Documentation started according to the project schedule after the patients had signed the informed consent form (ICF). An interim analysis was scheduled

approximately six months after the beginning of the observation period. The study-report was due three months after last patient last visit (LPLV).

4.3.3 Patient information and informed consent form (ICF)

Prior to their participation, patients had to sign the ICF. The patient information describes the objectives, contents and risks of the study. Furthermore, the patients were informed that withdrawal from the observational study was possible at any point in time without further consequences. The patient obtained a copy of the patient information and the ICF. The physician is obligated to keep the signed ICF records at least for 15 years.

4.3.4 Documentation of treatment

Socio-demographic data, the clinical variables regarding progress of the disease, as well as the treatment costs incurred for the attending physician were documented on standardized case report forms (CRF). All consultations during the observation period due to chronic back pain were documented. The consultations took place as they would within the scope of the treatment of chronic back pain and no study-specific visits were indicated. Physicians sent the completed CRF by postal service to IfEG.

4.3.5 Documentation by patients

During the observation period, patients actively participated in the documentation by completing standardized health-related quality of life questionnaires (SF-36 v2 Health Survey) at four points in time. Visits took place every quarter and the quality of life questionnaires were completed during the visits.

Intensity of pain and stool consistency was recorded daily for the first four weeks, followed by recording every two weeks on patient diaries.

The patients also completed standardized questionnaires regarding constipation and the pain intensity of the last seven days during each consultation.

4.4 Variables

The variables considered for this report are described in the following sections.

4.4.1 Socio-demographic and administrative variables

The following data were collected regarding at the first visit (V1):

- gender
- date of birth (month/year)
- height
- weight
- ethnic group
- patient's ability to comprehend the patient information and informed consent
- family status
- educational school level and training level
- status of occupation
- status of ability to work (and correlation with chronic back pain)
- exemption from additional payments
- type of health insurance
- physicians' specialization and additional pain therapy qualifications

4.4.2 Clinical variables

The following clinical data were collected at V1:

- diagnosis of chronic back pain (back pain causing disease)
- concomitant diseases
- medical pre-treatment outside of pain therapy
- assessment of previous pain therapy prior to enrolment (by physician and patient)
- other disorders apart from pain indication experienced within the last week before the beginning of observational study (separately for opioid-naïve patients and opioid-pretreated patients)
- previous and current drug therapy for chronic back pain treatment
- change/adjustment/withdrawal of therapy with oxycodone + naloxone or another opioid of WHO-step III
- dosage and application times of the therapy with oxycodone + naloxone or another opioid of WHO-step III
- concomitant medication
- rescue-medication
- assessment of pain, intensity of pain and general mobility of the patient (patient diary)
- average period of analgesia experienced by the patient

4.4.3 Variables of costs

The following variables of costs were included in the cost calculation. For all costs, a causal correlation to the underlying chronic back pain had to exist. Costs for the treatment of adverse events or adverse drug reactions were also included.

- ambulatory treatment costs (consultations including house calls, emergency treatments and medical specialist consultation) contributable to chronic back pain
- type (trade name and active ingredient) and amount (number of packages and package size) of prescribed and recommended drugs
- non-medicinal therapies
- inability to work within the last twelve months before the start and during the observation period
- early retirement
- reduction in earning capacity
- hospitalizations
- other medicinal interventions
- remedies and medical devices
- consultations at other physicians
- emergency treatments
- additional acquisitions or measures taken (e.g. conversion of an apartment)

4.5 Quality of life questionnaires

4.5.1 Quality of life questionnaires (SF-36 v2 Health Survey)

The SF-36 is a multi-purpose, short-form health survey with 36 questions. It provides an 8-scale profile of functional health and well-being scores, as well as a psychometrically-based physical and mental health summary and a preference-based health utility index. It is a

generic measure, as opposed to surveys that target a specific age, disease, or treatment group [16].

The taxonomy has three levels: (1) items; (2) eight scales with 2-10 items each; and (3) two summaries. All but one of the 36 items (self-reported health transition) are used to score the eight SF-36 scales. Each item is used in scoring only one scale.

The SF-36 has the following composition:

- Physical Functioning
- Role-Physical
- Physical Pain
- General Health
- Vitality
- Social Functioning
- Role-Emotional
- Mental Health

The calculations (pole reversal and recalibration of items, missing values, and transformation of scales) of the SF-36-subcales and the physical and mental summation scales are performed with the SSPS-program by Mogens Trab Damsgaard. The SSPS-program is described in the SF-36 manual. The totals from the 8 subscales are subsequently transformed to a percentage scale (co-domain 0-100). Norm-based scoring (NBS) algorithms are introduced for all eight scales and employ a linear T-score transformation with mean = 50 and standard deviation = 10. The weightings of subscales within summation scales are performed with the weight factor used in the American standard sample.

The SF-36 was completed for V1, V3 (after 4 weeks), V4 (after 6 months) and V5 (after 12 months).

4.5.2 Brief Pain Inventory Short Form (BPI-SF)

The Brief Pain Inventory is a standardized method applied for self assessment of pain and its outcomes in an abbreviated form. This inventory encompasses numeric rating scales for pain intensity and reduction in pain contributable to the treatment, as well as a graphic picture. Emphasis is placed on sensory pain components and the documentation of pain-related impairments.

The sum scale for pain intensity contains four questions: to most severe, minimum, and average pain severity experienced during the last 24 hours and at that moment (range 0-10 points per questions, total range 0-40 points). An increase in point score implies an increase in pain.

The sum scale for pain-related impairment consists of seven questions to self assessment of impairment in the daily routine (activity, mood, movement, occupation, relationships, sleep and vitality) within the last 24 hours (range 0-10 points per question, total range 0-70 points).

Cumulative values for pain intensity and pain-related impairment were calculated. An increase in cumulative values implies an increase in pain.

The third factor evaluated pain relief due to the analgesic therapy expressed as a percentage from the baseline value.

The BPI-SF was completed for V1 (beginning), V3 (after 4 weeks), V4 (after 6 months) and V5 (after 12 months).

4.6 Statistical analysis

4.6.1 Data entry

A data entry template for the complete documentation was designed by IfEG by using the program Oracle 11.1.06G. Data entry was conducted successively after CRFs were received.

4.6.2 Handling of dropouts

Patients were defined as dropouts if they were enrolled although the population criteria were not fulfilled, and if they did not receive any study-related medication. Dropouts were completely excluded from the effectiveness analysis.

Withdrawal patients were defined as patients who also include those patients who discontinued the therapy with oxycodone + naloxone or another WHO-step III opioid before the end of the observation period, withdrew their consent, or who became pregnant during the observation period. These patients are included in the effectiveness and efficacy analysis and are not considered to be dropouts, unless the therapy with oxycodone + naloxone or another WHO-step III opioid was administered for less than three months

4.6.3 Study population

The following populations were defined before data analysis:

- Safety-Population (SP): all patients who were included in the observational study and attended at least one follow-up visit
- Intent-to-Treat-Population (ITT-P): all patients for whom at least one examination regarding effectiveness (pain and bowel function) was conducted
- Per-Protocol-Population (PPP): all patients for whom all quarter and all BPI-SF assessment were completely documented

For the Per-Protocol-Population, only the CRFs completed for the whole observation period were considered, whereas for the Intent-To-Treat-Population, all available data were considered. Data in this paper refer to safety-population and intent-to-treat population only.

4.6.4 Statistical analysis

The data analyses are conducted with the software PASW 18.0 for Windows, as well as MS-Excel 2007 and MS-Access 2007. The evaluation is descriptive, based on the character of the documentation. An inferential statistic is performed for the comparison of the cohorts.

5. Analysis and results

5.1 Description of the study population

A total of 1,013 patients from 134 physicians were entered into the database (figure 1). 43 patients had to be excluded from the analysis: Of these, 24 patients did not receive any study-related medication and for 19 patients the physicians did not complete documentation to the end of the study. Therefore, 970 patients were included in the safety population (SP) comprising 583 patients from the cohort "oxycodone + naloxone" (cohort 1) and 371 from the cohort "other WHO-step III opioids" (cohort 2). No cohort classification was possible for 16 patients, because these patients did not take any strong opioid (oxycodone + naloxone or

other WHO-step III opioids). 560 cohort 1 and 364 cohort 2 patients were feasible for the Intent-To-Treat-Population. For the Per-Protocol-Population, 569 patients were included: 345 of cohort 1 and 224 of cohort 2.

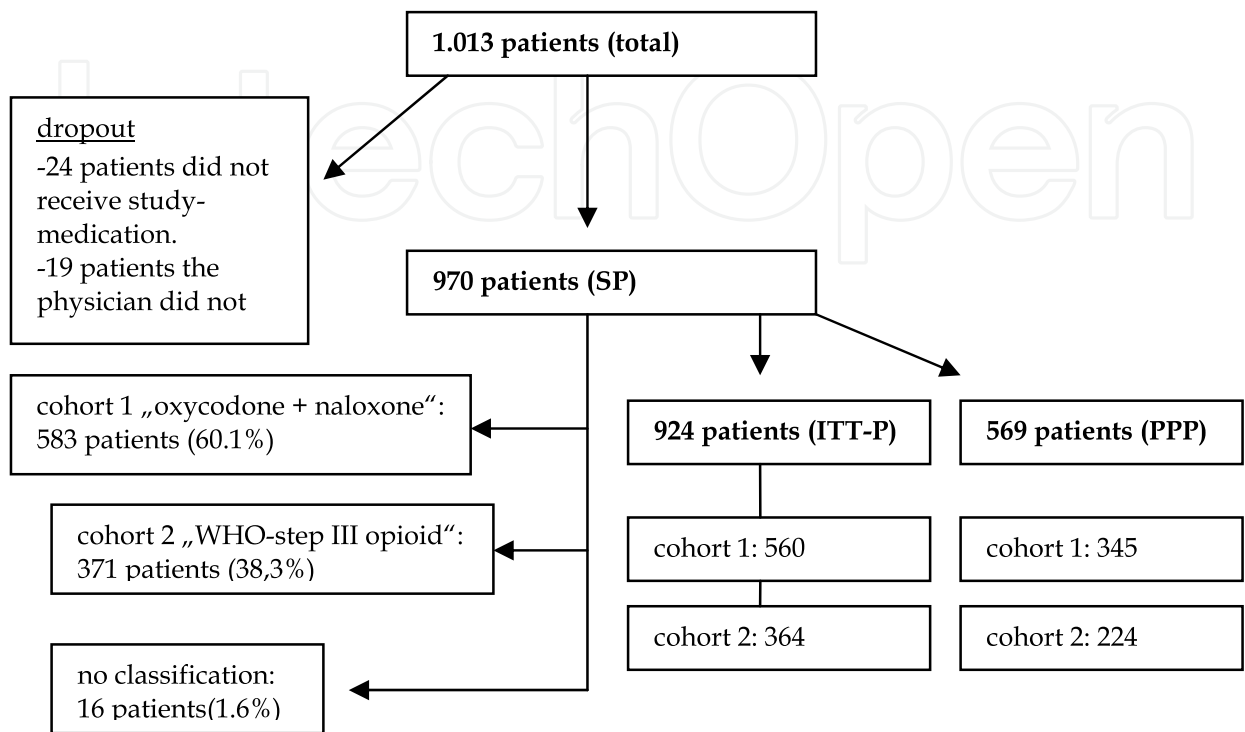


Fig. 1. Organigram of the study population

The majority of the patients were female (~60%) which refers to the epidemiological distribution in Germany within an aging population: the average age was around 64 years and by this most patients had been retired or were of least unable to work. Only 20% of the patients were employed (Table 1).

	cohort 1		cohort 2		p-value
	N	rate	N	rate	
female	350	62,5%	221	60,7%	P= 0,585
male	210	37,5%	143	39,3%	
age	560	63,4	364	64,9	p = 0,084
employed	121	21,6%	62	17,0%	p = 0,088
number of days off work 12 months before inclusion	81	75,0	40	95,4	p = 0,496

Table 1. Gender and age of the population

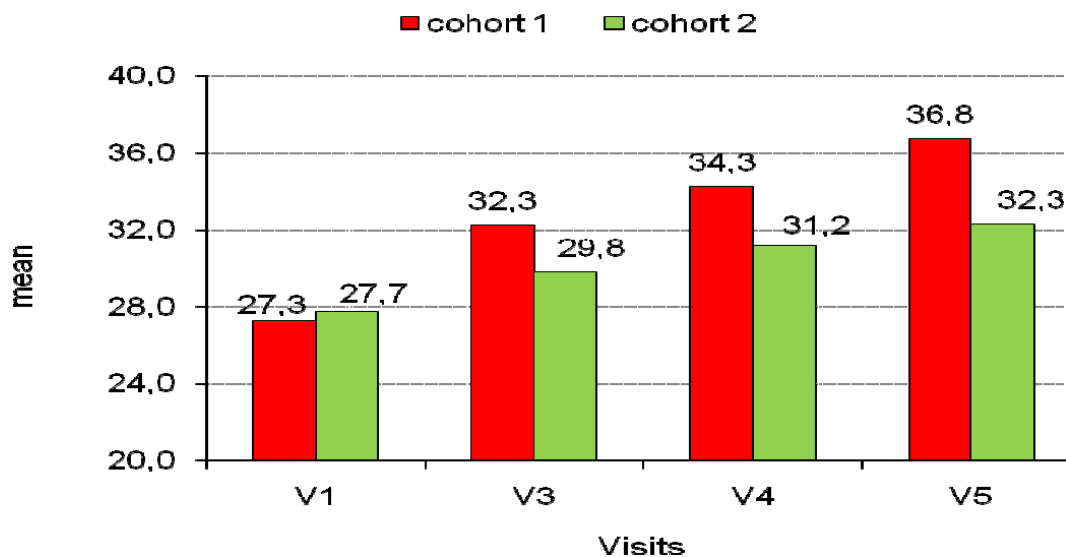
Almost all patients were classified as caucasians, more than half of the patients were married and app. 50% had an educational level above secondary general school. Less than 7% were ensured privately.

At visit 1 924 days off work in the last year were documented for both cohorts (560 in cohort 1). 17% of the included patients reported a reduction in earning capacity. 14,6% in cohort 1 and 16,8% in cohort 2 had been retired early due to chronic back pain.

Nearly 45% (!) of all patients reported a poor effectiveness of the applied pain therapies. During the course of the study both physicians and patients assessed a higher effectiveness increase in cohort 1 compared to cohort 2. This refers also to tolerability.

5.2 Quality of life
5.2.1 SF-36

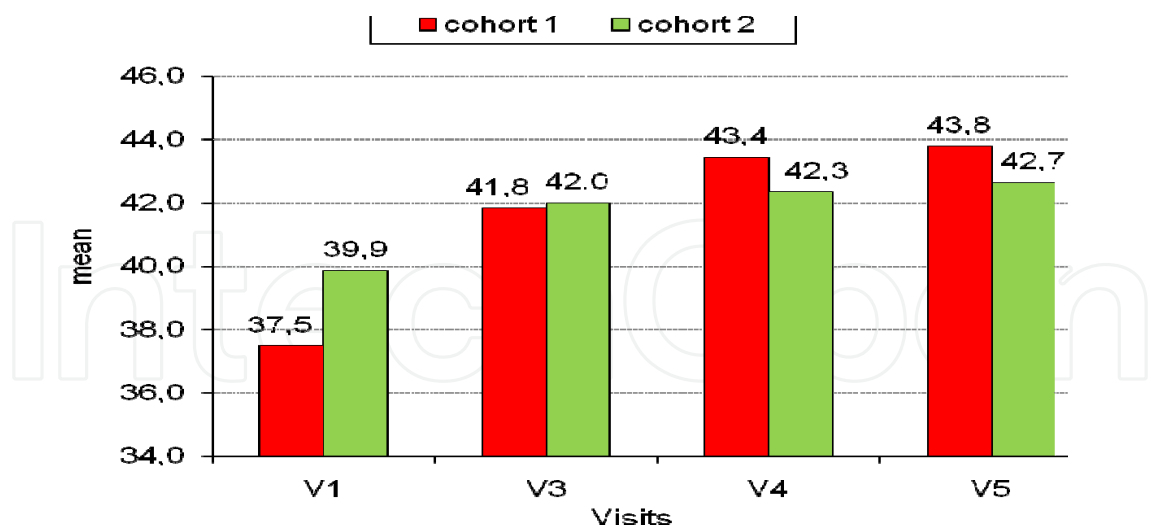
Figure 2 shows the results of the SF-36 evaluation for physical health.



	cohort 1			cohort 2			
	number	mean	SD	number	mean	SD	p-value
Standardized physical health	356	9,65	10,29	244	4,55	8,90	p < 0,001

Fig. 2. Standardized physical health SF-36 (means)

The difference between the physical health of cohort 1 compared to cohort 2 were significant for the periods V5>V3, V3>V1, V4 >V1 and V5>V4. The results for both cohorts indicate a continuous improvement, which was more pronounced in cohort 1. This result is also mirrored by the data on standardized mental health (Figure 3).



	cohort 1			cohort 2			
	number	mean	SD	number	mean	SD	p-value
Standardized mental health	356	6,34	12,82	244	2,58	12,33	p < 0,001

Fig. 3. Standardized mental health SF-36 (means)

In total statistical power reached significant level for all SF-36 positions except “Role-emotional” (Table 2). All items and positions of the SF-36 were in favour of the combination of oxycodone + naloxone.

SF-36 Positions	cohort 1			cohort 2			p-value
	number	mean	SD	number	mean	SD	
1 Physical function	392	23,09	29,79	272	8,52	26,36	< 0,001
2 Role-physical	370	31,28	44,62	261	16,44	41,15	< 0,001
3 Bodily Pain	379	25,66	25,97	263	11,97	19,10	< 0,001
4 General health	375	13,32	22,64	257	6,16	17,76	< 0,001
5 Vitality	376	16,21	22,64	261	5,77	18,69	< 0,001
6 Social functioning	377	19,46	28,50	263	6,65	25,91	< 0,001
7 Role-emotional	363	22,87	56,34	252	14,02	54,19	0,057
8 Mental health	376	15,13	22,88	261	6,27	19,75	< 0,001

Table 2. Summary of SF-36 positions

5.2.2 Brief Pain Inventory Short Form (BPI-SF)

The Brief Pain Inventory Short Form (BPI-SF) contains numeric rating scales for pain intensity and pain impairment as well as for pain relief. Fig. 4 shows the differences between

the total scores of pain intensity. Significant differences were found between cohort 1 and cohort 2 at V5, V4 and V3 compared to V1. Significant differences were also determined for the time periods V3 to V5 and V3 to V4.

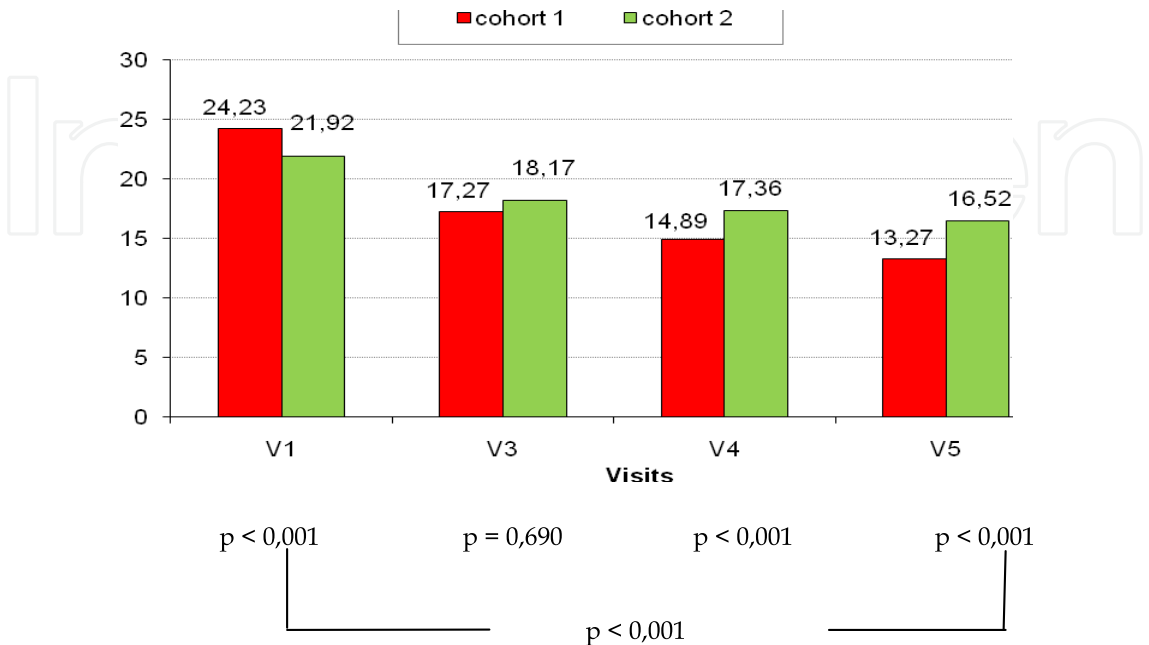


Fig. 4. Sum scale of pain intensity (means)
Brief Pain Inventory (BPI-Shortform)

Worst pain in the last 24 hours decreased in cohort 1 more over all periods than in cohort 2 although worst pain was significantly higher in cohort 1 at baseline (V1). After 12 months (V5) both cohorts revealed highly significant differences (Fig. 5).

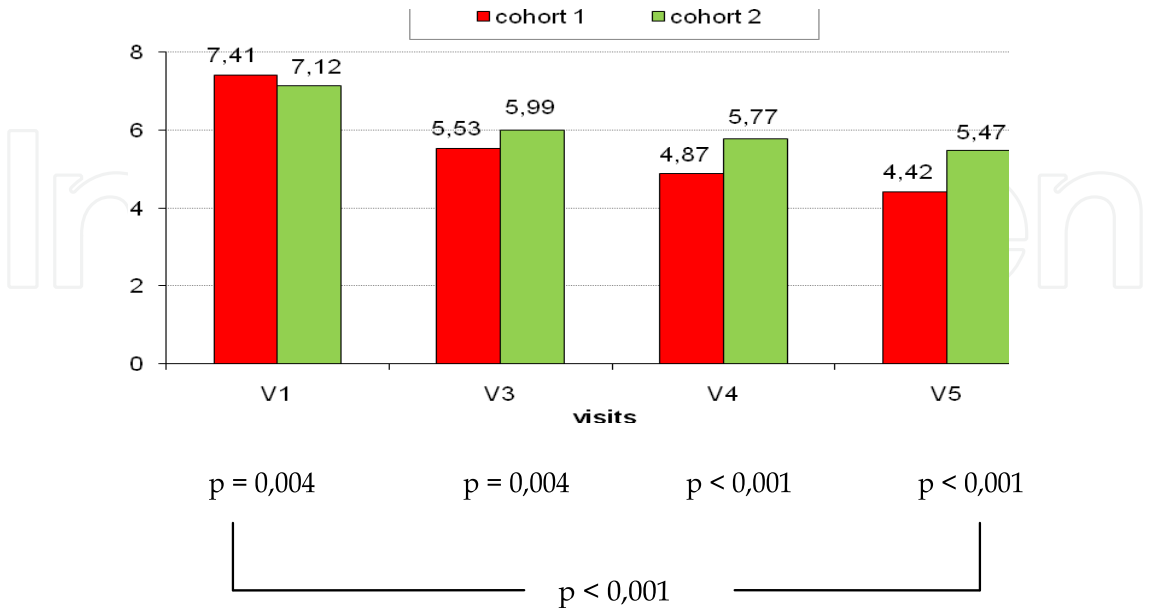


Fig. 5. Worst pain in the last 24 hours (means)
Brief Pain Inventory (BPI-Shortform)

Pain relief treatments or medications administered were also recorded. The patients had to mark the percentage that represents how much pain relief they have experienced (0%=no relief, 100%=complete relief). The pain relief of cohort 1 patients compared to cohort 2 was significant at V1 ($p < 0.001$) and at V5 ($p = 0.001$). At visit 1 the pain relief on average amounted to 39.2 % in cohort 1 and to 46.02 % in cohort 2. At the end of the study (V5) the averaged pain relief was 64.2 % in cohort 1 and 58.9 % in cohort 2 (Fig. 6).

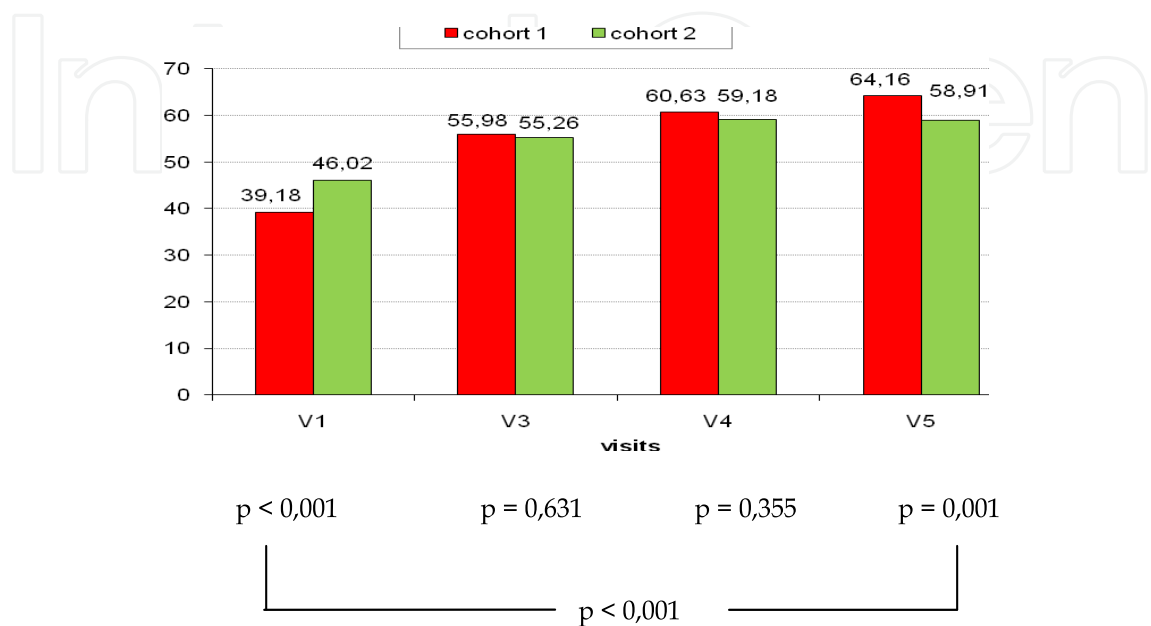


Fig. 6. Pain relief (means)
Brief Pain Inventory (BPI-Shortform)

6. Costs

Annual average direct costs of 2,403.45 € accumulated per patient in cohort 1 and 2,772.98 € per patient in cohort 2. The difference in annual average costs was not significant ($p = 0.195$). The approximately 13 % lower amount incurred in cohort 1 can be attributed to drug expenses, emergency treatment and hospitalisation/rehabilitation. The differences between both cohorts were significant for co-medication ($p < 0.001$) and rescue-medication ($p = 0.021$) (Tab. 3).

cost category	total	cohort 1	cohort 2
out-patient treatment	477,03 €	481,79 €	469,71 €
drug expenses	1.653,73 €	1.532,69 €	1.839,93 €
oxycodone + naloxone	812,17 €	1.270,16 €	107,57 €
opioid WHO-III	611,68 €	65,04 €	1.452,67 €
comedication	211,51 €	181,83 €	257,16 €
rescue medication	18,37 €	15,67 €	22,54 €
remedies	34,20 €	31,07 €	39,03 €
non-medical therapy	54,95 €	53,11 €	57,79 €
emergency treatments	64,76 €	52,57 €	83,52 €
hospitalization/rehabilitation	264,35 €	252,22 €	283,01 €
direct costs	2.549,02 €	2.403,45 €	2.772,98 €

Table 3. Direct costs categories

Fig. 7 shows the indirect costs for the cohorts. Higher averaged indirect costs per patient were calculated for cohort 2. The higher indirect costs resulted from higher costs due to reduction in earning capacity. Approximately 26 % less costs were documented for cohort 1 patients than for cohort 2 patients in this part of indirect costs.

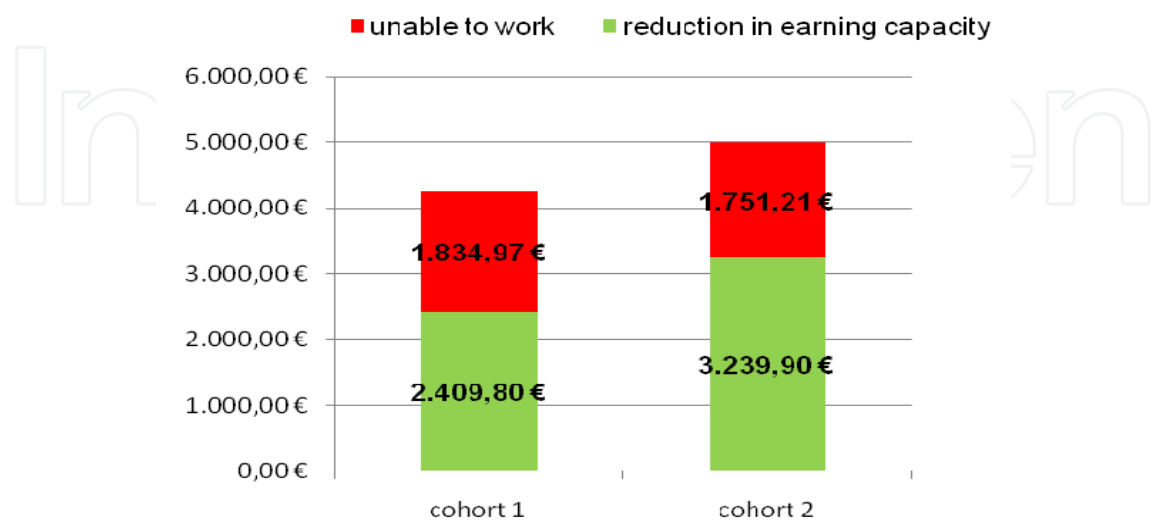


Fig. 7. Indirect cost categories for the cohorts

The incremental cost-effectiveness ratio (ICER) represents the ratio between the differences in treatment costs (ΔC) and treatment effects (ΔE) for cohort OXN and cohort “other strong opioids”. It presents the cost of an additional effect unit. The ICER was tested against the main parameters (Tab. 4).

parameter	cohort 1		cohort 2		ICER	$\Delta C/\Delta E$
	ΔE	CER	ΔE	CER		
direct costs (C)	2,403 €		2,773 €		---	-370 €
SF-36 (physical health)	9.65	249 €	4.55	610 €	-72 €	-370 €/5.10
SF-36 (mental health)	6.34	379 €	2.58	1,074 €	-98 €	-370 €/3.76
BPI-SF (pain relief)	24.14	100 €	12.44	223 €	-32 €	-370 €/11.7
CER: Cost-Effectiveness Ratio; ICER: Incremental Cost-Effectiveness Ratio						

Table 4. Cost-effectiveness ratio

The following formula was used for the calculation of the incremental cost-effectiveness ratio:

$$ICER = \frac{(\text{costs of cohort OXN}) - (\text{costs of cohort "other strong opioids"})}{(\text{effect of cohort OXN}) - (\text{effect of cohort "other strong opioids"})} = \frac{\text{cost difference}}{\text{effect difference}}$$

$$ICER = \frac{\bar{C}_{\text{cohort OXN}} - \bar{C}_{\text{cohort "other strong opioids"}}}{\bar{E}_{\text{cohort OXN}} - \bar{E}_{\text{cohort "other strong opioids"}}} = \frac{\Delta \bar{C}}{\Delta \bar{E}}$$

Negative values were calculated for the ICER of the main parameters, which implies more effectiveness at a lower price for the alternative therapy with Oxycodone + Naloxone (Fig. 8).

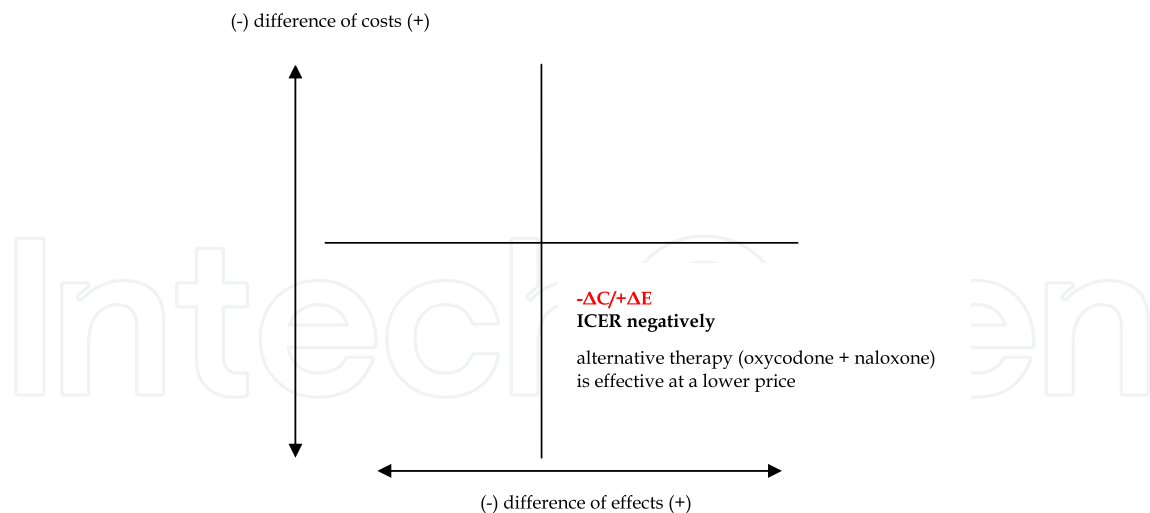


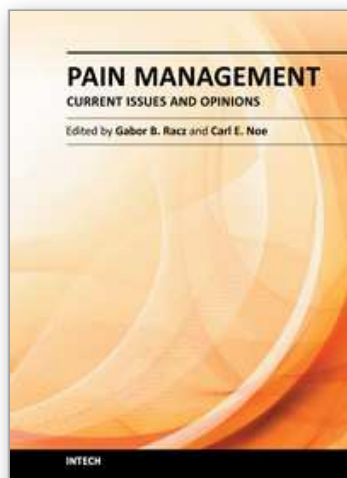
Fig. 8. Cost-effectiveness area

7. Conclusion

As a final conclusion it can be stated that patients of cohort 1 (oxycodone + naloxone) experienced a better quality of life and less back pain after twelve months compared to patients of cohort 2 (other WHO-step III opioids). According to the cost effectiveness-analysis therapy with oxycodone + naloxone is more effective and generates lower costs than cohort 2. These results and findings should be confirmed by a randomized, blinded controlled trial.

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Pain Management - Current Issues and Opinions is written by international experts who cover a number of topics about current pain management problems, and gives the reader a glimpse into the future of pain treatment. Several chapters report original research, while others summarize clinical information with specific treatment options. The international mix of authors reflects the "casting of a broad net" to recruit authors on the cutting edge of their area of interest. Pain Management - Current Issues and Opinions is a must read for the up-to-date pain clinician.

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