AUS DER KLINIK FÜR ANÄSTHESIE UND INTENSIVTHERAPIE
DES FACHBEREICHS MEDIZIN DER PHILIPPS-UNIVERSITÄT MARBURG
GESCHÄFTSFÜHRENDER DIREKTOR: PROF. DR. HINNERK WULF

Does opioid therapy improve the quality of life in patients with chronic pain?

A systematic review and meta-analysis

Inaugural-Dissertation zur Erlangung des Doktorgrades der gesamten Humanmedizin

dem Fachbereich Medizin der Philipps-Universität Marburg vorgelegt von

Karl Vincent León Kraft aus Reutlingen

Marburg, 2022

Angenommen vom Fachbereich Medizin der Philipps-Universität Marburg am 23. Sept. 2022

Dekanin: **Prof. Dr. Denise Hilfiker-Kleiner**

Referent: **Prof. Dr. Leopold Eberhart**

1. Koreferent/in: **PD Dr. H. Sitter**

Table of contents

List of figures

List of tables

Chapter 1

Introduction

1.1 Opioids - perfect drugs for chronic pain?

Without a doubt, pain is one of the most frequently mentioned symptoms associated with illness and injury. Often even the simple sensation of pain defines the boundary between being healthy and being sick. If acute pain, whose cause can often be remedied, becomes chronic, it will accompany the patient for a long lifetime. Not surprisingly, *chronic pain* can affect a variety of different aspects of a patient's life. A good therapy has to consider this.

Chronic pain is usually defined as lasting for at least three to six months. [79] It affects estimated 10-30 % of the world-wide population. [8, 28–30] Undoubtedly chronic pain is a major health issue with high social and economic impact on the society. [42, 18] Chronic pain affects sleep [59], mood and emotional health [15, 101], daily activities and social life [18, 8, 75]. After all, it affects the patient's entire *quality of life*. [8, 67, 72, 61, 47, 88, 41] So, if a therapy for chronic pain is only focusing on its effects on pain, several important aspects would be neglected. Therefore in the evaluation of a therapeutic strategy, not only pain relief should be considered, but also the patient's quality of life.

Opioids are among the oldest and most powerful agents used for anesthesia. Opium, which gave its name to this group of substances, was used in the Middle East as early as 4000 BC due to its analgesic and euphoric effects. In 1806 Sertüner isolated morphium, 41 years before its chemical formula was found. [62] Today, opioids are an indispensable part of modern pain therapy.

Whereas opioids nowadays are accepted as treatment for severe or malignant pain, their use in chronic, non-malignant pain remains controversial. [4, 87, 11] However, worldwide the number of opioid prescriptions increased significantly over the last decades. [73, 45, 100] In the US in 2016 4% of the adult population misused prescription opioids, while 33000

people died due opioid overdose. [70, 69] The death rate of heroine increased by 20 % from 2014 to 2015 [74]. This trend is not limited to the use of illicit opioids. From 2000 to 2014, the death rate caused by overdose of prescription opioids quadrupled. Finally in 2017 the US administration declared the opioid crisis a public health emergency. One of the factors of this development may be the increased availability of prescription drugs, starting in 1996 with the introduction of OxyContin, a new formulation of oxycodone, which was heavily promoted and whose prescription numbers increased rapidly over the next few years. [74]

However, the opioid crisis has led to a nationwide discussion to what extent medical prescription practices need to be reconsidered [24, 60] The high analgesic potential and efficiency of the drugs is associated with a broad spectrum of possible adverse events, ranging from constipation and emesis to dependency and overdose. [24, 22, 38] Because these side effects interfere with the patient's life in many ways it becomes clear, that a efficiency assessment of drug therapy should not only include pain intensity measurements and adverse events as separated dimensions but also a measurement of the patient's quality of life.

1.2 Health-related quality of life - a better outcome measurement?

Now what *is* quality of life (QoL)? Individually, everyone will be able to define the meaning of quality of life for him or herself, but giving a general and objective definition is difficult. Moreover, everyone would confirm the importance of QoL for his or her own level of satisfaction and well-being.

Dealing with chronic diseases in an aging society, clinicians should not exclusively focus medical action on curing diseases and preventing death. The self-perceived well-being becomes more and more important, as the patients want to live, not only to survive. [49] Therefore, adapted to the needs of modern medicine, the evaluation of QoL turns out to be an essential tool for assessing therapy outcome. Enhancing QoL should be concerned as a therapeutic goal.

But prior to aiming on QoL, the concept behind it must be defined. The World Health Organization (WHO) defines the concept of *health* as a

> state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. [98]

Table 1.1 HRQL assessment: primary and additional dimensions, according to [25]

Primary dimensions	Physical functioning
	Social functioning
	Psychological functioning
	Perceptions of well-being and health status
Additional dimensions	Neuropsychological functioning
	Personal productivity
	Intimacy and sexual functioning
	Sleep
	Pain
	Symptomes of specific diseases

Since this is a broad and multi-dimensional definition of health, measuring it becomes a difficult task. The model of quality of life is an approach to this problem. The WHO defines this term as

> individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. [97]

This definition is focusing on the individual and subjective perceptions of health and environmental factors. The term *health-related quality of life* (HRQL) narrows the model down to the aspects which are relevant from a medical point of view. However, according to this definition, the specific dimensions which should be included in HRQL analysis remain vague after all. Berzon et al. defined four primary dimensions of HRQL: physical health, social health, mental health and individual's perception of function and well-being. [7] Any HRQL measure should consider these essential dimensions. However, in some cases, aiming at specific interventions or diseases, less or even additional dimensions are needed to ensure an appropiate HRQL assessment. Primary and additional dimensions are listed in Table 1.1.

Chronic pain has a broad effect on patient's life. Most of the dimensions of HRQL listed above are potentially impacted by chronic pain. Obviously, the primary dimensions, like physical and social functioning or the patient's own perceptions of well-being, will be affected by chronic pain. Moreover it seems reasonable to assess additional dimensions like pain, sleep or sexual functioning. The specific adverse effects of opioids, like constipation or drowsiness may also affect different dimensions. On the other hand, an effective therapy with opioids, could improve these different aspects with different effect sizes.

So, to cope with the complex mutual interactions between pain, therapy and the individual patient, a multi-dimensional assessment of HRQL is an adequate tool to assess the effectiveness of the treatment. Furthermore, the specific therapy with opioids bears the potential of serious side effects, which would be reflected in the multi-dimensional measure. This is not the case if the assessment focuses on only one single-dimensional scale. Compared to the widely known pain scales, like the visual analog scale (VAS) or the numeric rating scale (NRS), a HRQL measure is a more valuable tool for any physician for reflection and reasoning of a treatment decision. Thus every HRQL assessment consists of a pain scale, but is not limited to it. For clinical decision-making sum scores of HRQL assessments are also available. So, eventually in daily practice it ends up in having one single number. But this number contains lots of more relevant information than a single pain score does.

1.3 Chronic pain, opioids and HRQL

We have now reached the key question to be answered in this review.

Does opioid therapy improve HRQL in chronic pain?

This question is important in many ways.

First, HRQL as a multi-dimensional approach can help to fully capture the interactions between highly potent drugs, chronic pain and patient. HRQL assessment allows the clinicians to have an insight into what matters: the patient's subjective benefit or harm from a therapy. In the light of the discussion about increased opioid prescriptions, like set out in section 1.1, this issue will continue to gain importance. Moreover, therapy of chronic pain and underlying chronic diseases is always a long-term issue. Compared to acute diseases relevant outcome is no longer binary and single-dimensional like "pain/no pain" or "healed/still ill". Like pointed out in section 1.2, relevant outcome is rather an image composed out of different factors on continuous scales.

Because patients often have to live *with* pain for a long period or even the rest of their lives, information on patients' subjective well-being and HRQL become crucial for designing a therapeutic strategy. Therefore, the question if opioids increase HRQL in chronic pain patients or not, is important in clinical decision making. The answer to this question would be a further argument for a physician, deciding whether a patient with chronic pain should receive opioids or an alternative medication.

The current evidence regarding this issue is of weak quality though. Whereas acute effects of opioids are well described, their general long-term efficiency [87] as well as their impact

on HRQL in chronic pain patients is still discussed controversially. Looking at the current research state, two systematic reviews focused on long-term effects and safety of opioids in chronic pain, also investigated HRQL as an endpoint. However, Chou et al. (2015) included no suitable study [12], whereas Noble et al. (2010) judged the findings as "inconclusive" [57]. A further review about opioids in neuropathic pain included HRQL as secondary endpoint, but could not demonstrate an improvement. [51] In 2005 Devulder et al. published a review which examined the impact of opioids on HRQL in chronic non-malignant pain. They included eleven studies and found little- to medium-quality evidence for an improvement of HRQL. [16] However, from today's perspective this statement is no longer tenable, due to obsolete methodological aspects of the review. In addition, since the number of studies on this topic increased significantly, a new analysis became necessary.

The goal of this systematic review is to evaluate the impact of opioid therapy on HRQL in chronic pain patients. To ensure high standards, the review has been done according to the PRISMA statement. [55] This summary of the current evidence could also show gaps in literature and indicate further research needs on this clinical important question.

Chapter 2

Theoretical Foundations

2.1 Chronic pain

As introduced in section 1.1 chronic pain is a worldwide major health problem with high socio-economic impact on our society. Primarily, the term “chronic” refers to the duration of pain of at least three to six months. But chronic pain is not merely a temporal prolongation of acute pain. There may also be qualitative diffences. This aspect is clarified below.

Pain in general can be categorized in terms of different features, like time course, location or underlying pathology. [77] However, these are not strictly divided classifications and overlap with each other.[1] Regarding the underlying mechanisms of pain generation, a commonly clinically used division is *nociceptive* pain versus *neuropathic* pain.

Nociceptive pain is due to extern noxious stimuli or tissue damage, which activate specialized sensory neurons, so called nociceptors. The signal is then transmitted to the spinal cord and the brain. To ensure that only potentially harmful stimuli could provoke a sensory response, the nociceptive system is a high-threshold system. It functions as a warning device, protecting the organism from threat and possible damage. Therefore nociceptive pain is a vital physiologic sensation.[2] [95]

Neuropathic pain, on the other hand, is caused by direct lesion to the nervous system. The lesions may be in the peripheral nervous system, as in diabetic polyneuropathy, or in the

[1] The ICD-11 classification for chronic pain suggests seven different categories, integrating different aspects like location, etiology and pathophysiology into one classification. [79] Nevertheless, this review uses classifications with regard to underlying pathomechanism (nociceptive pain versus neuropathic pain) and - albeit rarely - pathology (cancer pain versus non-cancer pain).

[2] Under certain circumstances, it could make sense to distinguish *inflammatory* pain from nociceptive pain. Inflammatory pain is caused by inflammatory response to tissue damage and should physiologically promote the healing process. [95] However in clinical context, inflammatory pain, as in rheumatoid arthritis or after surgery, is subsumed under nociceptive pain.

central nervous system, as in multiple sclerosis. This maladaptive pain may be disconnected from actual tissue damage and has no function for healing. The pain reaction to an noxious stimulus may be amplified and prolonged. Also pain may arise from a low-intensity, normally harmless stimulus, or spontaneously, without any stimulus.[3] [95]

So, chronic pain can be categorized into either nociceptive or neuropathic pain. If both pain types are present, the pain is referred to as being *mixed* pain. This categorization is made due to different criteria, like etiology, location and character of pain. Therefore the categorization is a clinical one. However, in a clinical setting, this decision may not be so obvious, because chronic diseases show often both components to different extent. As mentioned above, the transition of acute pain to chronic pain is not simply a matter of time, but may also include qualitative changes. The changes on the molecular and neural level during chronification of pain are current research topics. Processes such as long-term potentiation [39, 85] and pain wind-up [85, 82] take place at the dorsal root, leading to an enhancement of pain response and sensitivity. Due to neural and structural plasticity of the brain, chronic pain is associated with shifts of cortical representation, changes in functional connectivity and structural alterations of grey and white matter. [39] Moreover, genetic factors [17], psychological stress and evironmental triggers are associated with pain amplification and increased risk for chronic pain. [14] Due to this alterations in pain generation and signal procession chronic pain may lose any physiologic functionality. Chronic pain becomes a disease *itself*. Therefore, like mentioned above, chronic pain is not simply a temporal continuum of acute pain. [39]

Finally, it is worth mentioning that pain can also be classified in a cancer or malignant pain and a non-cancer or benign pain, according to its underlying disease. [77] But, there are also critical voices, arguing that this categorization is obsolete and misleading in its clinical implications. [64] However, this terminology is also considered in this review as many studies explicitly refer to it.

2.2 Opioids

The term *opioids* is a collective term and refers to various substances, all of which act on opioid receptors. *Opiates* are substances naturally found in the opium poppy plant (Papaver somniferum), such as morphine or codeine. The next step to modern opioid pharmacology

[3] *Functional* pain is caused by abnormal responseviness of the nervous system, without a lesion or neurological deficit being detectable, as in fibromyalgia. [95] In this review it is referred to as neuropathic pain or mixed pain, because functional diseases often show simultaneously neuropathic and nociceptive pain characteristics.

was the development of semi-synthetic opioids. These semi-synthetic opioids, like dihydrocodeine or heroine, are modifications of natural substances with changed pharmacological profile. In the late 1930s meperidine (pethidine) and methadone, the first fully-synthetic opioids, were synthetized. [9] Nowadays, there are plenty of different synthetic opioids on the market with different efficacy and safety profiles. [62]

All opioids are acting on the three opioid receptors, which are named μ, κ and δ.[4] These G-protein-coupled receptors[5] are expressed in the central and peripheral nervous system, but also within peripheral tissue of non-neural origin, such as the vas deferens or the knee joint. [62] This pain control and inhibition system is actived physiologically by endogenous ligands, like endorphins or dynorphins. Analgetic effects are mainly mediated through activation of μ-receptors in the midbrain or the spinal dorsal horn. Also peripher afferent neurons can be inhibited directly. In general, activation of the μ-receptor causes the main supraspinal analgesic effects, but is also responsible for common side-effects, like sedation, constipation and respiratory depression. The κ-receptor induces spinal analgesia, diuresis and dysphoria, while the δ-receptor may cause supraspinal and spinal analgesia. [62, 80] Besides other factors, molecular mechanism of receptor signaling may also play a role in development of tolerance and addiction. [2]

The potency of a given opioid depends on its affinity to the opioid receptors and its intrinsic activity. Hereby, the affinity describes the ability to bind to the receptor, whereas the intrinsic activity characterizes the capability to induce a functional response, that is, a conformational change of the receptor. Differencies in the pharmacological potencies of distinct opioids have also clinical implications. The WHO in 1986 published the "analgesic ladder", a therapeutic scheme for cancer pain relief. [96] This scheme differentiates between weak and strong opioids. Weak opioids, like codeine, are given at step two, while strong opioids, like morphine or buprenorphine, are reserved for step three. However, the definitive effect of opioids depends also on their route of administration and dose. But, due to low intrinsic activity, causing a ceiling effect, increase in dose may be limited in low-potency, weak opioids. Equianalgesic tables may be helpful in comparing different opioids at different doses [56] and are used for this review as a approximate guide.

As opioids have strong pharmacological effects on patient's mind and body, whenever it is possible, their use should be evidence-based to provide optimal efficacy and safety. In the

[4]The International Union of Pharmacology renamed the receptors in MOP, KOP and DOP, but the old nomenclature can still be used in parallel.

[5]There is also a fourth opioid receptor, the nociceptin receptor (NOP), which, for reasons of clarity, cannot be discussed in detail here.

light of the massive increase of opioid prescriptions, as described in section 1.1, this aspect becomes even more important.

2.3 Assessment tools of quality of life

In section 1.2 the idea of HRQL was introduced. To sufficiently work with this concept, further specifications and concepts are necessary. This chapter will introduce this concepts and some well-known HRQL questionnaires, which were included in this review.

2.3.1 Generic versus condition-specific measures

Assessment tools of HRQL could either be generic or condition-specific measures. Generic measures are designed for use in a broad spectrum of different diseases, conditions or therapies. [63] Examples for generic measures are the Short-Form-36 Health Survey (SF-36) [92] and the questionnaire of the EuroQol-Group (EQ-5D) [66]. Generic assessment tools allow a comparison between different populations. In other words, generic measures are independent of the individual's health state, because they can cover the full range of HRQL status. [10]

Whereas generic questionnaires are good at comparing different populations between each other, they may lack of detecting small changes under specific conditions. For this purpose, condition- or disease-specific HRQL measures were created. Disease-specific measures focus on relevant aspects for specific diseases or conditions. This allows the clinician to quickly assess the effectiveness of therapy for a specific disease.

An example for an disease-specific measurement is the The European Organization for Research and Treatment of Cancer Questionnaire (QLQ-C30) [1] which focuses on patients suffering from cancer. Here, mainly symptoms of oncologic patients in the clinical setting were considered. Other questionnaires adress even a more specific patient population like the King's Health Questionnaire (KHQ) for bladder insufficiency [43] or the Western Ontario and McMaster Osteoarthritis Index (WOMAC), which assesses functionality in osteoarthritis [48]. Table 2.1 shows a brief comparison of the different dimensions assessed by the generic SF-36 and the disease-specific QLQ-C30 and KHQ. Apparently, the questionnaires share several common dimensions in the physical (1st section of the table) and mental category (2nd section) of HRQL. The generic SF-36 reflects eight dimensions of general quality of life in great detail by using 36 individual items. The specific QLQ-C30 for cancer patients also gives a good overview of general quality of life dimensions (17 items). In addition, it also

Table 2.1 Dimensions of SF-36 [91], QLQ-C30 [1] and KHQ [43] in comparison. The dimensions are grouped by physical and mental components, as well as additional disease-specific symptoms. Dimensions related specifically to “bladder problems” are marked (*).

SF-36	QLQ-C30	KHQ
Physical functioning	Physical functioning	Physical limitation*
		Incontinence impact on life
Role-Physical	Role functioning	Role limitations*
Bodily pain	Pain	
General health	Global health	General health
Vitality		Sleep / energy*
Social functioning	Social functioning	Social limitations*
		Personal relationships*
Role-Emotional	Emotional functioning	Emotions*
Mental health	Cognitive functioning	
	Diverse symptoms (fatigue, nausea, dyspnoe, appetite loss…)	Severity measures and symptoms (frequency of urination, nocturia, urgency…)

asks about specific symptoms experienced by cancer patients (13 items). The KHQ, as the most specific of the three questionnaires, considers restrictions in general quality of life caused by "bladder problems" (16 items) and measures additional symptoms of incontinence (14 items).

In general, disease-specific questionnaires are capable of capture small changes in health status, as they include questions about disease-specific symptoms or impairments. Under specific circumstances specific questionnaires may have a greater responsiveness than generic HRQL tools. [93] However, as a disease-specific measure has a specific and limited functional scope, it cannot be applicated to another disease or compared with a non-patient reference population. The generalizability - or extern validity - of answers and conclusions, obtained in this way, is therefore limited to this specific condition.

This review wants to answer the general question whether opioids improve the HRQL in pain patients. There were no restrictions to specific diseases. A general conclusion is only possible if the assessment of HRQL is comparable throughout the various diseases, included in this review. Therefore studies, which assessed only a single disease-specific HRQL or functionality measure, such as the WOMAC or the QLQ-C30, were not included in this

Table 2.2 Dimensions of SF-36, according to [49]

PF:	Physical functioning
RP:	Role limitations due to physical health
SF:	Social functioning
BP:	Bodily pain
GH:	General mental health, covering psychological distress and well-being
RE:	Role-limitations due to emotional problems
VT:	Vitality, energy, fatigue
GH:	General health perceptions

review. So, this work mainly includes results from the generic questionnaires EQ-5D and SF-36.

In the following sections some of these generic or pain-specific HRQL measures are introduced.

2.3.2 Short-Form-36 Health Survey

The SF-36 is a generic HRQL questionnaire. It is based on the Medical Outcome Study (MOS) surveys, which include 20 different concepts and assess the health status of the patient in a comprehensive way. [92] The SF-36 contains eight different dimensions, which are depicted in table 2.2, and two summary scores, the Physical Component Summary Score (PCS) and the Mental Component Summary Score (MCS).

The final scores range from 0 (the worst possible HRQL status) to 100 (the best possible HRQL status). So, higher values indicate a better HRQL. Besides a simple, additive evaluation of this scores, there is also a normalized approach available. In this approach the score is standardized with population norms to a mean of 50 and a standard deviation of 10. [49] This fascilitates the interpretation of the results with regard to the standard population values.

A shorter version of the SF-36, is the SF-12 questionnaire. The SF-12 is an eight-dimension, well-validated generic HRQL measure, which contains less items per dimension than its more extensive pendant. The sum scores of the SF-12 should closely mirror the results of the SF-36, but at costs of a higher standard error. [91] Besides the SF-12 also other versions and variations of the SF-36 and the MOS questionnaires exist.

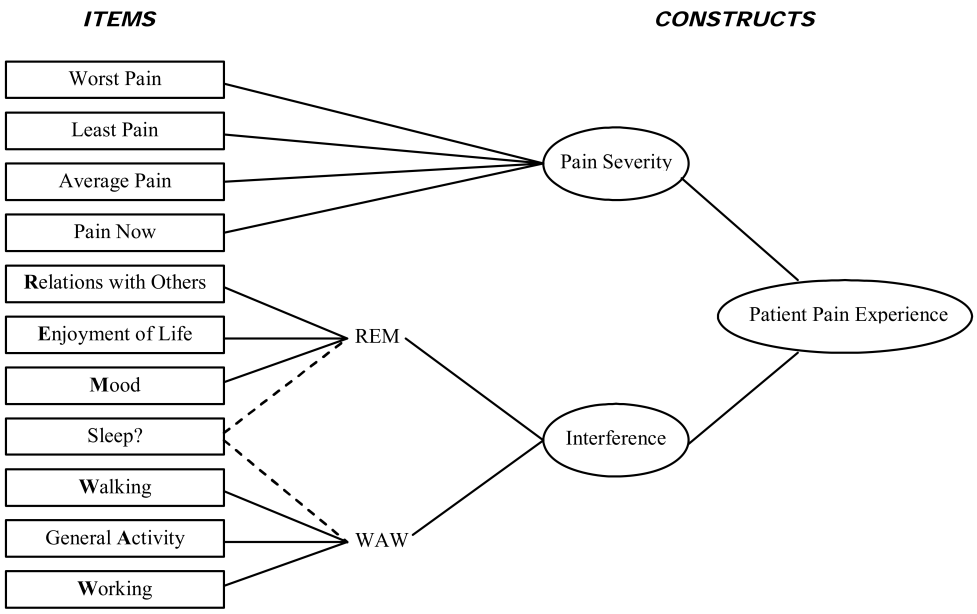

Fig. 2.1 Dimensions of BPI. The items of pain interference can be furter categorized into an affective subdimension (REM) and an activity subdimension (WAW). The categorization of sleep remains unclear. Taken from [13]

2.3.3 The EuroQol Quality of Life Scale

The EQ-5D questionnaire of the EuroQol group consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression and a 20 cm visual analogue scale (VAS). Valuation of EQ-5D may lead to a single index value between 0 (worst possible HRQLstate) and 1 (best possible HRQL state). [66] Higher values indicate a better HRQL. The EQ-5D is a concise generic health measure, with one item per dimension. Therefore it is suitable for the use in different conditions and diseases. However, it shows weaknesses in detecting small changes and has a ceiling effect.[6] [50]

The EQ-5D is available in different variations, regarding the number of levels per question. The standard version EQ-5D-3L includes a 3-level scale for each question, whereas the EQ-5D-5L contains 5-level scales. This should improve the sensitivity of the score and reduce ceiling effects. [84]

2.3.4 Brief Pain Inventory

The Brief Pain Inventory (BPI) is condition-specific tool for pain assessment. The BPI was originally designed for cancer pain, but is also widely used in non-cancer pain. [49] It consists of two parts: the "sensoric" and the "reactive" part. The sensoric part covers the pain intensity with four items, whereas the reactive part assesses the pain interference with daily life on seven items. The latter includes the interference of pain with general activity, mood or sleep. Further, the pain interference part of the BPI can be divided into an affective and an activity subdimension; these subdimensions and all other items are depicted in figure 2.1.[7] [13] The scores range from 0 ("no pain", "no interference") to 10 ("pain as bad as you can imagine", "interferes completely"). The mean of all interference items indicates the impact of pain on HRQL. Here, higher values indicate a greater pain interference and therefore a worse HRQL.

Although the BPI is a condition-specific assessment tool, it is a good complement to the generic HRQL measures and can be used in all types of pain. Therefore it is included in this analysis.

[6] A ceiling effect occurs when the range of possible HRQL states exceeds the functional range of the test at the top. In other words, it is relatively easy to get the best test result (EQ-5D index = 1) and the test fails at discriminating mild levels of HRQL impairment.

[7] Moreover, BPI contains some additional questions regarding pain location and pain relief. These items are often not reported and will not be considered in this review.

Chapter 3

Methods

3.1 Scientific objectives and PICO scheme

Like set out in section 1.3 following question should be answered in this systematical review:

Do opioids enhance HRQL in chronic pain?

In other words, the evidence regarding the impact of opioid therapy on HRQL in chronic pain should be summarized. To structure this clinical question and to bring it into a scientific form the PICO scheme [68] is used.[1] The scheme for this review is depicted in table 3.1.

Table 3.1 PICO scheme of this review

Patient:	Patients with chronic pain
Intervention:	Opioid therapy
Comparison:	Placebo
Outcome:	HRQL

To ensure high quality standards, this review is written in accordance with the PRISMA guidelines. [55] The PRISMA statement is shown in the appendices A.1.

The protocol of this review was registered on PROSPERO (ID: CRD42017073979).[2]

[1] PICO stands for patient or problem, intervention, comparison intervention and clinical outcome. This scheme is used in evidence-based medicine to formulate concise and concrete clinical questions.

[2] PROSPERO is an international database where protocols of systematic review can be registered. This database is funded by the National Institute of Health Research (NIH). More information can be accessed at https://www.crd.york.ac.uk/prospero/

Table 3.2 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Randomized controlled studies (RCT)	Uncontrolled studies
Adults ($\geq$ 18 years old) with chronic pain	Minority
Non-invasive opioid administration	Invasive Opioid administration (e.g. intrathecal or i. v. opioid administration)
Placebo-controlled	Comparative studies between different drugs without placebo
Generic or pain-specific HRQL measure	

3.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria were chosen in accordance with the PICO scheme, depicted in table 3.1.

Studies with adult patients (at least 18 years old) suffering from chronic pain and treated with opioids were included in this review. Studies had to assess HRQL, either with a generic assessment tool, as a primary or secondary outcome. Typical questionnaires, which feature a global concept of HRQL, are the SF-36 or the EQ-5D questionnaire. Also questionnaires which examine the interference of chronic pain with daily living, like the BPI pain interference scale are included. There were no restrictions regarding the type of pain (nociceptive or neuropathic, cancer or non-cancer). The opioid therapy had to be non-invasive, such as in oral or transdermal administration.

Exclusion criteria were minority of the included patients and invasive administration[3] of opioids. Studies, which assessed *exclusively* a disease-specific HRQL or functionality measure, such as the WOMAC scale in the case of osteoarthritis, were excluded from this review. This is because a global concept of HRQL is needed here. For example, a questionnaire, that adresses mainly arthritis-specific functionality cannot be applied to neuropathic pain, and therefore prevents comparability between different studies.

The studies had to be randomized and placebo-controlled. Comparative studies between different opioids without a placebo as a control were not included in this review. Regarding the length of the double-blind period or the follow-up, no restrictions were made in the inclusion criteria. The fully inclusion and exclusion criteria are depicted in table 3.2. This section corresponds to #6 of the PRISMA statement.

[3]Invasive methods are defined as methods, where the body is pierced with a device and the integument remains no longer intact.

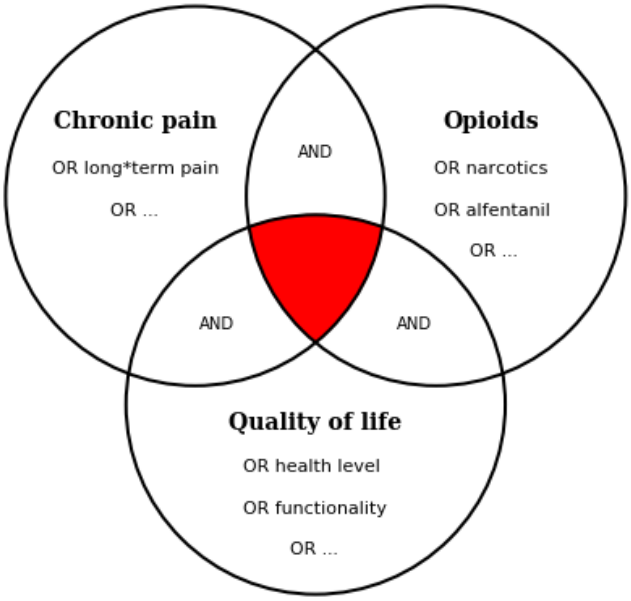

Fig. 3.1 Venn diagram of search strategy. The red center indicates the region of interest, that is, the intersection of the three keywords and their synonyms.

3.3 Literature search

3.3.1 Search strategy

The research strategy is based on three keywords: chronic pain, opioids and quality of life. These three keywords were connected through a logical "AND", forming a logical conjunction. For each of the keywords further synonyms were added through a connection with "OR", forming a logical disjunction. A Venn diagram of the search strategy is depicted in figure 3.1. Additionally, RCT filters provided by the Cochrane Collaboration were used.

3.3.2 Electronic database

I searched the following databases:

- PubMed, including:
  - MEDLINE
  - PubMed Central

- EMBASE
- The Cochrane Library, including - among others - :
  - Cochrane Database of Systematic Reviews
  - Cochrane Central Register of Controlled Trials

Moreover, relevant reviews were searched manually for suitable studies. Studies in five different languages English, German, Spanish, French, Italian were taken into account in this review. The last search update was made on 16 June 2020. A fully search strategy of the search in Medline via PubMed is depicted in the appendices A.2.

3.4 Data collection and analysis

3.4.1 Data screening

All search results were imported into a reference management software and duplicates were removed. I screened all titles and abstracts of the identified studies against the inclusion criteria. The full text of studies, which could possibly meet the inclusion criteria, was obtained. Then the full-text was again checked against the inclusion and exclusion criteria. At this point, reasons for exclusion of any study were noted and finally are given in the appendices.

3.4.2 Data extraction

Data of the included studies were extracted, using a standard form, and transferred into a spreadsheet. Extracted data includes information on study type, duration, number of patients enrolled and included in efficacy analysis, inclusion and exclusion criteria, interventions, HRQL measures, additional assessments and funding.

3.4.3 Assessment of methodological quality

The Cochrane Risk of Bias Tool was used for grading the methodological quality of the studies. [31] Following domains were assessed: random sequence generation, allocation concealment, blinding of participants and care personnel, blinding of outcome assessment and investigators, incomplete outcome data and selective reporting. The seventh domain was reserved for any other irregularities regarding the specific study. The rationale and criteria

for rating are described in the appendix, table A.1. These criteria are based on the Cochrane Handbook and further modified for this specific review.

In the evaluation of the risk of bias of the included studies, the single items are grouped into following dimensions:

- Randomization
  - Random sequence generation (selection bias)
  - Allocation concealment (selection bias)
- Blinding
  - Blinding of participants and care personnel (performance bias)
  - Blinding of outcome assessment and investigators (detection bias)
- Incomplete outcome data
  - Handling of incomplete outcome data (attrition bias)
- Reporting of results
  - Selective reporting (reporting bias)
- Other sources of bias
  - Other specific aspects of study design, i. e. enriched design or crossover studies.

Each of the single items of the risk of bias tool adresses a specific bias (round brackets).

3.4.4 Data analysis and synthesis

The extracted data was organized in a spreadsheet. Qualitative analysis of the HRQL results was structued along a vote counting approach. The vote counting approach allows for systematic comparability in the case of heterogeneous studies or incompletely reported results. The effect directions of the individual measurements are counted. In this method, effect strength and significance are not taken into consideration. Thus, only the sign of the effect is counted. In this work, the vote counts are also depicted graphically, according to a modified figure by Boon et al.[53]. A statistical analysis of the vote counting was not made. For the quantitative meta-analysis, data of the SF-36 summary scales PCS and MCS, and the EQ-5D Health scale was imported into R [65]. Analysis was made with the packages

"meta" [71] and "metafor" [94] in R. A generic inverse variance method with random effects was used for pooling effects in the case of continuous outcome values. The pooled mean difference and a prediction interval were calculated. In the case of binary outcome, like the analyses of premature drop-outs, Mantel-Haenszel method with a random effect model was used for pooling the results. Here, the effect measure was the pooled risk difference. The significant level was globally set to $\alpha = 0.05$.

In studies with multiple treatment groups, the different treatment groups using opioids were pooled into one large group and then compared to placebo treatment in order to avoid an unit-of-analysis error. Further information on this procedure and the estimation approach in the case of incompletely reported HRQL scales are given in chapter 4.3.1.

Heterogeneity was tested with the Chi^2 and I^2-Test. In order to examine the distribution of effects and to demask a possible publication a bias, funnel plots were made if more than 10 studies were pooled in the meta-analysis. In addition to other causes such as a large heterogeneity, an asymmetry in a funnel plot, in which the effect size is plotted against the effect precision, can be a sign for a publication bias. For example a publication bias might be caused by a overrepresentation of small studies with low precision and a positive effect of the experimental therapy. To quantify this asymmetry, Egger's test was used. [46] In Egger's test, a p-value of $p < 0.1$ describes a significant asymmetry. In the case of a significant asymmetry, the trim and fill method [19] estimates a corrected pooled mean difference. The trim and fill method generates virtual studies to compensate for the asymmetry of the effect distribution and finally estimate a more "relatistic" pooled mean difference.

Finally, this manuscript was written in LaTeX.

Chapter 4

Results

4.1 Characteristics of studies

4.1.1 Results of the literature search

The last update of the literature search was in June 2020. After removal of duplicates, overall, 2186 references were screened and 150 full-text articles were assessed. Finally, 35 studies were included in the qualitative analysis. The flowchart is depicted in Figure 4.1. To structurize the efficacy analysis, quantitative and qualitative analysis of the HRQL data is arranged in different groups according to their underlying disease. The Appendix B shows detailed characteristics of the included studies.

4.1.2 Included studies

35 different studies were included in the qualitative analysis. Since some studies were published several times under different aspects, 38 articles were included in the publication. If available, information from clinical registry ClinicalTrials.gov was also included in the analysis. Also some study authors were contacted to obtain missing information. In the following, the studies are classified and presented according to four groups, with respect to the underlying disease.

Osteoarthritis Eleven studies investigated the effect of opioids on chronic osteoarthritis (OA) pain. Three of these studies compared oxycodone versus placebo (Friedmann 2011 [111], Markenson 2005 [123] and Roth 2000 [128]). Three other studies investigated two active treatments groups, either tapentadol (Afilalo 2010 [102], Serrie 2017 [131]) or oxymor-

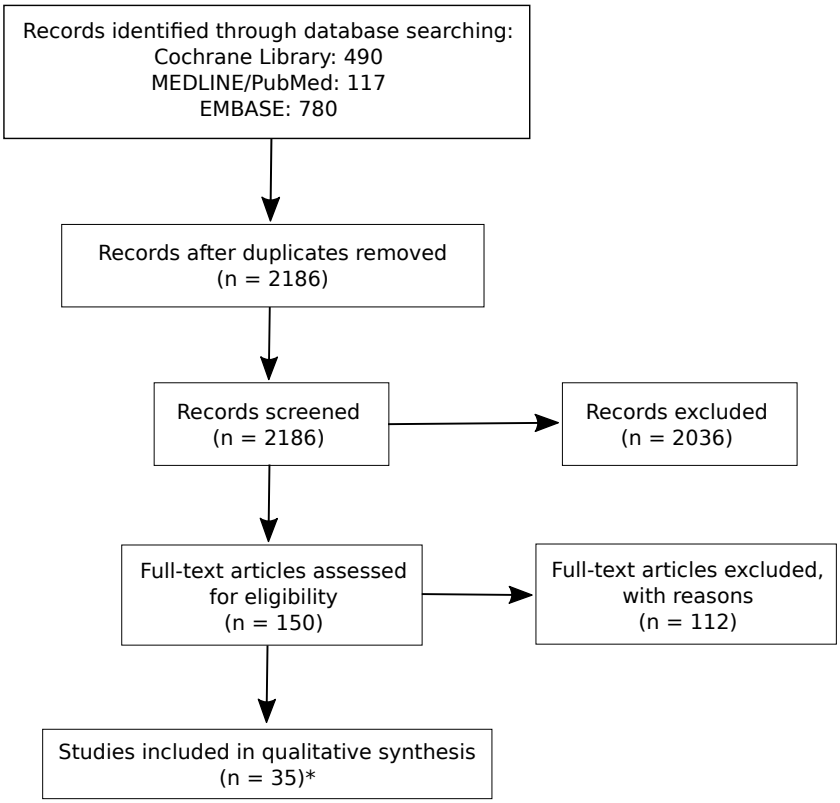

Fig. 4.1 Flowchart of search strategy, indicating the number of citations screened and studies finally included in the qualitative analysis. (*) The number of articles included (n = 38) differs from the number of studies (n = 35), because some studies were reported in multiple publications.

phone (Matsumoto 2005 [124]) and oxycodone as second active drug. Two studies administered tramadol (Gana 2006 [112] and Thorne 2008 [134]), another study used a fixed acetaminophen/tramadol combination as active drug (Emkey 2004 [110]). Further studies compared oxymorphone (Kivitz 2006 [120]), buprenorphine (Breivik 2010 [108]) or fentanyl (Arai N01 2015 [103]) with placebo. In this section, seven studies were long-term studies, lasting at least 12 weeks.

Low back pain Eight studies were dealing exclusively with chronic low back pain (LBP). Three of these studies were using buprenorphine as active drug (Gordon/Callaghan 2010 [115], Gordon/Rashiq 2010 [116] and Steiner 2011 [132]). Webster 2006 [137] studies the effect of oxycodone. Buynak 2010 [109] compares oxycodone and tapentadol versus placebo. Furthermore three studies were comparing a fixed tramadol/acetaminophen combination with

placebo (Lee 2013 [121], Peloso 2004 [126] and Ruoff 2003 [129]). One additional study, Arai N01 2015 [103] included patients with LBP and OA. The studies of Lee 2013, Gordon/Callaghan 2010 and Gordon/Rashiq 2010 were short-term studies with a study duration of 4 weeks. All others studies in this section were long-term studies lasting at least 12 weeks.

Neuropathic pain The third group includes studies regarding neuropathic pain of different etiology, like postherpetic neuralgia, diabetic neuropathy or sciatica. This group consists of 11 studies. Three of them used oxycodone as an active drug (Gimbel 2003 [114], Hanna 2008 [117] and Watson 2003 [136]), other three studies investigated the effect of morphine (Gilron 2005 [113], Khoromi 2007 [119] and Raja 2002 [127]). Further studies administered fentanyl (Arai N02 2015 [103]), tramadol (Boureau 2003 [107], Harati 1998 [118]) and tapentadol (Schwartz 2011 [130], Vinik 2014 [135]) as active drugs. In this section only four long-term studies were identified, lasting 12 weeks each.

Four other studies did not fit into the three categorization classes mentioned before. Arkinstall 1995 [104] and Moulin 1996 [125] are dealing with non-malignant pain of different origins, administering codeine or morphine, respectively. Bennett 2003 [105] investigates the effect of tramadol in fibromyalgia, Ma 2008 [122] compares oxycodone to placebo in chronic neck pain with acute pain flares.

4.1.3 Excluded Studies

Of 150 full-text articles assessed, 112 articles were excluded. The detailed reasoning for exclusion is shown in table C.1. The most common exclusion criteria were lack of placebo control and a missing or inadequate HRQL assessment.

4.2 Risk of bias in included studies

The risk of bias was assessed following a modified version of the “risk of bias” tool of the Cochrane Collaboration (see Chapter 3.4.3 and Table A.1). A summary of the distribution of the risk of bias is shown in Fig. 4.2. A further summary of the risk of bias of all studies listed by the authors is depicted in Figures A.2 and A.3 in the Appendix A.

4.2.1 Randomization

Overall 26 studies described their method of *random sequence generation* sufficiently and could be assigned a low risk of bias in the first subcategory of risk of bias table. The remaining

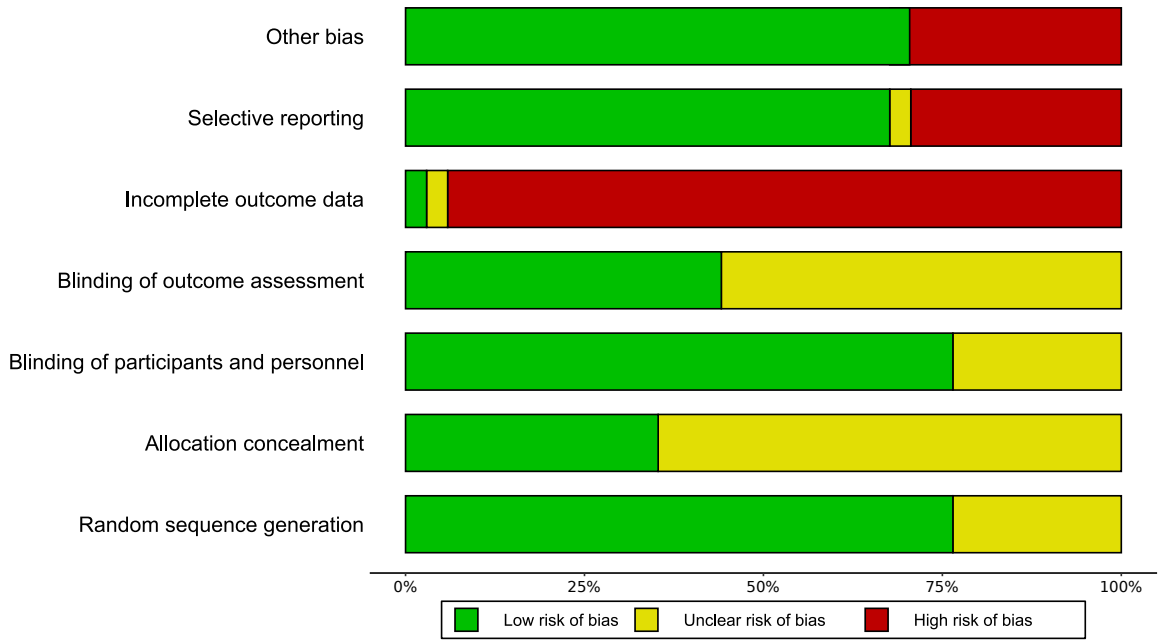

Fig. 4.2 Risk of bias of the included studies. It shows the distribution of the risk of bias of all studies included.

nine studies did not provide enough information so that they were rated as an unclear risk of bias. However, only 12 studies described their methods of *allocation concealment* properly and were assigned a low risk of bias in the second subdimension of the risk of bias table. The remaining 23 studies did not mention their method of allocation concealment adequately and were assigned an unclear risk of bias.

Overall 12 studies achieved a low risk of bias in these two subcategories *random sequence generation* and *allocation concealment*, which examine proper randomization (Afilalo 2010 [102], Breivik 2010 [108], Buynak 2010 [109], Gana 2006 [112], Gilron 2005 [113], Gimbel 2003 [114], Hanna 2008 [117], Raja 2002 [127], Schwartz 2011 [130], Serrie 2017 [131], Vinik 2014 [135], Webster 2006 [137]).

4.2.2 Blinding

Twenty-seven studies reported the *blinding of participants* adequately and were assigned a low risk of bias. The remaining eight studies missed information on their method of blinding the study medication with unclear risk of bias. Furthermore, 15 studies described their method of *blinding of outcome assessment and study investigators* adequately, and were rated as low risk of bias. Of the remaining 20 studies, 15 did not report their method of

blinding of outcome assessment and were rated as unclear risk of bias. Because the previous item (blinding of patients) was rated as unclear, other five studies (Afilalo 2010 [102], Buynak 2010 [109], Friedmann 2011 [111], Ruoff 2003 [129], Schwartz 2011 [130]) also had to be rated as unclear.

All in all 15 studies were assigned a low risk of bias in these two items adressing the blinding strategy and evaluating performance and detection bias. These studies are Bennett 2003 [105], Breivik 2010 [108], Emkey 2004 [110], Gilron 2005 [113], Gimbel 2003 [114], Gordon/Callaghan 2010 [115], Hanna 2008 [117], Harati 1998 [118], Khoromi 2007 [119], Kivitz 2006 [120], Lee 2013 [121], Matsumoto 2005 [124], Raja 2002 [127], Serrie 2017 [131], Webster 2006 [137].

4.2.3 Incomplete outcome data

In this category, which adresses attrition bias, only one study was rated low risk of bias (Emkey 2004 [110]). One study was rated as unclear risk because the number of patients in the effectiveness analysis was not reported. (Hanna 2008 [117]) The remaining 33 studies were assigned to a high risk of bias. Thirty-one studies, because more than 30% (long-term study) and 20% (short-term study), respectively, of the participants dropped out prematurely. Two studies because the population for HRQL-analysis was another than the intention-to-treat (ITT) population, with a lower number of individuals.

Alltogether, the vast majority of studies is rated high risk because of a high percentage of premature drop-outs. Only one study was rated low risk. Consequently, with regard to attrition bias, the study population shows a high risk of bias. Since a large number of studies are affected, the criterion for attrition bias may also be too strict. However, since such a high percentage of participants dropped out prematurely, the missing information on this patients may lead to an overestimation of the therapeutic effect on HRQL.

4.2.4 Selective reporting

Overall, 24 studies reported their efficacy results adequately (Afilalo 2010 [102], Arai N01 & N02 2015 [103], Arkinstall 1995 [104], Bennett 2003 [105], Boureau 2003 [107], Buynak 2010 [109], Emkey 2004 [110], Gana 2006 [112], Gilron 2005 [113], Gordon/Rashiq 2010 [116], Khoromi 2007 [119], Kivitz 2006 [120], Lee 2013 [121], Ma 2008 [122], Matsumoto 2005 [124], Moulin 1996 [125], Peloso 2004 [126], Raja 2002 [127], Ruoff 2003 [129], Serrie 2017 [131], Thorne 2008 [134], Vinik 2014 [135], Watson 2003 [136]). Eight studies were rated as high risk of bias, because of missing information on their results.

4.2.5 Other bias

Ten studies showed a high risk of bias due to other, specific causes. Six of these studies used an enriched or withdrawal design that administered the study opioid to all patients before randomization to include only patients who tolerated the opioid well(Arai N01 & N02 2015 [103], Friedmann 2011 [111], Schwartz 2011 [130], Steiner 2011 [132], Vinik 2014 [135]). Because of this preselection of the population before randomization, the therapeutic effect of opioids may be overestimated. Some studies were crossover studies with no washout-period between study phases. All studies performed a statistical test for carryover effect, but reported it incompletely as "not significant." However, the risk of carryover should be estimated individually, depending on the pharmacokinetics of the study drug and the study design.[32] Arkinstall 1995 [104] was classified with a high risk of bias, because the treatment phase lasts onlyone week, and it can be assumed that codeine CR is still effective during the first days of the consecutive treatment phase.[76] The studies Gordon/Callaghan 2010 [115] and Gordon/Rashiq 2010 [116] were also rated as of high risk of bias. They have a longer treatment phase of four weeks, but as transdermal buprenorphine has a very long elimination time [86], the opioid may affect the first week of the subsequent treatment phase. The remaining two studies were rated high risk because of different, individual issues, considered likely to bias the efficacy results. Lee 2013 [121] performed, after a first non-significant analysis, a second analysis on a corrected population in which individual patients were excluded. Ma 2008 [122] allowed patients who experienced a positive effect of medication during ongoing study to withdraw prematurely.

4.3 Effects of intervention

4.3.1 Qualitative analysis

The characteristics of the included studies and results of the quality of life assessment are shown in table 4.1. The qualitative analysis is based on the vote counting method. In the vote counting approach, the directions of the effects of the HRQL measurements are counted and compared, without considering significance (see chapter 3.4.4).

All in all, out of 26 studies assessing the PCS scale of the SF-36, 22 studies showed a positive direction of effects, indicating a beneficial effect of the opioid therapy. Three studies showed no effect or did not provide sufficient information, while one study showed a negative effect. For the MCS score, ten studies showed a positive trend, while eight studies showed a negative results. Six studies were rated as neutral. Out of seven studies, which

reported the EQ-5D Health scale, four studies showed a positive effect, while two studies reported no effect or no sufficient information and one study showed a negative effect of the opioid therapy compared to placebo. Six of seven studies reporting the BPI pain interference scale showed a positive result, while one study did not report sufficient information on this outcome. Further results from other HRQL questionnaires are shown in Tables 4.1-4.5. In the following, the studies are grouped and summarized according to their underlying diseases.

Table 4.1 Study characteristics. The study drugs, study duration and the characteristics and number of participants randomized and included in efficacy analysis of HRQL measures are reported. All studies are placebo-controlled trials. Drugs: Tra: tramadol, Mor: morphine, Met: methadone, Bup: buprenorphine, Tap: tapentadol, APAP: acetaminophen, Oxc: oxycodone, Oxm: oxymorphone, Fen: fentanyl, Cod: codeine, Pla: placebo. ER/CR/PR/SR: extended/controlled/prolonged/sustained release tablets, TDS: transdermal system. HRQL assessment: PCS: physical component score, MCS: mental component score, BPI: brief pain inventory, PGI: patient generated index, BPI: brief pain inventory, SIP: sickness impact profile, MPI: multidimensional pain inventory, MSHQ: modified Stanford health assessment questionnaire. Neuropathic pain - DPN: diabetic polyneuropathy. PHN: post-herpetic neuralgia, POP: post-operative pain, CRPS: complex regional pain syndrome. Age: mean $\pm$ SD [years], if not otherwise stated.

Author & Year	Duration	Intervention	Pain condition	Participants	Quality of Life Assessment
Afilalo 2010	15 weeks	Tap ER, Oxc CR	Osteoarthritis	Patients randomized: n = 1030 (Oxc: 346, Tap: 345, Pla: 339; age: 58.3 $\pm$ 9.9 yr., 60.4% female). HRQL analysis: n = 1023.	SF-36 and EQ-5D scores reported. SF-36: In PCS, Tap showed a significant and Oxc a non-significant advantage over Pla. In MCS Pla scored significantly better than Oxc and non-significantly higher than Tap. EQ-5D: significant improvement of Tap vs. Pla. No significant difference between Oxc and Pla.
Arai N01 2015	12 weeks	Fen TDS	Osteoarthritis, low back pain	Patients randomized: n = 150 (Fen: 73, Pla: 77; age: 66.5 $\pm$ 13.12 yr., 67.3% female). HRQL analysis: n = 150.	SF-36 scores reported. SF-36: Fen scored numerically, non-significantly worse than Pla in both scales, PCS and MCS.
Arai N02 2015	12 weeks	Fen TDS	Neuropathic pain (PHN, CRPS, POP)	Patients randomized: n = 163 (Fen: 84, Pla: 79; age: 66.5 $\pm$ 13.96 yr., 49.1% female). HRQL analysis: n = 163.	SF-36 scores reported. SF-36: In PCS, Fen scored numerically, non-significantly better than Pla, while in MCS Pla showed a non-significant advantage over Fen.
Arkinstall 1995	1 week	Cod CR, crossover study	Nonmalignant Pain	Patients enrolled: n = 46 (age: 55.1 $\pm$ 13.4 yr., 56.7% female). HRQL analysis: n = 30.	PDI scores reported. PDI: significant advantage of Cod over Pla.
Bennett 2003	13 weeks	Tra/APAP	Fibromyalgia	Patients randomized: n = 315 (Tra/APAP: 158, Pla: 157; age: 50.0 $\pm$ 10.5 yr., 93.9% female). HRQL analysis: n = 313.	SF-36 scores reported. SF-36: PCS showed a significant advantage, whereas MCS showed a numerical, non-significant advantage of Tra/APAP over Pla.
Boureau 2003	6 weeks	Tra	Neuropathic pain (PHN)	Patients randomized: n = 127 (Tra: 64, Pla: 64; age: 66.8 $\pm$ 11.8 yr., 72.4% female). HRQL analysis: n = 108.	Nottingham Scale reported. Nottingham Scale: No significant difference, Tra slightly better change to baseline than Pla.
Breivik 2010	24 weeks	Bup TDS	Osteoarthritis	Patients randomized: n = 199 (Bup: 100, Pla: 99; age: 62.9 $\pm$ 9.5 yr., 68.3% female). HRQL analysis: n = 199.	EQ-5D: "tendency for more improvement was seen in the Bup group [...] but no difference was seen between the groups in the subscales [...]"

continued from previous page

Author & Year	Duration	Intervention	Pain condition	Participants	Quality of Life Assessment
Buynak 2010	15 weeks	Tap ER, Oxc CR	Low back pain	Patients randomized: n = 981 (Tap: 321, Oxc: 334, Pla: 326; age: 49.9 ± 13.8 yr., 57.9% female). HRQL analysis: n = 951.	SF-36 and EQ-5D scores reported. SF-36: PCS showed significant advantages of Tap and Oxc over Pla. In MCS, Tap scored non-significantly better than Pla, while Pla showed a non-significant advantage over Oxc. EQ-5D: significant improvement of Tap and Oxc compared to Pla. However - maybe due to rounding error- in the case of Tap, difference was reported with 0.0.
Emkey 2004	13 weeks	Tra/APAP	Osteoarthritis	Patients randomized: n = 307 (Tra/APAP: 153, Pla: 154; age: 61 ± 9.0 yr., 68.3 % female). HRQL analysis: n = 306.	SF-36 scores reported. SF-36: In PCS, Tra/APAP had a non-significant better change to baseline, while in MCS, Tra/APAP scored numerically worse than Pla.
Friedmann 2011	12 weeks	Oxc ER	Osteoarthritis	Patients randomized: n = 412 (Oxc: 205, Pla: 207; age: 58.3 ± 8.2 yr., 69.9% female). HRQL analysis: n = 412.	SF-12: PCS: "change from pre-randomization was significantly higher" for Oxc. MCS: "mean change in MCS score was not significantly different."
Gana 2006	12 weeks	Tra ER, different dosing schemes	Osteoarthritis	Patients randomized: n = 1020 (Tra: 806, Pla: 205; age: 58.2 ± 10.0 yr., 62.4%). HRQL analysis: n = 1011.	SF-36 scores reported. SF-36: In PCS, Tra scored numerically, non-significantly better than Pla. In MCS, low-dose Tra showed a numerically better and high-dose Tra a numerically worse change to baseline compared with Pla.
Gilron 2005	5 weeks	Mor vs. active placebo (lorazepam), crossover study	Neuropathic pain (PHN, DPN)	Patients randomized: n = 57 (age: range 40-81 yr., 43.9% female). HRQL analysis: n = 44.	SF-36 single dimensions reported. PCS and MCS were estimated. PCS and MCS showed a numerical, non-significant advantage of Mor over Pla.
Gimbel 2003	6 weeks	Oxc CR	Neuropathic pain (DPN)	Patients randomized: n = 159 (Oxc: 82, Pla: 77; age: 58.9 ± 11.3 yr., 47.8% female). HRQL analysis: n = 44.	SF-36: "no significant differences were observed." SIP: one of 16 subscales showed "a significant difference." BIP: values were reported and showed a significant advantage of Oxc over Pla.
Gordon, Callaghan 2010	4 weeks	Bup TDS, crossover study	Low back pain	Patients randomized: n = 78 (age: 50.7 ± 11.9 yr., 60.4% female). HRQL analysis: n = 52.	SF-36: PCS: no significant difference between Pla and Bup, Bup numerically higher improvement from baseline. MCS: "no significant difference." PDI: numerically higher change from baseline in Bup, no significant difference.
Gordon, Rashiq 2010	4 weeks	Bup TDS, crossover study	Low back pain	Patients randomized: n = 79 (age: 54.5 ± 12.7 yr. , 47.2% female). HRQL analysis: n = 55	SF-36: In PCS, Bup showed a numerical, non-significant advantage over Pla, while in MCS Bup scored numerically worse than Pla. PDI: no significant differences, numerically higher change in overall score for Pla compared to Bup.
Hanna 2008	12 weeks	Oxc PR	Neuropathic pain (DPN)	Patients randomized: n = 338 (Oxc: 169, Pla: 169; age: 60.1 ± 10.2 yr., 35.9% female). HRQL analysis: 302.	BPI: mean pain interference "significantly lower" in Oxc compared to Pla. EQ-5D: in single dimensions increasements were seen "to a greater extent in Oxc." No statement about health score.

continued from previous page

Author & Year	Duration	Intervention	Pain condition	Participants	Quality of Life Assessment
Harati 1998	6 weeks	Tra	Neuropathic pain (DPN)	Patients randomized: 131 (Tra: 65, Pla: 66; mean age: 59 yr., 61.8% female). HRQL analysis: 127.	MOS: summary scales not reported. Three subscales were significantly better in Tra, other did not show any significant differences.
Khoromi 2007	9 weeks	Mor vs. active placebo (lorazepam), crossover study	Lumbar radiculopathy/sciatica	Patients randomized: 55 (age: range 19-65, 45.5% female). HRQL analysis: $n = 34$.	SF-36 single dimensions reported. PCS and MCS were estimated. PCS showed a numerical, non-significant advantage of Mor, while in MCS Mor scored numerically worse than Pla.
Kivitz 2006	2 weeks	Oxm ER, different dosing schemes.	Osteoarthritis	Patients randomized: n = 370 (Oxm: 279, Pla: 91; age: 61.8 ± 11.2 yr., 60.5% female). HRQL analysis: n = 357.	Only PCS score of SF-36 assessed. PCS: All Oxm groups showed a significantly better change from baseline than Pla.
Lee 2013	4 weeks	Tra ER/APAP	Low back pain	Patients randomized: n = 248 (Tra/APAP: 125, Pla: 120; age: 60.1 ± 10.3 yr., 74.7% female). HRQL analysis: n = 170.	SF-36 single dimensions reported. PCS and MCS scores were estimated. PCS and MCS showed a numerical but non-significant advantage of Tra/APAP over Pla.
Ma 2008	2 weeks	Oxc CR	Neck pain with acute pain flares	Patients randomized: n = 116 (Oxc: 58, Pla: 58, age: 55.7 ± 14.6 yr., 37.9% female). HRQL analysis: n = 116.	SF-36 single dimensions reported. PCS and MCS were estimated. Oxc showed in both scales a significant advantage over Pla.
Markenson 2005	90 days	Oxc CR	Osteoarthritis	Patients randomized: n = 109 (Oxc: 56, Pla: 51; mean age: 63, 72.9% female). HRQL analysis: n = 107.	BPI and PGI scores partially reported. PGI: no summary score was calculated. Only one dimension chosen by sponsor was evaluated and showed significant improvement in Oxc compared to Pla. BPI: pain interference score showed significant advantage of Oxc over Pla.
Matsumoto 2005	4 weeks	Oxm ER, Oxc CR, different dosing schemes of Oxm ER	Osteoarthritis	Patients randomized: n = 491 (Oxm: 242, Oxc: 125, Pla: 124; mean age: 58.8 ± 10.8, 60.7% female). HRQL analysis: n = 467.	SF-36 summary scores reported. SF-36: PCS showed a significant advantage of high-dose Oxm and Oxc over Pla. In MCS, Oxc scored significantly and Oxm numerically worse than Pla.
Moulin 1996	11 weeks	Mor SR vs. active placebo (benztropine), crossover study.	Non-cancer pain	Patients randomized: n = 61 (age: range 26-67, 59% female). HRQL analysis: n = 46.	SIP and PDI reported. PDI: no significant difference, Mor scored numerically better than Pla. SIP: no significant difference, Mor scored numerically worse than Pla.
Peloso 2004	13 weeks	Tra/APAP	Low back pain	Patients randomized: n = 338 (Tra/APAP: 167, Pla: 171; age: 57.5 ± 12.6 yr., 62.5% female). HRQL analysis: 336.	SF-36 scores reported. SF-36: PCS showed significant advantage of Tra/APAP over Pla. MCS showed numerical but non-significant advantage of Tra/APAP over Pla.
Raja 2002	8 weeks	Mor or Met, crossover study.	Neuropathic pain (PHN)	Patients randomized: n = 76 (age: 71 ± 12 yr., 55.3 % female). HRQL analysis: n = 71.	MPI: subdimensions pain interference and activity level showed no differences between groups.

continued from previous page

Author & Year	Duration	Intervention	Pain condition	Participants	Quality of Life Assessment
Roth 2000	2 weeks	Oxc CR, different dosing schemes of Oxc CR.	Osteoarthritis	Patients randomized: n = 133 (age: 62.3 ± 13.3, 73.7% female). HRQL analysis: n= 133.	BPI: high-dose Oxc in three pain interference subdimensions significantly higher than Pla, in all other subdimensions Oxc numerically better than Pla. Overall pain interference scale not reported. MSHQ: no improvements or difference throughout study.
Ruoff 2003	13 weeks	Tra/APAP	Low back pain	Patients randomized: n = 322 (Tra/APAP: 162, Pla: 160; age: 53.8 ± 11.9 yr., 63.2% female). HRQL analysis: n= 318.	SF-36 scores reported. SF-36: PCS showed a numerical, non-significant advantage of Tra/APAP, while in MCS Tra/APAP scored significantly better than Pla.
Schwartz 2011	12 weeks	Tap ER	Neuropathic pain (DPN)	Patients randomized: n = 395 (Tap: 199, Pla: 196; age: 60.2 ± 10.6 yr., 39.6% female). HRQL analysis: n = 389.	Scores of EQ-5D reported. SF-36 and BPI were only reported in a pooled analysis together with Vinik 2014. EQ-5D: Tap scored significantly better than Pla. Pooled analysis: SF-36: PCS showed a significant advantage and MCS a numerical, non-significant advantage of Tap over Pla. BPI: Tap showed significant advantages in pain interference over Pla.
Serrie 2017	15 weeks	Tap PR, Oxc CR	Osteoarthritis	Patients randomized: n = 990 (Tap: 337, Oxc: 320, Pla: 333; age: 62.1 ± 9.3, 71.6% female). HRQL analysis: 987.	SF-36 and EQ-5D scores reported. SF-36: In PCS, Tap scored numerically better and Oxc scored numerically worse than Pla. In MCS, Tap scored numerically and Oxc significantly worse than Pla. EQ-5D: no difference between Tap and Pla, while Oxc performed significantly worse than Pla.
Steiner 2011	12 weeks	Bup TDS	Low back pain	Patients randomized: n = 541 (Bup: 257, Pla:284; age: 49.5 ± 12.9 yr., 54.9% female). HRQL analysis: n = 369.	SF-36 and BPI scores reported. SF-36: In PCS and MCS, Bup scored significantly better than Pla. BPI: significant advantage in pain interference for Bup over Pla.
Thorne 2008	4 weeks	Tra CS, crossover study.	Osteoarthritis	Patients randomized: n = 100 (age: 61 ± 10.3, 55% female). HRQL analysis: n = 77.	PCS of SF-36 and PDI scores numerically reported. SF-36: PCS showed a significant advantage and MCS showed a numerical advantage of Tra over Pla. PDI: Tra scored in total score significantly better than Pla.
Vinik 2014	12 weeks	Tap ER	Neuropathic pain (DPN)	Patients randomized: n = 320 (Tap: 168, Pla: 152; age: $58.7 \pm 9,87$ yr., 41.2% female). HRQL analysis: n = 318.	SF-36, EQ-5D and BPI scores reported. SF-36: PCS showed a significant advantage, whilst MCS showed a numerical, non-significant advantage of Tap over Pla. BPI: Tap scored significantly better than Pla in pain interference score. EQ-5D: Tap scored significantly better than Pla.
Watson 2003	4 weeks	Oxc CR, crossover study	Neuropathic pain (DPN)	Patients randomized: n = 45 (age: 63 ± 9.4 yr., 47.2% female). HRQL analysis: n = 36.	SF-36: In PCS and MCS, Oxc showed a significant advantage over Pla. PDI: Oxc scored in total score significantly better than Pla.
Webster 2006	13 weeks	Oxc	Low back pain	Patients randomized: n = 307 (Oxc: 206, Pla: 101; mean age: 48.2, 61.5% female). HRQL analysis: n = 306.	SF-12: PCS: Oxc "showed significant improvements compared with Pla." MCS: "no significant differences."

Osteoarthritis Among 11 studies dealing with osteoarthritis as underlying pain cause, seven studies (Afilalo 2010, Emkey 2004, Friedmann 2011, Gana 2006, Matsumoto 2005, Serrie 2017, Thorne 2008) assessed the SF-36/SF-12 questionnaire and its PCS and MCS scores. Kivitz 2006 only assessed the PCS of the SF-36 questionnaire. Four studies (Friedmann 2011, Kivitz 2006, Matsumoto 2005, Thorne 2008) reported a significant advantage of the opioid therapy compared to placebo. Afilalo 2010 reported a significant advantage for tapentadol, but not for oxycodone compared to placebo. Two studies (Emkey 2004, Gana 2006) showed no significant difference, but a numerical advantage of opioid therapy. In Serrie 2017 oxycodone scored numerically worse and tapentadol numerically better than placebo.

The assessment of the MCS score showed only in Thorne 2008 a non-significant, numerical advantage of tramadol over placebo. Three studies (Afilalo 2010, Matsumoto 2005, Serrie 2017) showed a significant worsening with oxycodone and a non-significant, numerical worsening in the tapentadol group compared to placebo. The other studies showed numerical tendencies in favor of placebo (Emkey 2004) or no overall direction at all (Friedmann 2011, Gana 2006).

The studies assessing EQ-5D showed one positive result with a significant benefit for tapentadol (Afilalo 2010). Breivik 2010 shows an effect with unclear direction, whereas Serrie 2017 shows a numerical tendency favoring placebo. Table 4.2 shows the direction of effect of all studies assessing osteoarthritic pain. In this table the direction of the effect is shown, regardless if its a significant effect or only a numerical one.

Low back pain The PCS of the SF-36 questionnaire showed in all eight studies dealing with chronic low back pain a positive effect of opioid therapy. Four studies (Buynak 2010, Peloso 2004, Steiner 2011, Webster 2006) showed a significant benefit of the opioid therapy compared to placebo.

The results of the SF-36 MCS scale paint a more mixed picture. Two studies (Ruoff 2003, Steiner 2011) showed significant advantages and further two studies (Lee 2013, Peloso 2004) showed a numerical advantage for the opioid treatment. Three other studies (Buynak 2010, Gordon/Callaghan 2010, Webster 2006) showed no visible tendency or conflicting effects, while one study (Gordon/Rashiq 2010) showed a non-significant negative effect of buprenorphine compared to placebo. Furthermore Buynak 2010 reported a non-significant, numerical improvement of opioid in EQ-5D and Steiner 2011 showed a significant advantage of opioid in the BPI pain interference scale. Additional assessments and the direction of effects are depicted in Table 4.3.

Table 4.2 Table of effect direction in studies assessing osteoarthritis pain. The scores depicted are the SF-36 PCS and MCS summary scales, the EQ-5D Health scale, the BPI pain interference scale and other HRQL measures. Studies in which there are multiple opioid groups showing positive and negative effect directions were considered neutral. The signs differ in size, regarding the number of patients assessed for HRQL in the study. ▲ : positive effect of opioid, ◀▶: no change/neutral/mixed effects/no sufficient information, ▼ : negative effect of opioid. Drugs: Tap : tapentadol, Oxc: oxycodone, Oxm: oxymorphone, Tra/APAP: tramadol/acetaminophen, Tra: tramadol, Bup: buprenorphine. Sample size: ▲ : 0-200, ▲ : 201-500, ▲ : > 500.

Author & Year	Opioid	SF-36: PCS	SF-36: MCS	EQ-5D	BPI	Other
Afilalo 2010	Tap, Oxc	▲	▼	▲		
Breivik 2010	Bup			◀▶		
Emkey 2004	Tra/APAP	▲	▼			
Friedmann 2011	Oxc	▲	◀▶			
Gana 2006	Tra	▲	◀▶			
Kivitz 2006	Oxm	▲				
Markenson 2005	Oxc				▲	◀▶
Matsumoto 2005	Oxc, Oxm	▲	▼			
Roth 2000	Oxc				▲	◀▶
Serrie 2017	Tap, Oxc	◀▶	▼	▼		
Thorne 2008	Tra	▲	▲			▲

Neuropathic pain Six studies assessed the PCS of the SF-36 questionnaire. Vinik 2014 and Watson 2003 showed a significant advantage, while Arai N02 2015 and Gilron 2005 showed a non-significant effect, favoring the opioid therapy. Gimbel 2003 remains unclear in the direction of the reported effect. The MCS showed a significant advantage in Watson 2003 and numerical tendencies favoring opioid medication in Gilron 2005 and Vinik 2014. Arai N02 2015 showed a negative tendency favoring placebo. The SF-36 results of Schwartz 2011 could not be assessed separately as it is only reported in a pooled analysis together with Vinik 2014. The EQ-5D was reported by three studies, two studies (Schwartz 2011, Vinik 2014) reported a positive effect of opioid compared to placebo, while the result of Hanna 2008 remains unclear. Further significant advantages in the BPI interference scale were reported by Gimbel 2003, Hanna 2008 and Vinik 2014. The direction of effects and additional HRQL assessments are depicted in Table 4.4.

Other diseases Among the remaining studies assessing chronic pain caused by different underlying diseases, five studies reported the SF-36 summary scales. Bennett 2003 showed

Table 4.3 Table of effect direction in studies assessing low back pain. ▲ : positive effect of opioid, ◄►: no change/mixed effects/no sufficient information, ▼ : negative effect of opioid. Drugs: Tap : tapentadol, Oxc: oxycodone, Oxm: oxymorphone, Tra/APAP: tramadol/acetaminophen, Tra: tramadol, Bup: buprenorphine. Sample size: ▲ : 0-200, ▲ : 201-500, ▲ : > 500.

Author & Year	Opioid	SF-36: PCS	SF-36: MCS	EQ-5D	BPI	Other
Buynak 2010	Tap, Oxc	▲	◄►	▲		
Gordon/Callaghan 2010	Bup	▲	◄►			▲
Gordon/Rashiq 2010	Bup	▲	▼			▼
Lee 2013	Tra/APAP	▲	▲			
Peloso 2004	Tra/APAP	▲	▲			
Ruoff 2003	Tra/APAP	▲	▲			
Steiner 2011	Bup	▲	▲		▲	
Webster 2006	Oxc	▲	◄►			

a significant advantage for opioid in the PCS summary scale. Khoromi 2007 and Ma 2008 showed a positive non-significant tendency, while Arai N01 2015 reported a negative tendency of the opioid therapy compared to placebo. In the MCS scale two studies showed a non-significant, numerical advantage (Bennett 2003, Ma 2008) and another two studies showed a numerical disadvantage (Arai N01 2015, Khoromi 2017) of opioid compared to placebo. The direction of the effects and additional assessments are shown in Table 4.5.

4.3.2 Quantitative analysis

The parameters analyzed quantitatively were the mental and physical summary scores of the SF-36 and the health score of the EQ-5D as direct indicators of HRQL. As an indirect control parameter and because in many studies a high risk of attrition bias was found, the premature withdrawal rate was also quantitatively analyzed.

In the meta-analysis of HRQL measures mainly the change from baseline of each treatment group were used as outcome. If the studies included only provided baseline and post-treatment scores, the mean change from baseline and its standard deviation was calculated as suggested by the Cochrane Handbook [32]. The correlation coefficient between baseline and post-treatment measurements was calculated as $corr = 0.6$, using data from Peloso 2004 and Ruoff 2003. This correlation coefficient is compatible with similar finding in the literature. [23] In the case that only the post-treatment scores of treatment and placebo group were reported, these values were included in the meta-analysis. Finally, some studies

Table 4.4 Table of effect direction in studies assessing neuropathic pain. ▲ : positive effect of opioid, ◄►: no change/mixed effects/no sufficient information, ▼ : negative effect of opioid. Drugs: Tap : tapentadol, Oxc: oxycodone, Fen: fentanyl, Tra: tramadol, Mor: morphine, Met: methadone. Sample size: ▲ : 0-200, ▲ : 201-500, ▲ : > 500. * The results of Schwartz 2011 are only reported in a pooled analysis and are therefore regarded as neutral.

Author & Year	Opioid	SF-36: PCS	SF-36: MCS	EQ-5D	BPI	Other
Arai N02 2015	Fen	▲	▼			
Boureau 2003	Tra					▲
Gilron 2005	Mor	▲	▲			
Gimbel 2003	Oxc	◄►	◄►		▲	◄►
Hanna 2008	Oxc			◄►	▲	
Harati 1998	Tra					◄►
Raja 2002	Mor or Met					◄►
Schwartz 2011	Tap	◄►*	◄►*	▲	◄►*	
Vinik 2014	Tap	▲	▲	▲	▲	
Watson 2003	Oxc	▲	▲			▲

only reported the single dimensions of the SF-36 questionnaire and did not calculate the summary scales PCS and MCS. In this case the summary scales were calculated and the correlation matrix was imputed according to Ware's SF-36 Manual [90].

Some studies reported data of multiple intervention groups, because of different opioid substances or dosing schemes included. Inclusion of this active treatment groups as if they were separate trials would lead to a unit-of-analysis error and thus reduce the statistical power of the analysis. [32] To address this issue, the multiple treatment groups of one single study were pooled into one large group, and then compared to the placebo treatment.

SF-36

Physical component summary (PCS) The meta-analysis of the PCS of the SF-36 analyzed 18 studies, which provide data of 7391 patients (Fig. 4.3). The resulting overall effect shows a significant advantage in favor of the opioid group (mean difference: 1.82, $p < 0.01$). A significant advantage in this range was also observed in the three subgroups *Low Back Pain*, *Osteoarthritis* and *Neuropathic Pain*. Despite the studies show some moderate heterogeneity ($I^2 = 35\%$), the prediction interval of at least 0.41 to a maximum of 3.22 confirms the beneficial effect of opioid medication. A funnel plot of the studies included shows a relatively symmetrical distribution with no clear evidence of publication bias.

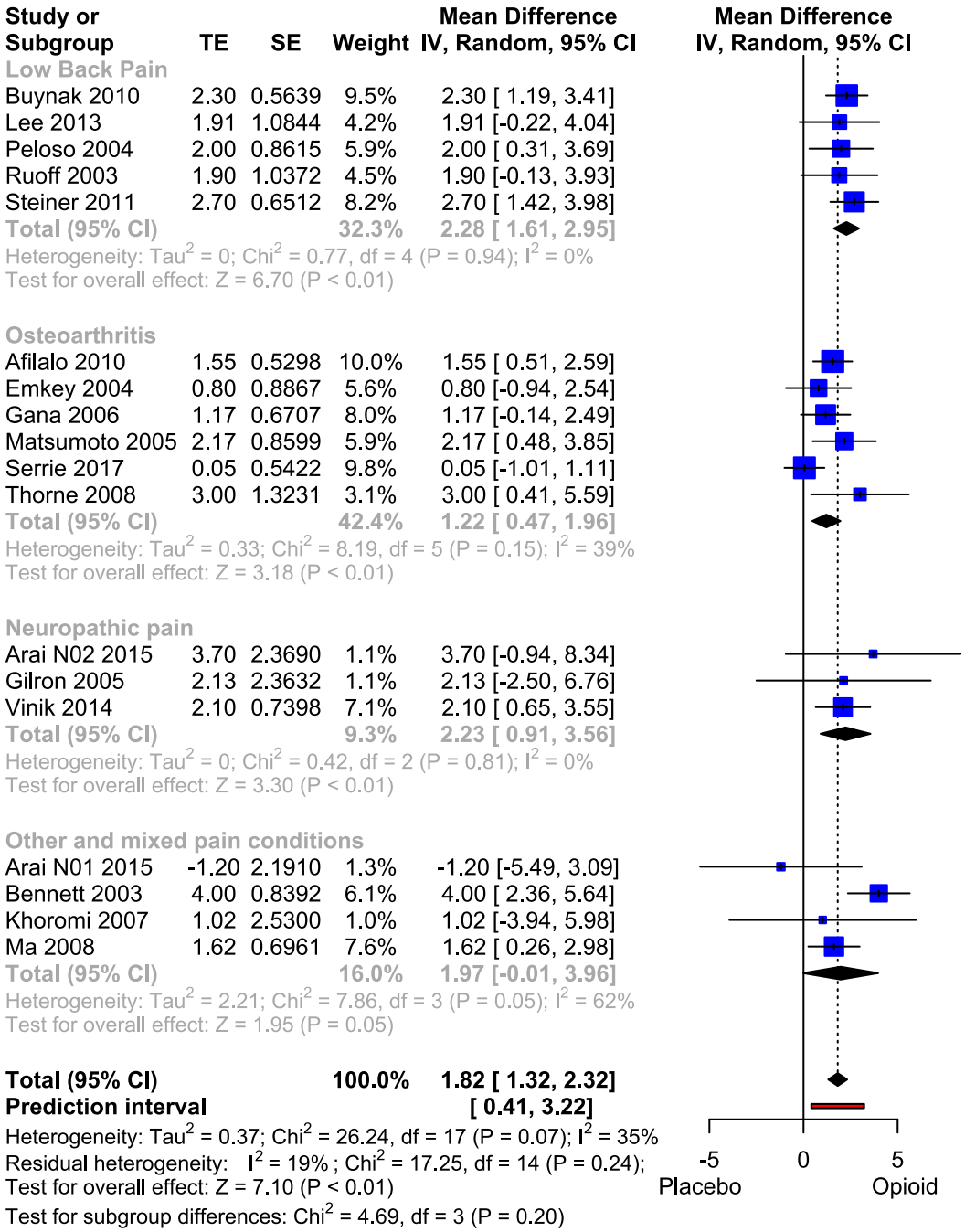

Fig. 4.3 Meta-analysis of all studies, which provided data for PCS. The analysis shows an significant overall effect in favor of opioid treatment (MD: 1.82, $p < 0.01$).

Table 4.5 Table of effect direction in studies assessing different underlying diseases. ▲ : positive effect of opioid, ◄►: no change/mixed effects/no sufficient information, ▼ : negative effect of opioid. Drugs: Tap: tapentadol, Oxc: oxycodone, Fen: fentanyl, Tra/APAP: tramadol/acetaminophen, Mor: morphine. Sample size: ▲ : 0-200, ▲ : 201-500.

Author & Year	Disease	Opioid	PCS	MCS	Other
Arai N01 2015	Osteoarthritis, low back pain	Fen	▼	▼	
Arkinstall 1995	Non-cancer pain	Cod			▲
Bennett 2003	Fibromyalgia	Tra/APAP	▲	▲	
Khoromi 2007	Lumbar radiculopathy/sciatica	Mor	▲	▼	
Ma 2008	Neck pain with acute pain flares	Oxc	▲	▲	
Moulin 1996	Non-cancer pain	Mor			◄►

However, since some studies show considerable differences in study design and some values of PCS were statistically estimated, sensitivity analysis was performed. A sensitivity analysis excluding studies using an enriched/withdrawal design (Arai N01 & N02 2015, Steiner 2011, Vinik 2014) or other designs favoring the active treatment group (Ma 2008) resulted in a slightly lower mean difference of 1.75 ($p < 0.01$) in favor of opioid (SI A.4). Further exclusion of studies, in which the PCS was estimated (Gilron 2005, Khoromi 2007, Lee 2013) led to a mean difference of 1.77 ($p < 0.01$) but an increase in heterogeneity ($I^2 = 57\%$).

Thus, there is a significant advantage of the opioid group compared to placebo, which remains stable in the sensitivity analyses (Fig. 4.6).

Mental component summary (MCS) 17 studies provided data of 7237 patients suitable for quantitative analysis of MCS. The analysis (Fig. 4.4) showed no significant outcome differences between opioid and placebo (MD: 0.65, p = 0.24). The subgroup analysis of Osteoarthritis showed a significant worsening of opioid compared to placebo ($p < 0.05$), while the low back pain subgroup shows an almost significant advantage of the opioid therapy (p = 0.05). In a sensitivity analysis, excluding studies which used study designs likely to favor the opioid treatment (Arai N01 & N02 2015, Steiner 2011, Vinik 2014, Ma 2008), the overall effect shifts more and more towards zero, resulting in a mean difference of 0.07 (p = 0.88). Other sensitivity analyses were also performed, but showed no significant differences (Fig. 4.6). The funnel plot showed a slight asymmetry, but a subsequent Egger's test did not indicate a significant asymmetry (p = 0.18). A pilot analysis by the trim and fill method, showed no signficant change in the corrected mean difference (MD = -0.70, p = 0.26).

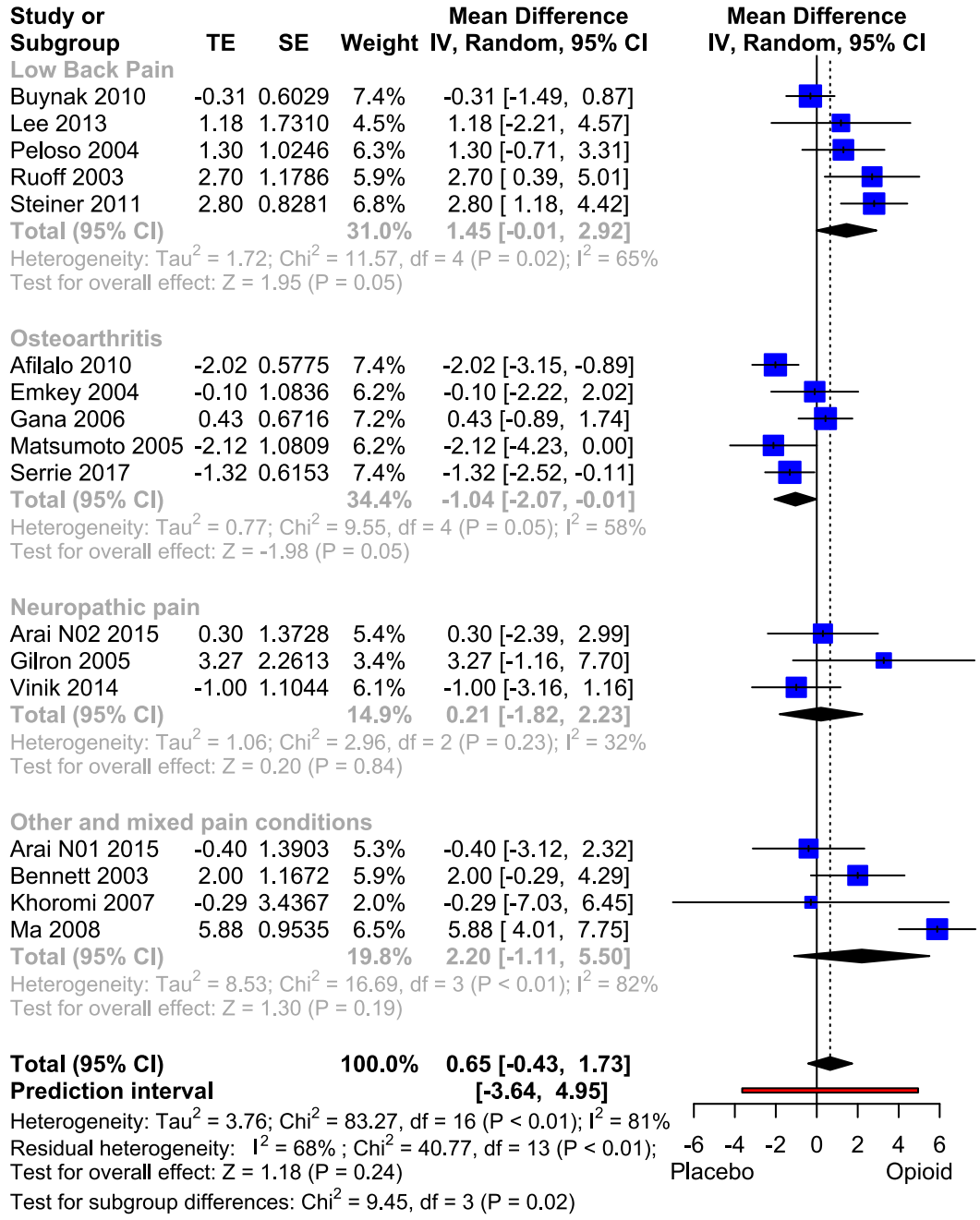

Fig. 4.4 Meta-analysis of all studies, which provided data for MCS. The analysis shows no significant treatment effect (MD: 0.43, p = 0.40).

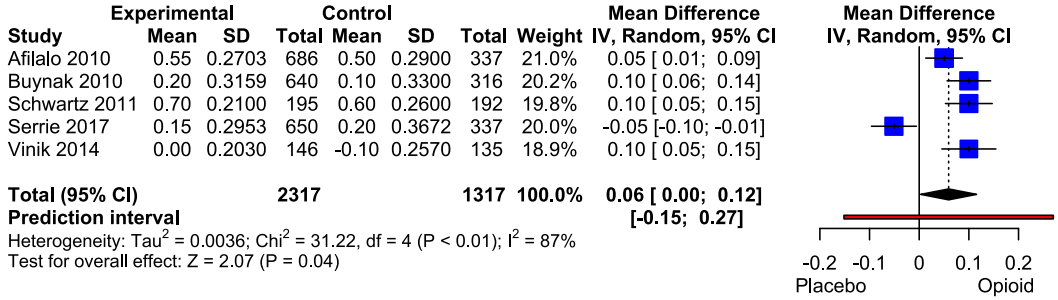

Fig. 4.5 Meta-analysis of EQ-5D. The analysis shows a significant benefit of opioid therapy compared to placebo (MD: 0.06, p = 0.04)

In summary, the analysis of the MCS shows no significant difference between opioioid therapy and placebo. The direction of the effect ist positive in the analysis of all studies, but changes its sign in the sensitivity analyzes towards a negative effect of the opioid therapy.

EQ-5D

The meta-analysis comprised five studies and data of 3634 patients. It shows a significant mean difference of 0.06 (p = 0.04) in favor of the opioid treatment (Fig. 4.5). However, a sensitivity analysis, excluding studies with withdrawal/enriched design (Schwartz 2011, Vinik 2014) showed no significant treatment effect (MD: 0.03, p = 0.43, Fig. 4.6). Because less than 10 studies were included, no analysis of funnel plot was made.

Thus, there is a significant advantage in the analysis of all studies, which is not stable in the sensitivity analysis. This may be due to the exclusion of studies with a favorable study design for the opioid therapy or due to the low statistical power, as only three studies are included in the sensitivity analysis.

Study withdrawals

Premature study withdrawals Figure 4.7 shows a meta-analysis of study withdrawals of 34 studies pooled, providing data of 6580 patients. All kinds of premature study withdrawals, regardless of their underlying cause were included into this analysis. Subgroup analyses were performed according to the classification in underlying diseases. All in all, the opioid group had an slightly higher risk of premature withdrawal, thereby not reaching statistical significance (risk difference mean: 0.04, p=0.07). However in the subgroup analysis of studies assessing osteoarthritis pain, the opioid group showed a significant higher rate of withdrawals than the placebo group (RD: 0.09, p = 0.04). Sensitivity analyses were performed, adressing two main concerns. On the one hand studies using an enriched design may bias the outcome

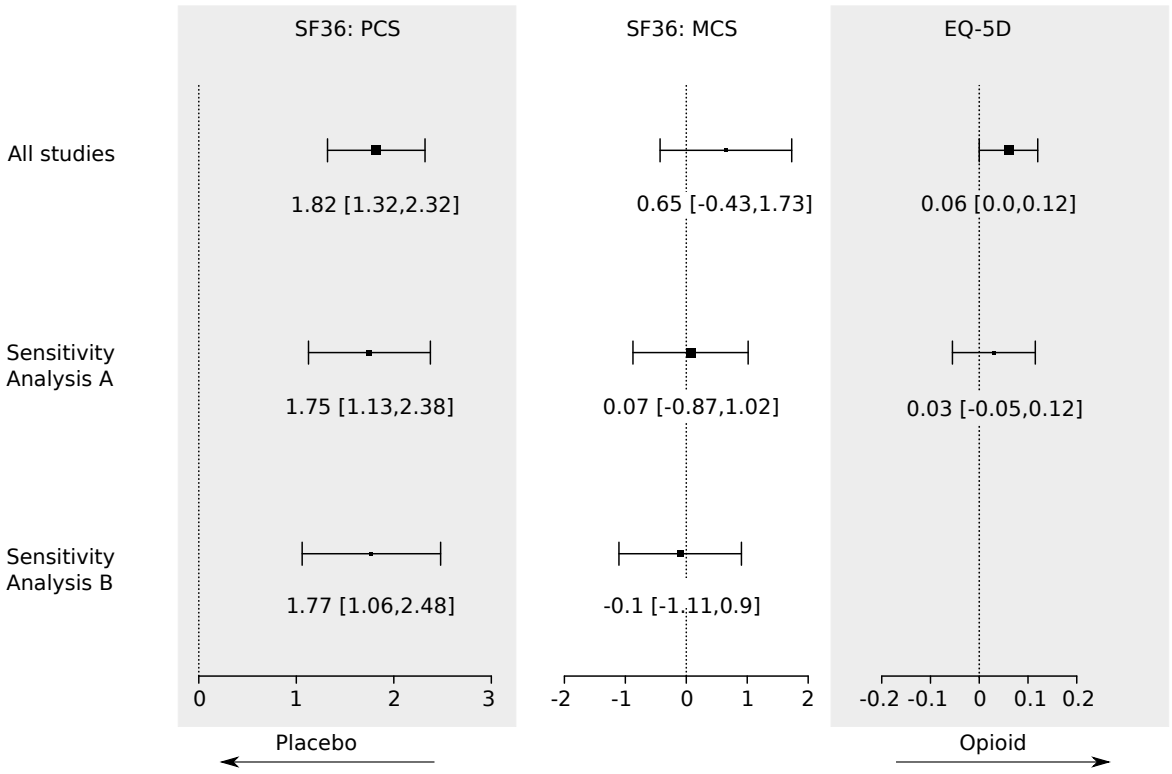

Fig. 4.6 The forest plots show the results of different sensitivity analyses of the SF-36 summary scores and the EQ-5D Health Score. The first row shows the pooled effect of all studies, which provided data of HRQL questionnaires. Sensitivity analysis A excludes studies with serious risk of bias due to enriched design or other issues (Arai N01 & N02 2015, Ma 2008, Schwartz 2011, Steiner 2011, Vinik 2014). Sensitivity analysis B further excludes studies in which, in the case of SF-36, the summary scores were estimated post-hoc from individual dimensions (Gilron 2005, Khoromi 2007, Lee 2013).

in favor of opioid therapy. On the other hand, crossover studies included, which inadequately report the study outcome may overestimate a treatment effect. However, sensitivity analyses performed (SI A.5) showed a slightly higher overall risk difference favoring placebo (RD: 0.05, p = 0.06), but no relevant differences in the subgroup analyses.

A funnel plot analysis of all studies (SI A.6) and a subsequent Egger's test showed a significant asymmetry (p = 0.03), indicating a possible risk of publication bias. However, this asymmetry may also be linked with high heterogeinity of studies included in the meta-analysis. An estimation of a corrected risk difference by the trim and fill method showed a significant higher risk for opioid group (RD: 0.09, $p < 0.01$). Thus, the results of the sensitivity analyses and especially the funnel plot analyses suggest that the original analysis of all studies (Fig. 4.7) slightly underestimates the overall risk difference of premature study withdrawal due to opioid therapy.

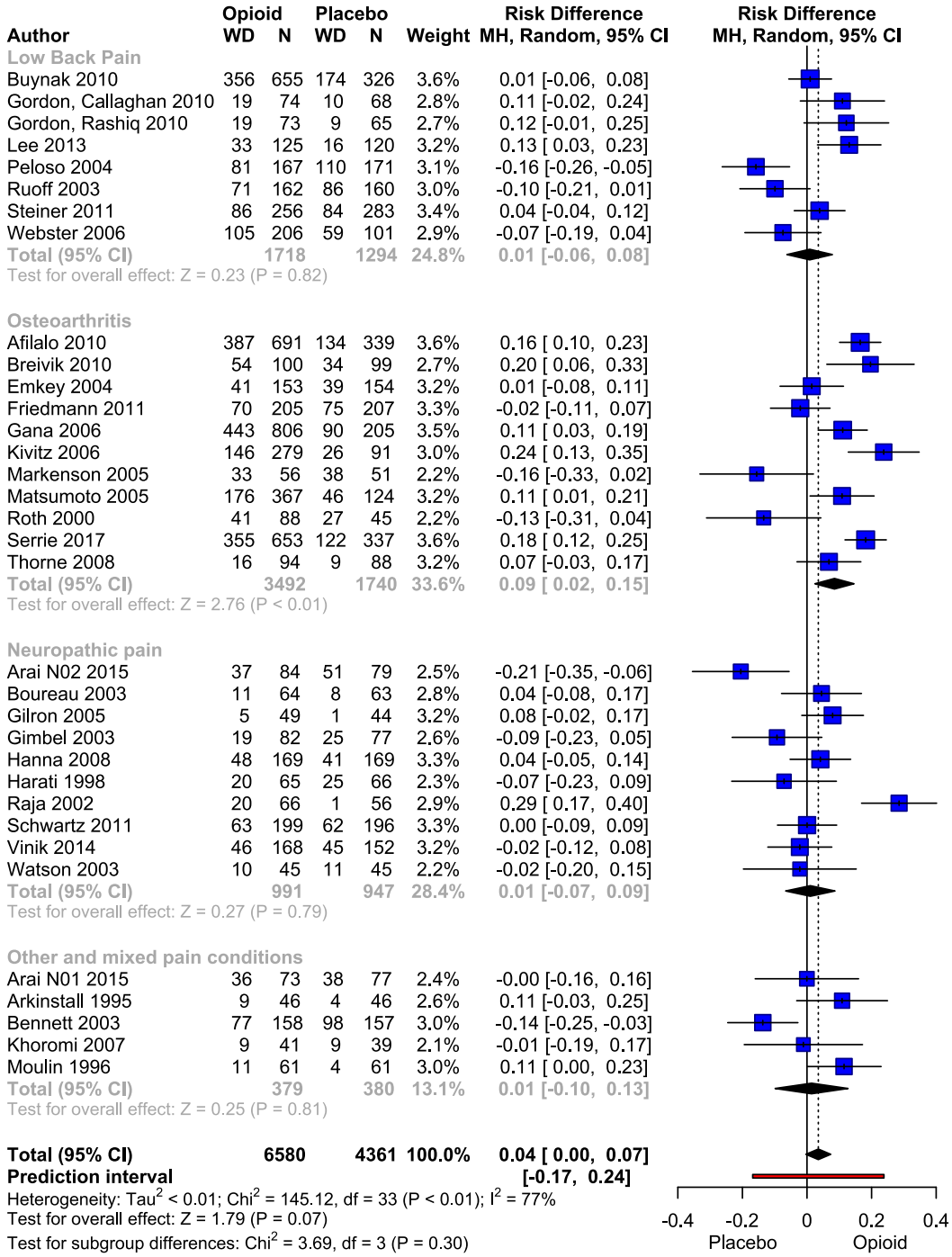

Fig. 4.7 Forestplot of meta-analysis of study withdrawals. The opioid group showed an approximately 4 % higher risk of premature discontinuation than the placebo group, but did not reach statistical significance (p = 0.07).

Study withdrawals due to adverse events The meta-analysis of study withdrawals due to adverse events (AE) was performed on 28 studies which provided data of 6183 patients. Overall, the opioid group showed a significant higher risk for withdrawals due to AE than the placebo group (RD: 0.15, $p < 0.01$, Fig. 4.8). These findings were consistent with the subgroup analysis regarding the underlying disease. Sensitivity analyses performed did not change the results significantly.

The studies showed statistically significant heterogeneity, sometimes even within subgroups. No significant asymmetry was observed in the funnel plot.

Study withdrawals due to lack of efficacy Twenty-seven studies, providing data of 6183 patients, were included in the quantitative analysis of withdrawals due to lack of therapeutical efficacy (Fig. 4.9). The analysis showed a significant higher risk of withdrawal due to lack of efficacy in the placebo group (RD: -0.11, $p < 0.01$). This effect was also significant in all subgroups. The funnel plot of the effects showed a decent heterogeneity confirmed by the Eggers test ($p < 0.01$), indicating that there might be an overestimation of the effect due to publication bias. A statistical estimation of the true risk difference by Duval's trim-and-fill procedure led to a corrected risk difference of -0.05 ($p < 0.01$). This estimation indicates that the true effect might be smaller than in the actual meta-analysis including all data available.

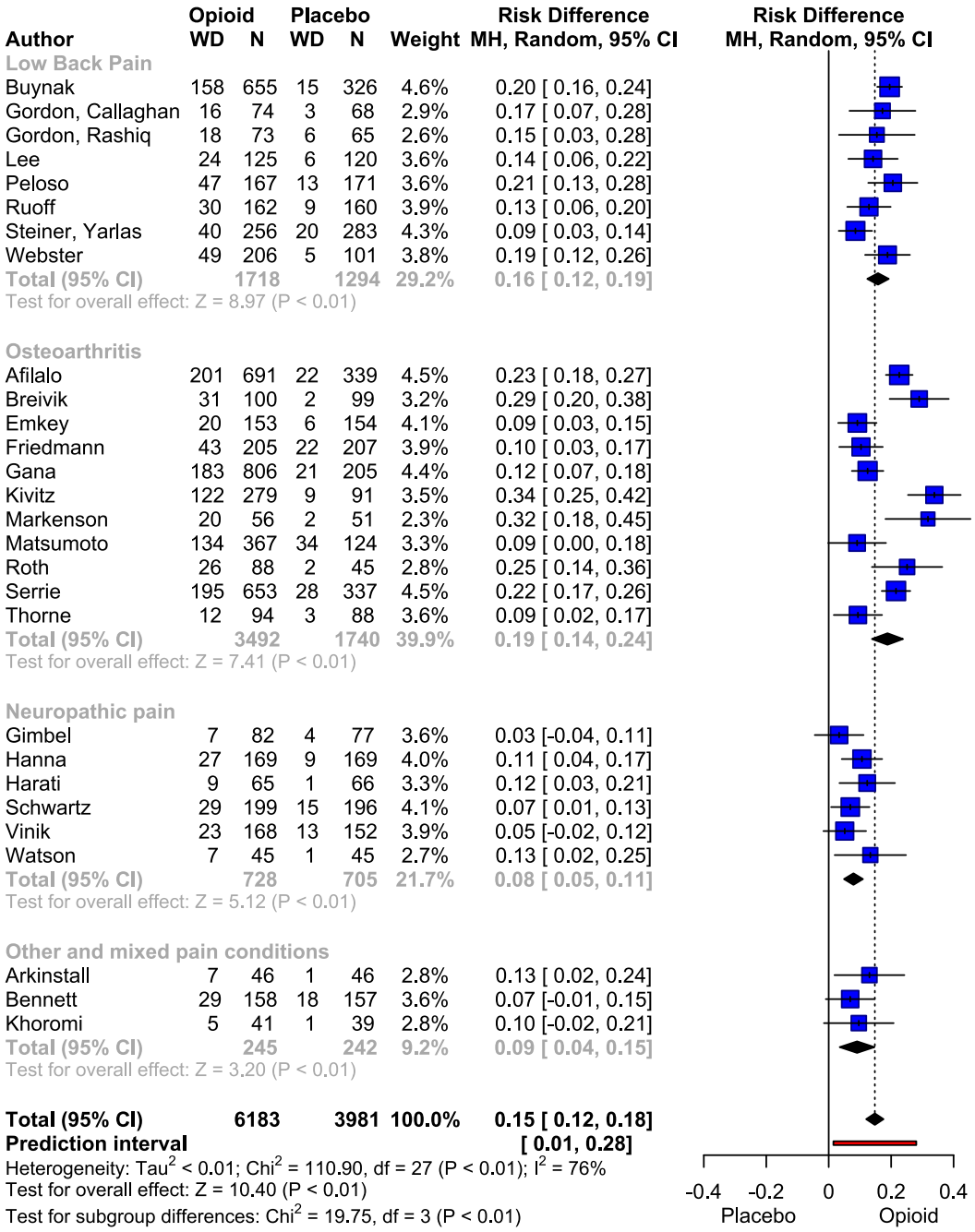

Fig. 4.8 Study withdrawals due to adverse events. The opioid group shows overall a 15 % higher risk of withdrawal due to AE than the placebo group ($p < 0.01$). Also all subgroups classified by pain origin showed a significant higher risk in the opioid group.

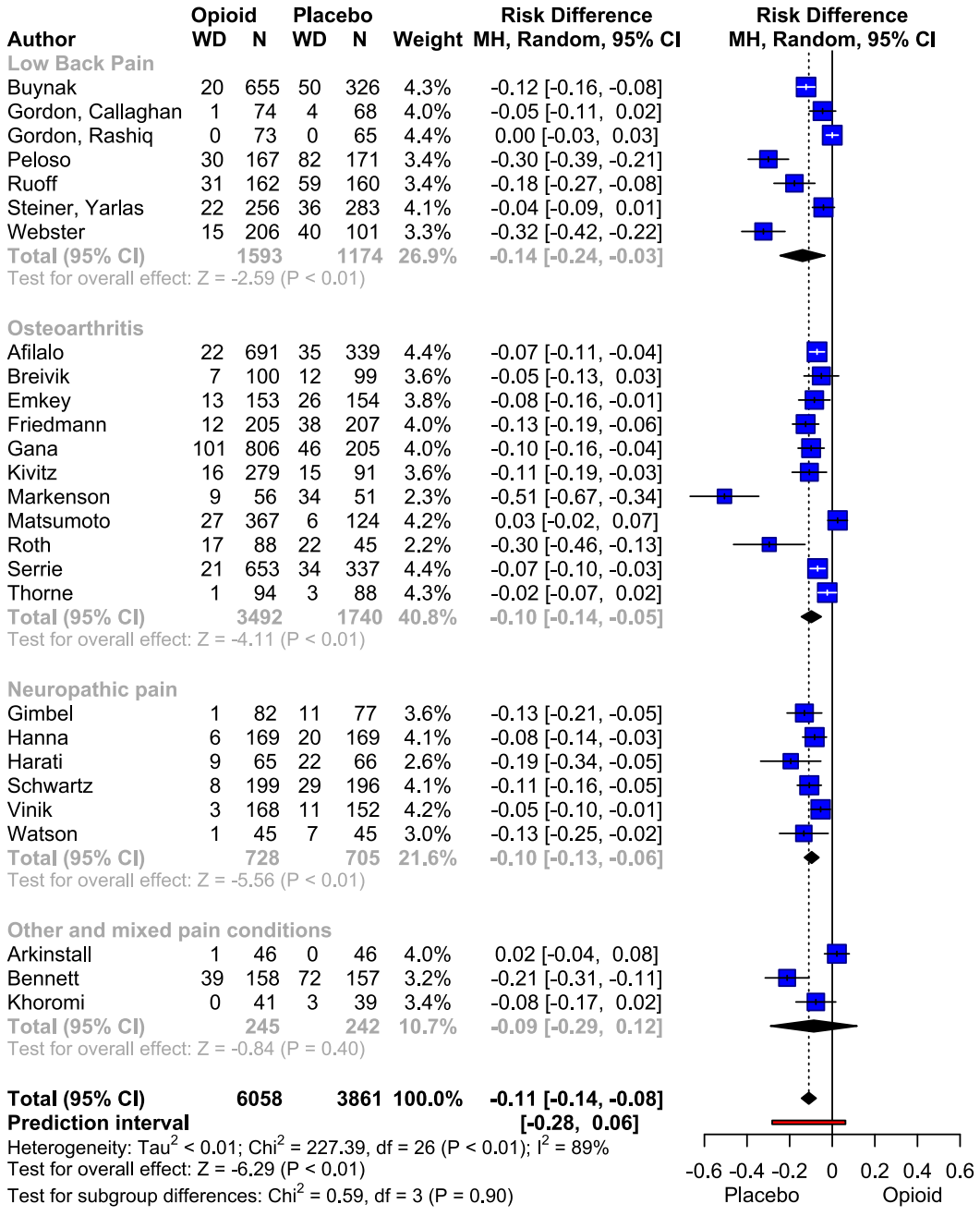

Fig. 4.9 Study withdrawals due to lack of therapeutical efficacy. The analysis shows a significant higher risk of withdrawals in the placebo group compared to the opioid group (RD: -0.11, $p < 0.01$). The subgroup analysis confirms the results of this analysis.

Chapter 5

Discussion

This review studies the impact of opioids on the HRQL of patients suffering from non-malignant chronic pain. This work is the most detailed and largest systematic review on this topic to my knowledge.

In 2005, Devulder et al. [16] published a first, descriptive review, summarizing 11 studies, including four double-blind, placebo-controlled studies and other controlled and open-label studies. A more recent analysis by Thornton et al. [78] assembled 19 studies, 11 of which were double-blind placebo-controlled RCTs. Thornton et al. focused on the analysis of the summary scales of the SF-36 and included in their statistical analysis data from five placebo-controlled RCTs, as well as data from opioid-opioid studies. Both reviews show initial evidence of a possible increase in HQRL caused by opioid therapy.

In this review 35 different RCTs were included, representing 11057 patient datasets. In order to generate the greatest possible evidence, this review focuses only on placebo-controlled, double-blind RCTs, which methodologically provide the highest grade of evidence. Furthermore, a broad search strategy was chosen to cover as many different types of chronic pain and opioids as possible and to get a quite extensive overview over the state of evidence. Since not all studies report the information necessary for a statistical metaanalysis, this review consists of a qualitative analysis, which is structured by a vote counting approach besides a quantitative metaanalysis.

The qualitative analysis of the SF-36 questionnaire shows in the PCS, the physical summary scale of the SF-36, a positive effect of opioid therapy in the vast majority of studies. Less studies assessed the EQ-5D score and the pain interference score of the BPI, but their qualitative analysis showed also in the most studies a positive effect of opioid therapy. The impression of this qualitative vote counting is confirmed by a quantitative analysis, which is based on data of 7391 patients. Here, the PCS scale shows a significant advantage with a

mean difference of 1.82 [CI: 1.32, 2.32], while the analysis of the EQ-5D index, which is based on 3634 patient datasets, shows a significant mean difference of 0.06 [0.00, 0.12], both favoring the opioid group. The result of the PCS is stable in different sensitivity analyses, whereas the effect measure of the EQ-5D becomes insignificant, when studies using an enriched design were excluded. In contrast to the PCS and the EQ-5D scores, which focus more on the *physical* dimensions of HRQL, the *mental* summary scale MCS of the SF-36 shows different results. In the vote counting, the number of studies indicating a negative effect almost equals the number of positive effects. The statistical meta-analysis, which is based on 7237 patient datasets, shows a non-significant mean difference of 0.65 [-0.43, 1.73] between opioid and placebo. However, in the sensitivity analyses the direction of the mean effect is not stable and changes finally its sign to a negative direction.

Thus, there is a significant positive effect of opioid therapy on the physical dimensions of HRQL. Although chronic pain is also generally associated with deterioration of mental health [21], no effect of opioid therapy in the mental dimensions of HRQL can be detected. A possible explanation might be that pain reduction in general does not show any strong effect on the mental HRQL dimension, or that an improvement in mental health might show up in the case of a longer treatment duration. However, contradictory statements were found in literature where a dose-response relationship between the degree of chronic pain and HRQL in the physical and mental dimensions is demonstrated.[33, 5, 89] Another very likely reason may be that common mental or neurological side effects of opioid therapy such as dizziness or somnolence neutralize a possible beneficial effect on mental HRQL.

The assessment of the risk of bias shows a particularly high risk of attrition bias due to a high premature dropout rate of participants. Averaged across all studies, approximately 41% of the participants discontinued the study prematurely. While patients in the placebo group dropped out mainly due to lack of efficacy, premature discontinuation in the opioid group was caused significantly more often due to adverse events. The overall risk for premature withdrawal was slightly higher in the opioid group than in the placebo group, however, not showing statistical significance in the main analysis but in some sensitivity analyses. This means that for many participants, the negative effects of adverse events were outweighing the positive effect on pain relief and HRQL, leading to dissatisfaction with therapy. Thus, the high dropout rate lowers the external and internal validity of the study, as the study population at study endpoint possibly may not represent the study population at randomization or the general population suffering from chronic pain.

Additional factors that limit the validity of the studies and result in a high risk of bias were incomplete reporting of HRQL results and certain study designs. Often studies did not report

non-significant results of HRQL and contacting the authors remained unsuccessful. These studies could not be included into the statistical analysis and therefore may bias the calculated results. The other main factor limiting external validity were certain study designs, which favor the opioid group. Study designs, such as the "enriched design", preselect the study sample by initially administering the opioid medication to all patients in an open-label phase and later only randomize patients who tolerate the medication well or who show a beneficial treatment response. In general, using an enriched design may bear the risk of unblinding due to side effects, as all participants experience possible side effects during the initial open-label phase.[20] There is also a tendency to underestimate the number of adverse events.[26, 99] Other authors argue that studies using enriched design may have a higher potential to detect small effects in subgroups and separation into responders and non-responders may be more similar to clinical practice.[27, 36]. The Food and Drug administration accepts enriched design trials in the drug development process and proof of concept studies, under certain restrictions on generalizability.[81] However, this review aims to answer the question whether opioids increase the HRQL in chronic pain *in general* to provide the practitioner with a good rationale for clinical decision making. Therefore, study sample should resemble the *general population* suffering from chronic pain as close as possible. Studies using an enriched design do not meet this requirement and thus may limit the internal and external validity. In this analysis, sensitivity analyses were used to detect a possible bias on the effect measures. Although no significant differences were found, the analysis showed a tendency to larger positive effects, when studies with enriched design were included.

Overall, the studies included, show a high clinical heterogeneity, covering a broad spectrum of different diseases and opioids. Most frequently, studies on chronic low back pain, osteoarthritis or neuropathic diseases, were found. Some other studies also dealt with fibromyalgia or neck pain. Overall, these conditions account for a large proportion of chronic pain conditions in the general population.[35] Studies on other frequent pain conditions like trigeminus neuralgia or migraine were not found, as opioids are generally not recommended as main therapy in these specific cases.[37, 40] Results from this meta-analysis may not apply to these diseases.

The opioids used in the studies range from weak opioids such as tramadol and codeine to strong opioids such as fentanyl or tapentadol. In addition to classic tablets, transdermal patches containing fentanyl or buprenorphine were also being studied. Trials administering tramadol/acetaminophen in a fixed combination were also included in this review, as acetaminophen has been widely used as a rescue medication in almost all other trials. In general, the effects on HRQL may also depend on the individual opioid substances, which

bear different pharmacological characteristics. However, this goes beyond the scope of this thesis. Possible differences between distinct substances could be addressed by further subgroup or network analysis. Also, a dependency of the effect on dosage regimen or the relative strength of the opioid substance should be considered in a subsequent work.

The study population is predominantly female (61.3%) and has a mean age of 57.3 years. In this respect, the study population reflects the general population in which chronic pain is associated with older age and female gender.[54] An important difference to clinical reality is that multi-morbid patients are often excluded from studies, although multi-morbidity is clearly associated with chronic pain.[37, 83] This may also limit the generalizability of the results of this review.

In total, 18 studies lasted at least 12 weeks, with a median study duration of 9.3 weeks. Thus, the conclusions of this analysis are primarily valid for the first months of therapy. Whether the therapeutical effect of opioid on HRQL is stable over long-term or if, for example, late side effects affect the outcome [22, 3] needs to be studied in further research works. This question is particularly important, because benign chronic pain with a middle age of onset requires long-term strategies.

To classify the *clinical* importance or significance of *statistically* significant results, the minimal clinically important difference (MID) [34] may provide some guidance. There is a variety of different approaches for calculating the MID. One approach is the distribution method with a commonly used MID of 0.5xSD of the baseline value.[58] Other more recent methods include the anchor method, which, for example, calculates for rheumatoid arthritis a MID of 7.2 on the PCS scale.[52] The baseline standard deviations of the PCS scale were not given for all studies, but 0.5xSD ranges approximately from 1.16 in Ma 2008 to 8.49 in AraiN02 2015. Thus, for the calculated confidence interval [1.32, 2.32] in the PCS, clinical significance cannot be demonstrated. This is also the case for the EQ-5D score. The statistical significant advantage of opioids may be clinically not significant. However, because of the high clinical heterogeneity and the varying definitions of the MID, this assessment of the clinical significancy can only be a rough estimate and needs further review.

In summary, this review shows a statistically significant benefit of opioids over placebo in the physical dimensions of HRQL. This confirms and quantifies the impressions of previous analyses.[16, 78] However, a clinical significance of this advantage compared to placebo cannot be demonstrated. On the other hand, the mental dimensions of HRQL show no difference between opioid and placebo. The overall quality of evidence is rated as low to medium, since a substantial number of RCTs included has a high risk of bias. The studies show also a high degree of methodological and statistical heterogeneity.

The strength of this review is the combination of a qualitative vote-counting analysis with a rigorous statistical analysis, permitting the inclusion and evaluation of a large number of placebo-controlled RCTs. This distinguishes this analysis from previous reviews [16, 78] and provides a comprehensive overview of the current state of the evidence.

Further research is needed on the long-term effects on HRQL, as the included studies mainly focused on the first weeks and months of therapy. Furthermore, this reviews demonstrates the important role of adverse events on therapeutic adherence. Adverse events, which were the main cause of premature dropouts in the opioid group, may limit the beneficial impact on HRQL. Further research may investigate this relationship between side effects and HRQL. The introduction of new substances or therapeutic strategies [44, 6] may possibly improve the management of side effects and lead to a better HRQL for patients suffering from chronic pain.

Chapter 6

Clinical impact

This systematic review proves, at least partially, a positive and statistically significant effect of opioids on HRQL in non-malignant chronic pain. However, this effect is small and restricted to the physical dimensions of HRQL. The analysis does not support clinical significance of a beneficial effect. There was no significant effect on the mental dimensions of HRQL, the sensitivity analyses showed negative and positive directions of effect.

This means for clinical practice, that patients who show a decrease in functionality and physical dimensions of HRQL due to chronic non-malignant pain, may profit from opioid therapy. However, as opioids could potentially lower the mental dimensions of HRQL, the psychological and the emotional state of the patients should be considered before and during therapy, especially in the presence of psychological comorbidities such as depression. Furthermore, a sufficient management and minimization of side effects seems to be crucial for therapeutic success, as physical and mental side effects of opioids are the main cause for early discontinuation and treatment failure.

Because of the small effect size and the possible side effects, each decision for an opioid therapy in non-malignant chronic pain should be made individually. The duration of treatment with opioids should be set carefully, keeping in mind that the current review provides only information about the first months of treatment.

The current evidence is not sufficient for a *general* recommendation of opioid treatment as first line in non-malignant chronic pain in order to enhance long-term HRQL.

Zusammenfassung

Chronische Schmerzen sind weltweit ein großes gesundheitliches Problem mit bedeutender gesellschaftlicher Auswirkung. Sie beeinflussen unterschiedlichste Lebensbereiche der Betroffenen und bedingen damit nachweislich den Verlust von Lebensqualität.
Zur Therapie chronischer Schmerzen werden häufig Opioide angewandt. Opioide sind als potente Analgetika unverzichtbar für die Schmerztherapie, weisen aber auch eine Vielzahl unerwünschter Nebenwirkungen auf.
Diese systematische Übersichtsarbeit mit integrierter Metaanalyse widmet sich nun der klinisch bedeutsamen Frage: verbessern Opioide die Lebensqualität bei Patient*innen mit nicht-malignem, chronischem Schmerz?

Dazu wurde im Juni 2020 eine umfangreiche Literaturrecherche in den Datenbanken PubMed (MEDLINE und PubMed Central), EMBASE und The Cochrane Library durchgeführt. Es wurden Studien zu chronischem Schmerz unter nicht-invasiver Opioidtherapie, wie z. B. oraler oder transdermaler Wirkstoffgabe, eingeschlossen. Die Studien mussten weiterhin die Messung eines validen krankheitsspezifischen oder generischen Lebensqualitätsfragebogens beinhalten. Gesucht wurde ausschließlich nach doppelblinden, placebokontrollierten randomisierten Studien (RCTs). Studien mit intrathekaler Gabe von Opioiden und mit kombinierter Gabe von Opioiden und Naloxon wurden ausgeschlossen. Aus den RCTs wurden Informationen zu Studienpopulation, Studiendesign, Interventionen, Lebensqualität und Nebenwirkungen extrahiert.
Die Übersichtsarbeit gliedert sich in zwei Teile. In einer ersten qualitativen Analyse wurden die Informationen zur Lebensqualität mittels eines Vote-counting Verfahrens ausgewertet. Beim Vote-counting Verfahren werden die Vorzeichen bzw. Richtungen der Effekte der einzelnen Studien ausgezählt, ohne Berücksichtigung von Effektstärke oder Signifikanz. In einer anschließenden Metaanalyse wurden die Lebensqualitätsfragebögen SF-36, BPI Pain Interference Scale und EQ-5D analysiert. In diesem Rahmen wurde weiterhin auch das

Risiko eines vorzeitigen Studienabbruchs untersucht.

Insgesamt ergab die Literaturrecherche 2186 Artikel, von denen schließlich 35 Studien mit Daten zu 11057 Patient*innen in dieser Arbeit analysiert wurden.
In der qualitativen Analyse des *physischen* Summenscores (physical summary scale - PCS) des SF-36 Fragebogens, welcher von 26 Studien erhoben wurde, zeigten 22 Studien einen positiven Effekt der Opioidtherapie im Vergleich zum Placebo. Deutlich weniger Studien erhoben den EQ-5D Fragebogen und die Pain Interference Skala des BPI, doch auch hier zeigte sich eine klare Mehrheit der Studien mit positivem Effekt. Die statistische Metaanalyse bestätigte diesen Eindruck. Hier zeigte sich bei analysierten Daten von 7391 Patient*innen, ein signifikanter, mittlerer Vorteil von 1.82 [Konfidenzintervall: 1.32, 2.32] der Opioidtherapie gegenüber Placebo. Bei der Analyse von 3634 Datensätzen des EQ-5D zeigte sich ein signifikanter, mittlerer Vorteil von 0.06 [0.00, 0.12]. In weiteren Sensitivitätsanalysen des PCS blieb der Vorteil der Opioidtherapie stabil, beim EQ-5D wurde er hingegen insignifikant.
Die Analyse des *mentalen* Summenscores (mental summary scale - MCS) zeigte ein anderes Bild. Hier wiesen in der qualitativen Analyse annähernd so viele Studien einen negativen wie einen positiven Effekt der Opioidtherapie gegenüber Placebo auf. In der Metaanalyse zeigte sich, bei Daten von 7237 Proband*innen, mit einer mittleren Differenz von 0.65 [-0.43, 1.73] kein signifikanter Effekt. In Sensitivitätsanalysen, in denen Studien mit methodischen Schwächen ausgeschlossen wurden, wechselte der Effekt zudem sein Vorzeichen hin zu einem negativen Effekt.
Wegen eines durchschnittlich hohen Risikos einer Verzerrung (Risk of Bias) ist umfassend betrachtet die Evidenz dieser Datenlage von niedriger bis mittlerer Qualität. Auffallend ist zudem eine hohe vorzeitige Studienabbruchquote von ca. 40%. Als häufigsten Grund für einen vorzeitigen Studienabbruch während Opioideinnahme wurden unerwünschte Nebenwirkungen angegeben.

Während bei der *mentalen* Dimension der Lebensqualität kein Unterschied zwischen Opioid und Placebo gefunden werden konnte, zeigt sich bei den *physischen* Dimensionen ein *statistisch* signifikanter Vorteil der Opioidtherapie. Eine Abschätzung der *klinischen* Signifikanz dieses Effektes, welche sich auf den individuellen Nutzen für die Patient*innen bezieht, konnte jedoch mittels gängiger Definition keinen klinisch signifikanten Effekt nachweisen.
Mit einer durchschnittlichen Studiendauer von 9.3 Wochen bezieht sich diese Arbeit hauptsächlich auf die ersten Wochen und Monate der Therapie. Es besteht weiterer Forschungsbedarf hinsichtlich der Langzeiteffektivität und den Langzeitfolgen der Opioidtherapie.

Weiterhin zeigt diese Übersichtsarbeit, dass die Studienabbruchquote und damit die therapeutische Adhärenz maßgeblich vom Nebenwirkungsprofil der Opioidtherapie limitiert wird. Auch hier bedarf es weiterer Forschung um die Verträglichkeit der Opioidtherapie zu verbessern und damit auch die Effektivität der chronischen Schmerztherapie hinsichtlich der Lebensqualität der vom chronischen Schmerz Betroffenen zu erhöhen.

Abstract

Chronic pain is a worldwide major health issue in all modern societies. It affects the patient's life in various dimensions of daily living and is associated with a significant loss of health-related quality of life (HRQL).
Opioids are often used to treat chronic pain. As potent analgesics, they have become indispensable in pain therapy, but have also the potential of severe side effects.
This systematic review with meta-analysis aims to answer the clinically important question if opioid therapy improves the HRQL in patients with chronic non-malignant pain.

For this purpose, the databases PubMed (MEDLINE, PubMed Central), EMBASE and The Cochrane Library were searched in June 2020. Studies were included if they were double-blind, randomized trials (RCTs), which compared opioid therapy to placebo for chronic pain and assessed a valid generic HRQL questionnaire. Studies investigating intrathecal or invasive opioid administration and fixed combinations of opioid and naloxone were excluded. Information on study population, study design, intervention, HRQL assessment and adverse events were extracted. The review is divided into two parts.
A first qualitative part consists of a vote-counting approach, which assesses the direction of effects on HRQL, without considering effect size or significance. The second part is a meta-analysis of the results of the HRQL questionnaires SF-36, EQ-5D and the BPI pain interference scale. Also, the risk for premature study withdrawal was statistically analyzed.

Altogether 2186 articles were screened and finally 35 RCTs, consisting of 11057 patient datasets were included in this review.
In the qualitative analysis of the *physical* sum score PCS of the SF-36 questionnaire 22 out of 26 studies showed a positive effect favoring the opioid therapy. Also, the majority of studies which assessed the EQ-5D or the BPI showed a positive direction of effect. The statistical meta-analysis of the PCS, consisting of 7391 patient records, showed a mean difference of 1.82 [confidence interval: 1.32, 2.32] favoring opioid over placebo. Also the analysis of the

EQ-5D, with data of 3634 patients, showed a significant advantage of 0.06 [0.00, 0.12] in favor of opioid therapy. A sensitivity analysis proved the stability of the significant effect in the PCS, whereas the effect in the EQ-5D becomes insignificant.
The qualitative analysis of the *mental* summary scale MCS of the SF-36 showed an almost equal number of studies with a positive and a negative direction of effect. The meta-analysis on data of 7237 patients showed no significant differences (0.65 [-0.43, 1.73]) in the MCS. In the sensitivity analysis, the effect changes its sign to a negative direction.
Due to an average high risk of bias, the overall evidence of the studies included is of low to medium quality. Especially remarkable is a high premature dropout rate of around 40% of the participants. Adverse events were reported as the most common reason for a premature study withdrawal during opioid therapy.

In contrast to the *mental* dimensions of HRQL, which showed no significant effect of opioid therapy, the *physical* dimensions of HRQL demonstrated a *statistically* significant advantage over placebo. However, a *clinical* significance of this effect, which refers to individual clinical benefit for the patients, could not be demonstrated. As the mean study duration was about 9.3 weeks, the results of this analysis are valid for the first weeks and months of therapy. Further research on the long-time effect on HRQL in non-malignant pain may be necessary. Furthermore, this review shows that the dropout rate and, thus, the therapeutic adherence are significantly limited by the side effects associated with opioid intake. Further research may increase the tolerability of opioid therapy in order to enhance the efficacy in the therapy of chronic pain.

References

[1] Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., Filiberti, A., Flechtner, H., Fleishman, S. B., and de Haes, J. C. (1993). The european organization for research and treatment of cancer qlq-c30: A quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute*, 85(5):365–376.

[2] Al-Hasani, R. and Bruchas, M. R. (2011). Molecular mechanisms of opioid receptor-dependent signaling and behavior. *Anesthesiology*, 115(6):1363–1381.

[3] Baldini, A., von Korff, M., and Lin, E. H. B. (2012). A review of potential adverse effects of long-term opioid therapy: A practitioner's guide. *The Primary Care Companion to CNS Disorders*, 14(3).

[4] Ballantyne, J. C. and Mao, J. (2003). Opioid therapy for chronic pain. *The New England journal of medicine*, 349(20):1943–1953.

[5] Becker, N., Thomsen, A. B., Olsen, A. K., Sjøgren, P., Bech, P., and Eriksen, J. (1997). Pain epidemiology and health related quality of life in chronic non-malignant pain patients referred to a danish multidisciplinary pain center. *Pain*, 73(3).

[6] Benyamin, R., Am Trescot, Datta, S., Buenaventura, R., Adlaka, R., Sehgal, N., Glaser, S. E., and Vallejo, R. (2008). Opioid complications and side effects. *Pain physician*, 11(2 Suppl).

[7] Berzon, R., Hays, R. D., and Shumaker, S. A. (1993). International use, application and performance of health-related quality of life instruments. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*, 2(6):367–368.

[8] Breivik, H., Collett, B., Ventafridda, V., Cohen, R., and Gallacher, D. (2006). Survey of chronic pain in europe: Prevalence, impact on daily life, and treatment. *European journal of pain (London, England)*, 10(4):287–333.

[9] Brownstein, M. J. (1993). A brief history of opiates, opioid peptides, and opioid receptors. *Proceedings of the National Academy of Sciences*, 90(12):5391–5393.

[10] Bullinger, M. and Quitmann, J. (2014). Quality of life as patient-reported outcomes: Principles of assessment. *Dialogues in Clinical Neuroscience*, 16(2):137–145.

[11] Chou, R., Fanciullo, G. J., Fine, P. G., Adler, J. A., Ballantyne, J. C., Davies, P., Donovan, M. I., Fishbain, D. A., Foley, K. M., Fudin, J., Gilson, A. M., Kelter, A., Mauskop, A., O'Connor, P. G., Passik, S. D., Pasternak, G. W., Portenoy, R. K., Rich, B. A., Roberts, R. G., Todd, K. H., and Miaskowski, C. (2009). Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *The journal of pain : official journal of the American Pain Society*, 10(2):113–130.

[12] Chou, R., Turner, J. A., Devine, E. B., Hansen, R. N., Sullivan, S. D., Blazina, I., Dana, T., Bougatsos, C., and Deyo, R. A. (2015). The effectiveness and risks of long-term opioid therapy for chronic pain: A systematic review for a national institutes of health pathways to prevention workshop. *Annals of internal medicine*, 162(4):276–286.

[13] Cleeland, C. S. (2011). *The Brief Pain Inventory: User Guide*.

[14] Crofford, L. J. (2015). Chronic pain: Where the body meets the brain. *Transactions of the American Clinical and Climatological Association*, 126:167–183.

[15] de Heer, E. W., Gerrits, M. M. J. G., Beekman, A. T. F., Dekker, J., van Marwijk, H. W. J., de Waal, M. W. M., Spinhoven, P., Penninx, B. W. J. H., and van der Feltz-Cornelis, C. M. (2014). The association of depression and anxiety with pain: A study from nesda. *PloS one*, 9(10):e106907.

[16] Devulder, J., Richarz, U., and Nataraja, S. H. (2005). Impact of long-term use of opioids on quality of life in patients with chronic, non-malignant pain. *Current medical research and opinion*, 21(10):1555–1568.

[17] Diatchenko, L., Fillingim, R. B., Smith, S. B., and Maixner, W. (2013). The phenotypic and genetic signatures of common musculoskeletal pain conditions. *Nature reviews. Rheumatology*, 9(6):340–350.

[18] Dueñas, M., Ojeda, B., Salazar, A., Mico, J. A., and Failde, I. (2016). A review of chronic pain impact on patients, their social environment and the health care system. *Journal of pain research*, 9:457–467.

[19] Duval, S. and Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*, 56(2).

[20] Dworkin, R. H., Turk, D. C., Peirce-Sandner, S., Burke, L. B., Farrar, J. T., Gilron, I., Jensen, M. P., Katz, N. P., Raja, S. N., Rappaport, B. A., Rowbotham, M. C., Backonja, M. M., Baron, R., Bellamy, N., Bhagwagar, Z., Costello, A., Cowan, P., Fang, W. C., Hertz, S., Jay, G. W., Junor, R., Kerns, R. D., Kerwin, R., Kopecky, E. A., Lissin, D., Malamut, R., Markman, J. D., McDermott, M. P., Munera, C., Porter, L., Rauschkolb, C., Rice, A. S., Sampaio, C., Skljarevski, V., Sommerville, K., Stacey, B. R., Steigerwald, I., Tobias, J., Am Trentacosti, Wasan, A. D., Wells, G. A., Williams, J., Witter, J., and Ziegler, D. (2012). Considerations for improving assay sensitivity in chronic pain clinical trials: Immpact recommendations. *Pain*, 153(6).

[21] Elliott, T. E., Renier, C. M., and Palcher, J. A. (2003). Chronic pain, depression, and quality of life: Correlations and predictive value of the sf-36. *Pain Medicine*, 4(4):331–339.

[22] Els, C., Jackson, T. D., Kunyk, D., Lappi, V. G., Sonnenberg, B., Hagtvedt, R., Sharma, S., Kolahdooz, F., and Straube, S. (2017). Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: An overview of cochrane reviews. *The Cochrane database of systematic reviews*, 10:CD012509.

[23] Follmann, D., Elliott, P., Suh, I., and Cutler, J. (1992). Variance imputation for overviews of clinical trials with continuous response. *Journal of clinical epidemiology*, 45(7).

[24] Franklin, G. M. (2014). Opioids for chronic noncancer pain: A position paper of the american academy of neurology. *Neurology*, 83(14):1277–1284.

[25] Friedman, L. M., Furberg, C. D., and DeMets, D. L. (2010). Assessment of health-related quality of life. In Friedman, L. M., Furberg, C. D., and DeMets, D. L., editors, *Fundamentals of Clinical Trials*, pages 233–249. Springer, New York, NY.

[26] Furlan, A. D., Irvin, E. L., van Eerd, D., Carnide, N., Munhall, C., Fortune, M., and Kim, J. (2014). Function and quality of life with long-term opioid use for chronic non-cancer pain. *Archives of Physical Medicine and Rehabilitation*, 95(10):e40.

[27] Gewandter J.S., Chaudari J., Iwan K.B., Kitt R., As-Sanie S., Bachmann G., Clemens Q., Lai H.H., Tu F., Verne G.N., Vincent K., Wesselmann U., Zhou Q., Turk D.C., Dworkin R.H., and Smith S.M. (2018). Research design characteristics of published pharmacologic randomized clinical trials for irritable bowel syndrome and chronic pelvic pain conditions: An acttion systematic review. *Journal of Pain*, 19(7):717–726.

[28] Goldberg, D. S. and McGee, S. J. (2011). Pain as a global public health priority. *BMC public health*, 11:770.

[29] Gureje, O., von Korff, M., Kola, L., Demyttenaere, K., He, Y., Posada-Villa, J., Lepine, J. P., Angermeyer, M. C., Levinson, D., de Girolamo, G., Iwata, N., Karam, A., Guimaraes Borges, G. L., de Graaf, R., Browne, M. O., Stein, D. J., Haro, J. M., Bromet, E. J., Kessler, R. C., and Alonso, J. (2008). The relation between multiple pains and mental disorders: Results from the world mental health surveys. *Pain*, 135(1-2):82–91.

[30] Harstall, C. and Ospina, M. (2003). How prevalent is chronic pain? *Pain Clinical Updates*, 11(2):1–4.

[31] Higgins, J. P., Altman, D. G., and Sterne, J. A. (2011). Chapter 8: Assessing risk of bias in included studies. In Higgins, J. P. and Green, S., editors, *Cochrane Handbook for Systematic Reviews of Interventions*.

[32] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor (2021). *Cochrane Handbook for Systematic Reviews of Interventions*. version 6.2 edition.

[33] Hunfeld, J. A., Perquin, C. W., Duivenvoorden, H. J., Hazebroek-Kampschreur, A. A., Passchier, J., van, S.-S. L. W., and van, d. W. J. (2001). Chronic pain and its impact on quality of life in adolescents and their families. *Journal of pediatric psychology*, 26(3).

[34] Jaeschke, R., Singer, J., and Guyatt, G. H. (1989). Measurement of health status. ascertaining the minimal clinically important difference. *Controlled clinical trials*, 10(4).

[35] Johannes, C. B., Le, T. K., Zhou, X., Johnston, J. A., and Dworkin, R. H. (2010). The prevalence of chronic pain in united states adults: results of an internet-based survey. *The journal of pain*, 11(11).

[36] Katz, N. (2009). Enriched enrollment randomized withdrawal trial designs of analgesics: focus on methodology. *The Clinical journal of pain*, 25(9).

[37] Kelley, N. E. and Tepper, D. E. (2012). Rescue therapy for acute migraine, part 3: opioids, nsaids, steroids, and post-discharge medications. *Headache*, 52(3).

[38] Kolodny, A., Courtwright, D. T., Hwang, C. S., Kreiner, P., Eadie, J. L., Clark, T. W., and Alexander, G. C. (2015). The prescription opioid and heroin crisis: A public health approach to an epidemic of addiction. *Annual review of public health*, 36:559–574.

[39] Kuner, R. and Flor, H. (2016). Structural plasticity and reorganisation in chronic pain. *Nature reviews. Neuroscience*, 18(1):20–30.

[40] L. Bendtsen, J. M. Zakrzewska, J. Abbott, M. Braschinsky, G. Di Stefano, A. Donnet, P. K. Eide, P. R. L. Leal, S. Maarbjerg, A. May, T. Nurmikko, M. Obermann, T. S. Jensen, and G. Cruccu (2019). European academy of neurology guideline on trigeminal neuralgia. *European Journal of Neurology*, 26(6):831–849.

[41] Lapane, K. L., Quilliam, B. J., Benson, C., Chow, W., and Kim, M. S. (2015). Impact of noncancer pain on health-related quality of life. *Pain practice : the official journal of World Institute of Pain*, 15(4):333–342.

[42] Leadley, R. M., Armstrong, N., Lee, Y. C., Allen, A., and Kleijnen, J. (2012). Chronic diseases in the european union: The prevalence and health cost implications of chronic pain. *Journal of pain & palliative care pharmacotherapy*, 26(4):310–325.

[43] Luz, R., Pereira, I., Henriques, A., Ribeirinho, A. L., and Valentim-Lourenço, A. (2017). King's health questionnaire to assess subjective outcomes after surgical treatment for urinary incontinence: can it be useful? *International urogynecology journal*, 28(1).

[44] Machelska, H. and Celik, M. Ö. (2018). Advances in achieving opioid analgesia without side effects. *Frontiers in Pharmacology*, 9:1388.

[45] Manchikanti, L., Helm, S., Fellows, B., Janata, J. W., Pampati, V., Grider, J. S., and Boswell, M. V. (2012). Opioid epidemic in the united states. *Pain physician*, 15(3 Suppl):ES9–38.

[46] Matthias Egger, George Davey Smith, Martin Schneider, and Christoph Minder (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, 315(7109):629–634.

[47] McCarberg, B. H., Nicholson, B. D., Todd, K. H., Palmer, T., and Penles, L. (2008). The impact of pain on quality of life and the unmet needs of pain management: Results from pain sufferers and physicians participating in an internet survey. *American journal of therapeutics*, 15(4):312–320.

[48] McConnell, S., Kolopack, P., and Davis, A. M. (2001). The western ontario and mcmaster universities osteoarthritis index (womac): a review of its utility and measurement properties. *Arthritis & Rheumatism*, 45(5):453–461.

[49] McDowell, I. (2006a). Measuring health: A guide to rating scales and questionnaires. In McDowell, I., editor, *Measuring health*, pages 520–704. Oxford University Press, New York and Oxford.

[50] McDowell, I., editor (2006b). *Measuring health: A guide to rating scales and questionnaires*. Oxford University Press, New York and Oxford, 3rd ed. edition.

[51] McNicol, E. D., Midbari, A., and Eisenberg, E. (2013). Opioids for neuropathic pain. *The Cochrane database of systematic reviews*, (8):CD006146.

[52] Michael M. Ward, Lori C. Guthrie, and Maria I. Alba (2014). Clinically important changes in short form 36 health survey scales for use in rheumatoid arthritis clinical trials: The impact of low responsiveness. *Arthritis care & research*, 66(12):1783–1789.

[53] Michele Hilton Boon and Hilary Thomson (2021). The effect direction plot revisited: Application of the 2019 cochrane handbook guidance on alternative synthesis methods. *Research Synthesis Methods*, 12(1):29–33.

[54] Mills, S. E., Nicolson, K. P., and Smith, B. H. (2019). Chronic pain: a review of its epidemiology and associated factors in population-based studies. *BJA: British Journal of Anaesthesia*, 123(2):e273–83.

[55] Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., and Group, T. P. (2009). Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. *PLOS Medicine*, 6(7):e1000097.

[56] Natusch, D. (2012). Equianalgesic doses of opioids - their use in clinical practice. *British journal of pain*, 6(1):43–46.

[57] Noble, M., Treadwell, J. R., Tregear, S. J., Coates, V. H., Wiffen, P. J., Akafomo, C., and Schoelles, K. M. (2010). Long-term opioid management for chronic noncancer pain. *The Cochrane database of systematic reviews*, (1):CD006605.

[58] Norman, G. R., Sloan, J. A., and Wyrwich, K. W. (2003). Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. *Medical Care*, 41(5):582–592.

[59] O'Brien, E. M., Waxenberg, L. B., Atchison, J. W., Gremillion, H. A., Staud, R. M., McCrae, C. S., and Robinson, M. E. (2011). Intraindividual variability in daily sleep and pain ratings among chronic pain patients: Bidirectional association and the role of negative mood. *The Clinical journal of pain*, 27(5):425–433.

[60] Okie, S. (2010). A flood of opioids, a rising tide of deaths. *The New England journal of medicine*, 363(21):1981–1985.

[61] Orenius, T., Koskela, T., Koho, P., Pohjolainen, T., Kautiainen, H., Haanpää, M., and Hurri, H. (2013). Anxiety and depression are independent predictors of quality of life of patients with chronic musculoskeletal pain. *Journal of health psychology*, 18(2):167–175.

[62] Pathan, H. and Williams, J. (2012). Basic opioid pharmacology: An update. *British journal of pain*, 6(1):11–16.

[63] Patrick, D. L. and Deyo, R. A. (1989). Generic and disease-specific measures in assessing health status and quality of life. *Medical Care*, 27(3):S217–S232.

[64] Peppin, J. F. and Schatman, M. E. (2016). Terminology of chronic pain: The need to "level the playing field". *Journal of pain research*, 9:23–24.

[65] R Core Team (2020). R: A language and environment for statistical computing.

[66] Rabin, R. and de Charro, F. (2001). Eq-5d: A measure of health status from the euroqol group. *Annals of medicine*, 33(5):337–343.

[67] Rauf, W. N., Meyer, H. P., Marcus, T. S., and Becker, P. J. (2014). Prevalence of chronic pain in patients attending primary healthcare facilities in south-west tshwane. *South African Family Practice*, 55(1):85–89.

[68] Richardson, W. S., Wilson, M. C., Nishikawa, J., and Hayward, R. S. (1995). The well-built clinical question: A key to evidence-based decisions. *ACP journal club*, 123(3):A12–3.

[69] Rose A. Rudd (2016). Increases in drug and opioid-involved overdose deaths — united states, 2010–2015. *MMWR. Morbidity and Mortality Weekly Report*, 65.

[70] Saha, T. D., Kerridge, B. T., Goldstein, R. B., Chou, S. P., Zhang, H., Jung, J., Pickering, R. P., Ruan, W. J., Smith, S. M., Huang, B., Hasin, D. S., and Grant, B. F. (2016). Non-medical prescription opioid use and dsm-5 nonmedical prescription opioid use disorder in the united states. *The Journal of clinical psychiatry*, 77(6).

[71] Sara Balduzzi, Gerta Rücker, and Guido Schwarzer (2019). How to perform a meta-analysis with r: a practical tutorial. *Evidence-Based Mental Health*, (22):153–160.

[72] Scholich, S. L., Hallner, D., Wittenberg, R. H., Hasenbring, M. I., and Rusu, A. C. (2012). The relationship between pain, disability, quality of life and cognitive-behavioural factors in chronic back pain. *Disability and rehabilitation*, 34(23):1993–2000.

[73] Schubert, I., Ihle, P., and Sabatowski, R. (2013). Increase in opiate prescription in germany between 2000 and 2010: A study based on insurance data. *Deutsches Arzteblatt international*, 110(4):45–51.

[74] Skolnick, P. (2018). The opioid epidemic: Crisis and solutions. *Annual review of pharmacology and toxicology*, 58:143–159.

[75] Smith, B. H., Elliott, A. M., Chambers, W. A., Smith, W. C., Hannaford, P. C., and Penny, K. (2001). The impact of chronic pain in the community. *Family practice*, 18(3):292–299.

[76] Stefan Grond and Armin Sablotzki (2004). Clinical pharmacology of tramadol. *Clinical Pharmacokinetics*, 43(13):879–923.

[77] Thienhaus, O. and Cole, B. E. (2002). The classification of pain. In Weiner, R. S., editor, *Pain Management*, pages 27–36. CRC Press, Boca Raton u.a.

[78] Thornton, J. D., Goyat, R., Dwibedi, N., and Kelley, G. A. (2017). Health-related quality of life in patients receiving long-term opioid therapy: a systematic review with meta-analysis. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*, 26(8).

[79] Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N. B., First, M. B., Giamberardino, M. A., Kaasa, S., Kosek, E., Lavandhomme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., Smith, B. H., Svensson, P., Vlaeyen, J. W. S., and Wang, S.-J. (2015). A classification of chronic pain for icd-11. *Pain*, 156(6):1003–1007.

[80] Trescot, A. M., Datta, S., Lee, M., and Hansen, H. (2008). Opioid pharmacology. *Pain physician*, 11(2 Suppl):S133–53.

[81] U.S. Department of Health and Human Services. Food and Drug Administration. (2019). Enrichment strategies for clinical trials to support determination of effectiveness of human drugs and biological products guidance for industry.

[82] Vadivelu, N. and Sinatra, R. (2005). Recent advances in elucidating pain mechanisms. *Current opinion in anaesthesiology*, 18(5):540–547.

[83] van Hecke, O., Torrance, N., and Smith, B. H. (2013). Chronic pain epidemiology and its clinical relevance. *British journal of anaesthesia*, 111(1):13–18.

[84] van Reenen, M. and Janssen, B. (2015). *EQ-5D-5L User Guide: Basic information on how to use the EQ-5D-5L instrument*. EuroQol Research Foundation, Rotterdam.

[85] Vikman, K. S., Kristensson, K., and Hill, R. H. (2001). Sensitization of dorsal horn neurons in a two-compartment cell culture model: Wind-up and long-term potentiation-like responses. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 21(19):RC169.

[86] Vithlani, R. H. and Baranidharan, G. (2010). Transdermal opioids for cancer pain management. *Reviews in Pain*, 4(2):8–13.

[87] von Korff, M., Kolodny, A., Deyo, R. A., and Chou, R. (2011). Long-term opioid therapy reconsidered. *Annals of internal medicine*, 155(5):325–328.

[88] Waheed, A., Bhat, S., Hameed, A., and Nabi, V. (2013). Quality of life in patients with chronic pain- a study in indian population using european organization for research and treatment of cancer(eortc) questionnaire. *Applied Research in Quality of Life*, 8(1):77–86.

[89] Wang, X. S., Cleeland, C. S., Mendoza, T. R., Engstrom, M. C., Liu, S., Xu, G., Hao, X., Wang, Y., and Ren, X. S. (1999). The effects of pain severity on health-related quality of life: a study of chinese cancer patients. *Cancer*, 86(9).

[90] Ware, J., Kosinski, M., and Gandek, B. (1993). Sf-36 health survey: Manual & interpretation guide. *Lincoln, RI: QualityMetric Incorporated*.

[91] Ware, J., Kosinski, M., and Keller, S. D. (1996). A 12-item short-form health survey: Construction of scales and preliminary tests of reliability and validity. *Medical Care*, 34(3):220–233.

[92] Ware, J. E. and Sherbourne, C. D. (1992). The mos 36-item short-form health survey (sf-36). i. conceptual framework and item selection. *Medical Care*, 30(6):473–483.

[93] Wiebe, S., Guyatt, G., Weaver, B., Matijevic, S., and Sidwell, C. (2003). Comparative responsiveness of generic and specific quality-of-life instruments. *Journal of clinical epidemiology*, 56(1).

[94] Wolfgang Viechtbauer (2010). Conducting meta-analyses in r with the metafor package. *Journal of Statistical Software*, 36(3):1–48.

[95] Woolf, C. J. (2004). Pain: Moving from symptom control toward mechanism-specific pharmacologic management. *Annals of internal medicine*, 140(6):441.

[96] World Health Organization (1986). *Cancer pain relief*. WHO, Geneva.

[97] World Health Organization (1995). The world health organization quality of life assessment (whoqol): Position paper from the world health organization. *Social science & medicine (1982)*, 41(10):1403–1409.

[98] World Health Organization (2006). Constitution of the world health organization. basic documents, supplement, october 2006. geneva: Wold health organisation.

[99] Yamato, T. P., Maher, C. G., Saragiotto, B. T., Shaheed, C. A., Moseley, A. M., Lin, C.-W. C., Koes, B., and McLachlan, A. J. (2017). Comparison of effect sizes between enriched and nonenriched trials of analgesics for chronic musculoskeletal pain: a systematic review. *British journal of clinical pharmacology*, 83(11):2347–2355.

[100] Zin, C. S., Chen, L. C., and Knaggs, R. D. (2014). Changes in trends and pattern of strong opioid prescribing in primary care. *European journal of pain (London, England)*, 18(9):1343–1351.

[101] Zis, P., Daskalaki, A., Bountouni, I., Sykioti, P., Varrassi, G., and Paladini, A. (2017). Depression and chronic pain in the elderly: Links and management challenges. *Clinical interventions in aging*, 12:709–720.

Included studies

[102] Afilalo, M., Etropolski, M. S., Kuperwasser, B., Kelly, K., Okamoto, A., van Hove, I., Steup, A., Lange, B., Rauschkolb, C., and Haeussler, J. (2010). Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase iii study. *Clinical drug investigation*, 30(8):489–505.

[103] Arai, T., Kashimoto, Y., Ukyo, Y., Tominaga, Y., and Imanaka, K. (2015). Two placebo-controlled, randomized withdrawal studies to evaluate the fentanyl 1 day patch in opioid-naïve patients with chronic pain. *Current medical research and opinion*, 31(12):2207–2218.

[104] Arkinstall, W., Sandler, A., Goughnour, B., Babul, N., Harsanyi, Z., and Darke, A. C. (1995). Efficacy of controlled-release codeine in chronic non-malignant pain: a randomized, placebo-controlled clinical trial. *Pain*, 62(2):169–178.

[105] Bennett, R. M., Kamin, M., Karim, R., and Rosenthal, N. (2003). Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: A double-blind, randomized, placebo-controlled study. *The American Journal of Medicine*, 114(7):537–545.

[106] Bennett, R. M., Schein, J., Kosinski, M. R., Hewitt, D. J., Jordan, D. M., and Rosenthal, N. R. (2005). Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/acetaminophen. *Arthritis and rheumatism*, 53(4):519–527.

[107] Boureau, F., Legallicier, P., and Kabir-Ahmadi, M. (2003). Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. *Pain*, 104(1-2):323–331.

[108] Breivik, H., Ljosaa, T. M., Stengaard-Pedersen, K., Persson, J., Aro, H., Villumsen, J., and Tvinnemose, D. (2010). A 6-months, randomised, placebo-controlled evaluation of efficacy and tolerability of a low-dose 7-day buprenorphine transdermal patch in osteoarthritis patients naïve to potent opioids. *Scandinavian Journal of Pain*, 1(3):122–141.

[109] Buynak, R., Shapiro, D. Y., Okamoto, A., van Hove, I., Rauschkolb, C., Steup, A., Lange, B., Lange, C., and Etropolski, M. (2010). Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled phase iii study. *Expert opinion on pharmacotherapy*, 11(11):1787–1804.

[110] Emkey, R., Rosenthal, N., Wu, S.-C., Jordan, D., and Kamin, M. (2004). Efficacy and safety of tramadol/acetaminophen tablets (ultracet) as add-on therapy for osteoarthritis pain in subjects receiving a cox-2 nonsteroidal antiinflammatory drug: A multicenter, randomized, double-blind, placebo-controlled trial. *The Journal of rheumatology*, 31(1):150–156.

[111] Friedmann, N., Klutzaritz, V., and Webster, L. (2011). Efficacy and safety of an extended-release oxycodone (remoxy) formulation in patients with moderate to severe osteoarthritic pain. *Journal of opioid management*, 7(3):193–202.

[112] Gana, T. J., Pascual, M. L. G., Fleming, R. R. B., Schein, J. R., Janagap, C. C., Xiang, J., and Vorsanger, G. J. (2006). Extended-release tramadol in the treatment of osteoarthritis: a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Current medical research and opinion*, 22(7):1391–1401.

[113] Gilron, I., Bailey, J. M., Tu, D., Holden, R. R., Weaver, D. F., and Houlden, R. L. (2005). Morphine, gabapentin, or their combination for neuropathic pain. *The New England journal of medicine*, 352(13):1324–1334.

[114] Gimbel, J. S., Richards, P., and Portenoy, R. K. (2003). Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology*, 60(6):927–934.

[115] Gordon, A., Callaghan, D., Spink, D., Cloutier, C., Dzongowski, P., O'Mahony, W., Sinclair, D., Rashiq, S., Buckley, N., Cohen, G., Kim, J., Boulanger, A., Piraino, P. S., Eisenhoffer, J., Harsanyi, Z., Darke, A. C., and Michalko, K. J. (2010a). Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. *Clinical therapeutics*, 32(5):844–860.

[116] Gordon, A., Rashiq, S., Moulin, D. E., Clark, A. J., Beaulieu, A. D., Eisenhoffer, J., Piraino, P. S., Quigley, P., Harsanyi, Z., and Darke, A. C. (2010b). Buprenorphine transdermal system for opioid therapy in patients with chronic low back pain. *Pain research & management*, 15(3):169–178.

[117] Hanna, M., O'Brien, C., and Wilson, M. C. (2008). Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. *European journal of pain (London, England)*, 12(6):804–813.

[118] Harati, Y., Gooch, C., Swenson, M., Edelman, S., Greene, D., Raskin, P., Donofrio, P., Cornblath, D., Sachdeo, R., Siu, C. O., and Kamin, M. (1998). Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology*, 50(6):1842–1846.

[119] Khoromi, S., Cui, L., Nackers, L., and Max, M. B. (2007). Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. *Pain*, 130(1-2):66–75.

[120] Kivitz, A., Ma, C., Ahdieh, H., and Galer, B. S. (2006). A 2-week, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, phase iii trial comparing the efficacy of oxymorphone extended release and placebo in adults with pain associated with osteoarthritis of the hip or knee. *Clinical therapeutics*, 28(3):352–364.

[121] Lee, J. H. and Lee, C.-S. (2013). A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of the extended-release tramadol hydrochloride/acetaminophen fixed-dose combination tablet for the treatment of chronic low back pain. *Clinical therapeutics*, 35(11):1830–1840.

[122] Ma, K., Jiang, W., Zhou, Q., and Du, D.-P. (2008). The efficacy of oxycodone for management of acute pain episodes in chronic neck pain patients. *International journal of clinical practice*, 62(2):241–247.

[123] Markenson, J. A., Croft, J., Zhang, P. G., and Richards, P. (2005). Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial. *The Clinical journal of pain*, 21(6):524–535.

[124] Matsumoto, A. K., Babul, N., and Ahdieh, H. (2005). Oxymorphone extended-release tablets relieve moderate to severe pain and improve physical function in osteoarthritis: results of a randomized, double-blind, placebo- and active-controlled phase iii trial. *Pain medicine (Malden, Mass.)*, 6(5):357–366.

[125] Moulin, D. E., Iezzi, A., Amireh, R., Sharpe, W. K., Boyd, D., and Merskey, H. (1996). Randomised trial of oral morphine for chronic non-cancer pain. *Lancet (London, England)*, 347(8995):143–147.

[126] Peloso, P. M., Fortin, L., Beaulieu, A., Kamin, M., and Rosenthal, N. (2004). Analgesic efficacy and safety of tramadol/ acetaminophen combination tablets (ultracet) in treatment of chronic low back pain: a multicenter, outpatient, randomized, double blind, placebo controlled trial. *The Journal of rheumatology*, 31(12):2454–2463.

[127] Raja, S. N., Haythornthwaite, J. A., Pappagallo, M., Clark, M. R., Travison, T. G., Sabeen, S., Royall, R. M., and Max, M. B. (2002). Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology*, 59(7):1015–1021.

[128] Roth, S. H., Fleischmann, R. M., Burch, F. X., Dietz, F., Bockow, B., Rapoport, R. J., Rutstein, J., and Lacouture, P. G. (2000). Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation. *Archives of internal medicine*, 160(6):853–860.

[129] Ruoff, G. E., Rosenthal, N., Jordan, D., Karim, R., and Kamin, M. (2003). Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: A multicenter, randomized, double-blind, placebo-controlled outpatient study. *Clinical therapeutics*, 25(4):1123–1141.

[130] Schwartz, S., Etropolski, M., Shapiro, D. Y., Okamoto, A., Lange, R., Haeussler, J., and Rauschkolb, C. (2011). Safety and efficacy of tapentadol er in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Current medical research and opinion*, 27(1):151–162.

[131] Serrie, A., Lange, B., and Steup, A. (2017). Tapentadol prolonged-release for moderate-to-severe chronic osteoarthritis knee pain: A double-blind, randomized, placebo- and oxycodone controlled release-controlled study. *Current medical research and opinion*, 33(8):1423–1432.

[132] Steiner, D. J., Sitar, S., Wen, W., Sawyerr, G., Munera, C., Ripa, S. R., and Landau, C. (2011). Efficacy and safety of the seven-day buprenorphine transdermal system in opioid-naive patients with moderate to severe chronic low back pain: an enriched, randomized, double-blind, placebo-controlled study. *Journal of pain and symptom management*, 42(6):903–917.

[133] Thorne, C., Beaulieu, A. D., Callaghan, D. J., O'Mahony, W. F., Bartlett, J. M., Knight, R., Kraag, G. R., Akhras, R., Piraino, P. S., Eisenhoffer, J., Harsanyi, Z., and Darke, A. C. (2008). A randomized, double-blind, crossover comparison of the efficacy and safety of oral controlled-release tramadol and placebo in patients with painful osteoarthritis. *Pain Research and Management*, 13(2):93–102.

[134] Thorne C., Beaulieu A.D., Callaghan D.J., O'Mahony W.F., Bartlett J.M., Knight R., Kraag G.R., Akhras R., Piraino P.S., Eisenhoffer J., Harsanyi Z., and Darke A.C. (2008). A randomized, double-blind, crossover comparison of the efficacy and safety of oral controlled-release tramadol and placebo in patients with painful osteoarthritis. *Pain Research and Management*, 13(2):93–102.

[135] Vinik, A. I., Shapiro, D. Y., Rauschkolb, C., Lange, B., Karcher, K., Pennett, D., and Etropolski, M. S. (2014). A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. *Diabetes care*, 37(8):2302–2309.

[136] Watson, C. P. N., Moulin, D., Watt-Watson, J., Gordon, A., and Eisenhoffer, J. (2003). Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain*, 105(1-2):71–78.

[137] Webster, L. R., Butera, P. G., Moran, L. V., Wu, N., Burns, L. H., and Friedmann, N. (2006). Oxytrex minimizes physical dependence while providing effective analgesia: A randomized controlled trial in low back pain. *The journal of pain : official journal of the American Pain Society*, 7(12):937–946.

[247] Yarlas, A., Miller, K., Wen, W., Dain, B., Lynch, S. Y., Pergolizzi, J. V., Raffa, R. B., and Ripa, S. R. (2013). A randomized, placebo-controlled study of the impact of the 7-day buprenorphine transdermal system on health-related quality of life in opioid-naive patients with moderate-to-severe chronic low back pain. *The journal of pain : official journal of the American Pain Society*, 14(1):14–23.

Excluded studies

[139] Ahmedzai, S. H., Nauck, F., Bar-Sela, G., Bosse, B., Leyendecker, P., and Hopp, M. (2012). A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. *Palliative medicine*, 26(1):50–60.

[140] Allan, L., Hays, H., Jensen, N. H., de Waroux, B. L., Bolt, M., Donald, R., and Kalso, E. (2001). Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *BMJ (Clinical research ed.)*, 322(7295):1154–1158.

[141] Allan, L., Richarz, U., Simpson, K., and Slappendel, R. (2005). Transdermal fentanyl versus sustained release oral morphine in strong-opioid naive patients with chronic low back pain. *Spine*, 30(22):2484–2490.

[142] Am Ionescu, Popa, R., Manolescu, B. N., Tache, S., and Berteanu, M. (2016). Tramadol's respiratory effects in subjects with chronic non-specific low back pain: a randomised controlled trial. *Annals of the Rheumatic Diseases*, 75:1191–.

[143] Amato, F., Ceniti, S., Mameli, S., Pisanu, G. M., Vellucci, R., Palmieri, V., Consoletti, L., Magaldi, D., Notaro, P., and Marcassa, C. (2017). High dosage of a fixed combination oxycodone/naloxone prolonged release: efficacy and tolerability in patients with chronic cancer pain. *Supportive Care in Cancer*, pages 1–8.

[144] Babul, N., Noveck, R., Chipman, H., Roth, S. H., Gana, T., and Albert, K. (2004). Efficacy and safety of extended-release, once-daily tramadol in chronic pain: a randomized 12-week clinical trial in osteoarthritis of the knee. *Journal of pain and symptom management*, 28(1):59–71.

[145] Banerjee, M., Mondal, S., Sarkar, R., Mondal, H., and Bhattacharya, K. (2016). Comparative study of efficacy and safety of tapentadol versus etoricoxib in mild to moderate grades of chronic osteorthritis of knee. 11(1):21–25.

[146] Binsfeld, H., Szczepanski, L., Waechter, S., Richarz, U., and Sabatowski, R. (2010). A randomized study to demonstrate noninferiority of once-daily oros((r)) hydromorphone with twice-daily sustained-release oxycodone for moderate to severe chronic noncancer pain. *Pain practice : the official journal of World Institute of Pain*, 10(5):404–415.

[147] Bohme, K. (2002). Buprenorphine in a transdermal therapeutic system–a new option. *Clinical rheumatology*, 21 Suppl 1:S13–6.

[148] Boureau, F., Saudubray, F., d'Arnoux, C., Vedrenne, J., Esteve, M., Roquefeuil, B., Siou, D. K., Brunet, R., Ranchere, J. Y., and Roussel, P. (1992). A comparative study of controlled-release morphine (crm) suspension and crm tablets in chronic cancer pain. *Journal of pain and symptom management*, 7(7):393–399.

[149] Brema, F., Pastorino, G., Martini, M. C., Gottlieb, A., Luzzani, M., Libretti, A., Sacca, L., and Cigolari, S. (1996). Oral tramadol and buprenorphine in tumour pain. an italian multicentre trial. *International journal of clinical pharmacology research*, 16(4-5):109–116.

[150] Ceniti, S., Amato, F., Mameli, S., Pisanu, G. M., Vellucci, R., Palmieri, V., Consoletti, L., Magaldi, D., Notaro, P., and Conforti, S. (2016). High dosages of the fixed combination oxycodone/ naloxone in cancer pain: mid-term efficacy and tolerability. 27(no pagination).

[151] Chindalore, V. L., Craven, R. A., Yu, K. P., Butera, P. G., Burns, L. H., and Friedmann, N. (2005). Adding ultralow-dose naltrexone to oxycodone enhances and prolongs analgesia: A randomized, controlled trial of oxytrex. *The journal of pain : official journal of the American Pain Society*, 6(6):392–399.

[152] Chu, L. F., D'Arcy, N., Brady, C., Zamora, A. K., Young, C. A., Kim, J. E., Clemenson, A. M., Angst, M. S., and Clark, J. D. (2012). Analgesic tolerance without demonstrable opioid-induced hyperalgesia: a double-blinded, randomized, placebo-controlled trial of sustained-release morphine for treatment of chronic nonradicular low-back pain. *Pain*, 153(8):1583–1592.

[153] Cowan, D. T., Wilson-Barnett, J., Griffiths, P., Vaughan, D. J. A., Gondhia, A., and Allan, L. G. (2005). A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. *Pain medicine (Malden, Mass.)*, 6(2):113–121.

[154] de Hoogd S., Ahlers S.J.G.M., van Dongen E.P.A., van de Garde E.M.W., Daeter E.J., Dahan A., Tibboel D., and Knibbe C.A.J. (2018). Randomized controlled trial on the influence of intraoperative remifentanil versus fentanyl on acute and chronic pain after cardiac surgery. *Pain Practice*, 18(4):443–451.

[155] Dellemijn, P. L., van Duijn, H., and Vanneste, J. A. (1998). Prolonged treatment with transdermal fentanyl in neuropathic pain. *Journal of pain and symptom management*, 16(4):220–229.

[Derry et al.] Derry, S., Stannard, C., Cole, P., Wiffen, P. J., Knaggs, R., Aldington, D., and Moore, R. A. Fentanyl for neuropathic pain in adults.

[157] Dupoiron, D., Stachowiak, A., Loewenstein, O., Ellery, A., Kremers, W., Bosse, B., and Hopp, M. (2017). A phase iii randomized controlled study on the efficacy and improved bowel function of prolonged-release (pr) oxycodone-naloxone (up to 160/80 mg daily) vs oxycodone pr. *European journal of pain (London, England)*, 21(9):1528–1537.

[158] Etropolski, M., Kuperwasser, B., Flugel, M., Haufel, T., Lange, B., Rauschkolb, C., and Laschewski, F. (2014). Safety and tolerability of tapentadol extended release in moderate to severe chronic osteoarthritis or low back pain management: pooled analysis of randomized controlled trials. *Advances in therapy*, 31(6):604–620.

[159] EUCTR2007-001313-42-DE (2007). A randomised, double-blind, active-controlled, double-dummy, parallel group study to determine the safety and efficacy of oxycodone / naloxone prolonged release tablets in subjects with moderate to severe, chronic cancer pain.

[160] EUCTR2009-010423-58-DE (2009). An evaluation of the effectiveness and tolerability of tapentadol hydrochloride prolonged release, and tapentadol hydrochloride immediate release on demand, in subjects with uncontrolled severe chronic pain due to osteoarthritis of the knee taking either who step i or step ii analgesics or no regular analgesics.

[161] EUCTR2009-010425-39-DE (2009). An evaluation of the effectiveness and tolerability of tapentadol hydrochloride prolonged release, and tapentadol hydrochloride immediate release on demand, in subjects with severe chronic pain due to osteoarthritis of the knee taking who step iii analgesics but showing a lack of tolerability.

[162] EUCTR2009-010427-12-PL (2009). An evaluation of the effectiveness and tolerability of tapentadol hydrochloride prolonged release, and tapentadol hydrochloride immediate release on demand, in subjects with uncontrolled severe chronic nociceptive, mixed or neuropathic low back pain taking either who step i or step ii analgesics or no regular analgesics.

[163] EUCTR2009-010428-25-NL (2009). An evaluation of the effectiveness and tolerability of tapentadol hydrochloride prolonged release, and tapentadol hydrochloride immediate release on demand, in subjects with severe chronic nociceptive, mixed or neuropathic low back pain taking who step iii analgesics but showing a lack of tolerability.

[164] EUCTR2010-019998-14-DE (2010). Evaluation of the effectiveness, safety, and tolerability of tapentadol pr versus a combination of tapentadol pr and pregabalin in subjects with severe chronic low back pain with a neuropathic pain component.

[165] EUCTR2012-002943-11-AT (2013). Comparison of tapentadol pr and oxycodone/naloxone pr.

[166] EUCTR2014-004718-27-PL (2016). A study comparing the effectiveness and safety of tramadol and micronized magnesium lactate as functional excipient to tramadol alone for the treatment of moderate to severe pain due to osteoarthritis (oa).

[167] EUCTR2014-004851-30-NL (2016). Efficacy and safety study to compare gabapentin versus tramadol in paediatric patients affected by cronic moderate to severe pain.

[168] EUCTR2014-004897-40-DE (2017). Efficacy and safety study of gabapentin as add-on to morphine in paediatric patients affected by chronic severe pain.

[169] Ferreira, D. H., Louw, S., McCloud, P., Fazekas, B., McDonald, C. F., Agar, M. R., Clark, K., McCaffrey, N., Ekstrom, M., and Currow, D. C. (2020). Controlled-release oxycodone vs. placebo in the treatment of chronic breathlessness-a multisite randomized placebo controlled trial. *Journal of pain and symptom management*, 59(3):581–589.

[170] Ferrell, B., Wisdom, C., Wenzl, C., and Brown, J. (1989). Effects of controlled-released morphine on quality of life for cancer pain. *Oncology nursing forum*, 16(4):521–526.

[171] Franco, M. L., Seoane, A., Jesus Berro, M., Calvo, I., Pezonaga, L., Sulleiro, R., Carceller, J. M., Santilla, R., and et al. (2002). Usefulness of transdermal fentanyl in the management of nonmalignant chronic pain: a prospective, observational, multicenter study. 14(2):99–112.

[172] Frank, B., Serpell, M. G., Hughes, J., Matthews, J. N. S., and Kapur, D. (2008). Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ (Clinical research ed.)*, 336(7637):199–201.

[173] Fredheim, O. M. S., Kaasa, S., Dale, O., Klepstad, P., Landro, N. I., and Borchgrevink, P. C. (2006). Opioid switching from oral slow release morphine to oral methadone may improve pain control in chronic non-malignant pain: a nine-month follow-up study. *Palliative medicine*, 20(1):35–41.

[174] Gammaitoni, A. R., Galer, B. S., Lacouture, P., Domingos, J., and Schlagheck, T. (2003). Effectiveness and safety of new oxycodone/acetaminophen formulations with reduced acetaminophen for the treatment of low back pain. *Pain medicine (Malden, Mass.)*, 4(1):21–30.

[175] Gatti, A., Dauri, M., Leonardis, F., Longo, G., Marinangeli, F., Mammucari, M., and Sabato, A. F. (2010). Transdermal buprenorphine in non-oncological moderate-to-severe chronic pain. *Clinical drug investigation*, 30 Suppl 2:31–38.

[176] Griffin, M. L., Bennett, H. E., Fitzmaurice, G. M., Hill, K. P., Provost, S. E., and Weiss, R. D. (2015). Health-related quality of life among prescription opioid-dependent patients: Results from a multi-site study. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions*, 24(4):308–314.

[177] Grond, S., Zech, D., Lehmann, K. A., Radbruch, L., Breitenbach, H., and Hertel, D. (1997). Transdermal fentanyl in the long-term treatment of cancer pain: a prospective study of 50 patients with advanced cancer of the gastrointestinal tract or the head and neck region. *Pain*, 69(1-2):191–198.

[178] Hale, M., Tudor, I. C., Khanna, S., and Thipphawong, J. (2007). Efficacy and tolerability of once-daily oros hydromorphone and twice-daily extended-release oxycodone in patients with chronic, moderate to severe osteoarthritis pain: results of a 6-week, randomized, open-label, noninferiority analysis. *Clinical therapeutics*, 29(5):874–888.

[179] Hanna, M. and Thipphawong, J. (2008). A randomized, double-blind comparison of oros(r) hydromorphone and controlled-release morphine for the control of chronic cancer pain. *BMC palliative care*, 7:17.

[180] Herbst, L. H. and Strause, L. G. (1992). Transdermal fentanyl use in hospice home-care patients with chronic cancer pain. *Journal of pain and symptom management*, 7(3 Suppl):S54–7.

[181] Hesselbarth, S., Löwenstein, O., and Cegla, T. (2014). Effects of prolonged-release oxycodone/naloxone on pain control, bowel function and quality of life: A prospective observational study. *Scandinavian Journal of Pain*, 5(2):75–81.

[182] James, I. G. V., O'Brien, C. M., and McDonald, C. J. (2010). A randomized, double-blind, double-dummy comparison of the efficacy and tolerability of low-dose transdermal buprenorphine (butrans seven-day patches) with buprenorphine sublingual tablets (temgesic) in patients with osteoarthritis pain. *Journal of pain and symptom management*, 40(2):266–278.

[183] Jamison, R. N., Raymond, S. A., Slawsby, E. A., Nedeljkovic, S. S., and Katz, N. P. (1998). Opioid therapy for chronic noncancer back pain. a randomized prospective study. *Spine*, 23(23):2591–2600.

[184] Jensen, M. K., Thomsen, A. B., and Hojsted, J. (2006). 10-year follow-up of chronic non-malignant pain patients: opioid use, health related quality of life and health care utilization. *European journal of pain (London, England)*, 10(5):423–433.

[185] Julius, D., Sturesson, B., Kools, D., Prestamburgo, D., Pflugmacher, R., and Vajkoczy, P. (2017). Opioid use in relation to treatment outcome in patients with low back pain: data from a prospective randomized controlled trial. 7(2):109S–.

[186] Kamboj, S. K., Conroy, L., Tookman, A., Carroll, E., Jones, L., and Curran, H. V. (2014). Effects of immediate-release opioid on memory functioning: a randomized-controlled study in patients receiving sustained-release opioids. *European journal of pain (London, England)*, 18(10):1376–1384.

[187] Kaplan, R., Conant, M., Cundiff, D., Maciewicz, R., Ries, K., Slagle, S., Slywka, J., and Buckley, B. (1996). Sustained-release morphine sulfate in the management of pain associated with acquired immune deficiency syndrome. *Journal of pain and symptom management*, 12(3):150–160.

[188] Karlsson, M. and Berggren, A.-C. (2009). Efficacy and safety of low-dose transdermal buprenorphine patches (5, 10, and 20 microg/h) versus prolonged-release tramadol tablets (75, 100, 150, and 200 mg) in patients with chronic osteoarthritis pain: a 12-week, randomized, open-label, controlled, parallel-group noninferiority study. *Clinical therapeutics*, 31(3):503–513.

[189] Krocker, D., Ullrich, H., Buttgereit, F., and Perka, C. (2008). Influence of adjuvant pain medication on quality of life in the treatment of postmenopausal osteoporosis. *Der Orthopade*, 37(5):435–439.

[190] Lange, B., Kuperwasser, B., Okamoto, A., Steup, A., Haufel, T., Ashworth, J., and Etropolski, M. (2010). Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. *Advances in therapy*, 27(6):381–399.

[191] Lange, B., Zabern von, D., Elling, C., and Dubois, C. (2017). Efficacy and safety of tapentadol prolonged release for moderate-to-severe chronic osteoarthritis knee pain: A pooled analysis of two double-blind, randomized, placebo- and oxycodone controlled release-controlled studies. *Current medical research and opinion*, 33(8):1413–1422.

[192] Leppert W. and Nosek K. (2019). Comparison of the quality of life of cancer patients with pain treated with oral controlled-release morphine and oxycodone and transdermal buprenorphine and fentanyl. *Current Pharmaceutical Design*, 25(30):3216–3224.

[193] Liguori, S., Gottardi, M., Micheletto, G., and Bruno, L. (2010). Pharmacological approach to chronic visceral pain. focus on oxycodone controlled release: an open multicentric study. *European review for medical and pharmacological sciences*, 14(3):185–190.

[194] Likar, R., Lorenz, V., Korak-Leiter, M., Kager, I., and Sittl, R. (2007). Transdermal buprenorphine patches applied in a 4-day regimen versus a 3-day regimen: a single-site, phase iii, randomized, open-label, crossover comparison. *Clinical therapeutics*, 29(8):1591–1606.

[195] Miller, K., Yarlas, A., Wen, W., Kowalski, M., Lynch, S. Y., Dain, B., and Ripa, S. R. (2013). Correlates of improvement in physical quality of life and quality of sleep among chronic low back pain patients with treatment with buprenorphine transdermal system (btds). *Value in Health*, 16(3):A122.

[196] Milligan, K., Lanteri-Minet, M., Borchert, K., Helmers, H., Donald, R., Kress, H. G., Adriaensen, H., Moulin, D., Jarvimaki, V., and Haazen, L. (2001). Evaluation of long-term efficacy and safety of transdermal fentanyl in the treatment of chronic noncancer pain. *The journal of pain : official journal of the American Pain Society*, 2(4):197–204.

[197] Müller, M., Groblschegg, S., Samper, D., Bonezzi, C., and Steigerwald, I. (2011). T616 changes in quality of life parameters in patients with severe, chronic low back pain treated with tapentadol prolonged release (pr). *European Journal of Pain Supplements*, 5(1):85.

[198] Muriel, C., Failde, I., Mico, J. A., Neira, M., and Sanchez-Magro, I. (2005). Effectiveness and tolerability of the buprenorphine transdermal system in patients with moderate to severe chronic pain: a multicenter, open-label, uncontrolled, prospective, observational clinical study. *Clinical therapeutics*, 27(4):451–462.

[199] Muriel Villoria, C., Perez-Castejon Garrote, J. M., Sanchez Magro, I., and Neira Alvarez, M. (2007). Effectiveness and safety of transdermal buprenorphine for chronic pain treatment in the elderly: a prospective observational study. *Medicina clinica*, 128(6):204–210.

[200] Mystakidou, K., Parpa, E., Tsilika, E., Katsouda, E., Kouloulias, V., Kouvaris, J., Georgaki, S., and Vlahos, L. (2004). Pain management of cancer patients with transdermal fentanyl: a study of 1828 step i, ii, & iii transfers. *The journal of pain : official journal of the American Pain Society*, 5(2):119–132.

[201] Mystakidou, K., Parpa, E., Tsilika, E., Mavromati, A., Smyrniotis, V., Georgaki, S., and Vlahos, L. (2003). Long-term management of noncancer pain with transdermal therapeutic system-fentanyl. *The journal of pain : official journal of the American Pain Society*, 4(6):298–306.

[202] NCT00399048 (2006). An effectiveness, safety and quality of life measures with hydromorphone hcl, dilaudid cr (controlled release).

[203] NCT00495404 (2007). Health outcomes from opioid therapy for chronic pain.

[204] NCT00547885 (2007). Randomized controlled double blind trial of short vs long acting dihydrocodeine in chronic non-malignant pain.

[205] NCT00771758 (2008). Tapentadol ir vs oxycodone ir vs placebo in acute pain from vertebral compression fracture associated with osteoporosis.

[206] NCT01352741 (2011). Comparison of increasing doses of tapentadol versus a combination of tapentadol and pregabalin.

[207] NCT01559454 (2012). Buprenorphine and methadone for opioid-dependent chronic back pain patients.

[208] NCT01728246 (2012). An efficacy, safety and effects on quality of life of tramadol/paracetamol as add-on therapy in chronic osteoarthritis.

[209] NCT01811186 (2013). An interventional study to compare the efficacy and tolerability with targin® in non-malignant chronic pain (glory).

[210] NCT01875848 (2013). Buprenorphine vs. opioid dose escalation among patients with chronic pain.

[211] NCT02464813 (2015). Effect of pregabalin on immediate post-operative and longterm pain.

[212] NCT03967327 (2019). A study to evaluate buprenorphine transdermal patch in chinese subjects with moderate to severe chronic cancer pain.

[213] NCT04013529 (2019). Connected health to decrease opioid use in patients with chronic pain.

[214] Nicholson, B., Ross, E., Sasaki, J., and Weil, A. (2006a). Randomized trial comparing polymer-coated extended-release morphine sulfate to controlled-release oxycodone hcl in moderate to severe nonmalignant pain. *Current medical research and opinion*, 22(8):1503–1514.

[215] Nicholson, B., Ross, E., Weil, A., Sasaki, J., and Sacks, G. (2006b). Treatment of chronic moderate-to-severe non-malignant pain with polymer-coated extended-release morphine sulfate capsules. *Current medical research and opinion*, 22(3):539–550.

[216] Niemann, T., Madsen, L. G., Larsen, S., and Thorsgaard, N. (2000). Opioid treatment of painful chronic pancreatitis. *International journal of pancreatology : official journal of the International Association of Pancreatology*, 27(3):235–240.

[217] Niesters, M., Proto, P. L., Aarts, L., Sarton, E. Y., Drewes, A. M., and Dahan, A. (2014). Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. *British journal of anaesthesia*, 113(1):148–156.

[218] Norrlid, H., Dahm, P., and Tennvall, G. R. (2015). Evaluation of the cost-effectiveness of buprenorphine in treatment of chronic pain using competing eq-5d weights. *Scandinavian Journal of Pain*, 6(1):24–30.

[219] Oliva, P., Carbonell, R., Giron, J. A., Bueno, A., Sanz, J. M., and Urieta, A. (2000). Extended-release oral opiates: tramadol versus dihydrocodeine in chronic tumor pain associated to prostate cancer. 7(5):285–290.

[220] Pace, M. C., Passavanti, M. B., Grella, E., Mazzariello, L., Maisto, M., Barbarisi, M., Baccari, E., Sansone, P., and Aurilio, C. (2007). Buprenorphine in long-term control of chronic pain in cancer patients. *Frontiers in bioscience : a journal and virtual library*, 12:1291–1299.

[221] Parr, G., Darekar, B., Fletcher, A., and Bulpitt, C. J. (1989). Joint pain and quality of life; results of a randomised trial. *British journal of clinical pharmacology*, 27(2):235–242.

[222] Pavelka, K., Le Loet, X., Bjorneboe, O., Herrero-Beaumont, G., and Richarz, U. (2004). Benefits of transdermal fentanyl in patients with rheumatoid arthritis or with osteoarthritis of the knee or hip: an open-label study to assess pain control. *Current medical research and opinion*, 20(12):1967–1977.

[223] Pedersen, L., Borchgrevink, P. C., Breivik, H. P., and Fredheim, O. M. S. (2014). A randomized, double-blind, double-dummy comparison of short- and long-acting dihydrocodeine in chronic non-malignant pain. *Pain*, 155(5):881–888.

[224] Raffaeli, W., Pari, C., Corvetta, A., Sarti, D., Di Sabatino, V., Biasi, G., and Galeazzi, M. (2010). Oxycodone/acetaminophen at low dosage: an alternative pain treatment for patients with rheumatoid arthritis. *Journal of opioid management*, 6(1):40–46.

[225] Rauck, R. L., Bookbinder, S. A., Bunker, T. R., Alftine, C. D., Gershon, S., de Jong, E., Negro-Vilar, A., and Ghalie, R. (2007). A randomized, open-label, multicenter trial comparing once-a-day avinza (morphine sulfate extended-release capsules) versus twice-a-day oxycontin (oxycodone hydrochloride controlled-release tablets) for the treatment of chronic, moderate to severe low back pain: improved physical functioning in the action trial. *Journal of opioid management*, 3(1):35–43.

[226] Rauck, R. L., Tark, M., Reyes, E., Hayes, T. G., Bartkowiak, A. J., Hassman, D., Nalamachu, S., Derrick, R., and Howell, J. (2009). Efficacy and long-term tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain. *Current medical research and opinion*, 25(12):2877–2885.

[227] Reimer, M., Hullemann, P., Hukauf, M., Keller, T., Binder, A., Gierthmuhlen, J., and Baron, R. (2017). Prediction of response to tapentadol in chronic low back pain. 21(2):322–333.

[228] Richarz, U., Waechter, S., Sabatowski, R., Szczepanski, L., and Binsfeld, H. (2013). Sustained safety and efficacy of once-daily hydromorphone extended-release (oros(r) hydromorphone er) compared with twice-daily oxycodone controlled-release over 52 weeks in patients with moderate to severe chronic noncancer pain. *Pain practice : the official journal of World Institute of Pain*, 13(1):30–40.

[229] Roberto, A., Galli, F., Floriani, I., and Corli, O. (2016). Are strong opioids equally effective and safe in the treatment of chronic cancer pain? results from cerp study. *Palliative medicine*, 30(6):NP34–NP35.

[230] Rowbotham, M. C., Twilling, L., Davies, P. S., Reisner, L., Taylor, K., and Mohr, D. (2003). Oral opioid therapy for chronic peripheral and central neuropathic pain. *The New England journal of medicine*, 348(13):1223–1232.

[231] Sindrup, S. H., Andersen, G., Madsen, C., Smith, T., Brøsen, K., and Jensen, T. S. (1999). Tramadol relieves pain and allodynia in polyneuropathy: A randomised, double-blind, controlled trial. *Pain*, 83(1):85–90.

[232] Soin, A., Cheng, J., Brown, L., Moufawad, S., and Mekhail, N. (2008). Functional outcomes in patients with chronic nonmalignant pain on long-term opioid therapy. *Pain practice : the official journal of World Institute of Pain*, 8(5):379–384.

[233] Sorge, J. and Stadler, T. (1997). Comparison of the analgesic efficacy and tolerability of tramadol 100 mg sustained-release tablets and tramadol 50 mg capsules for the treatment of chronic low back pain. *Clinical drug investigation*, 14(3):157–164.

[234] Steigerwald, I., Muller, M., Kujawa, J., Balblanc, J.-C., and Calvo-Alen, J. (2012). Effectiveness and safety of tapentadol prolonged release with tapentadol immediate release on-demand for the management of severe, chronic osteoarthritis-related knee pain: results of an open-label, phase 3b study. *Journal of pain research*, 5:121–138.

[235] Stepanovic, A., Pirc, J., and Lahajnar Cavlovic, S. (2011). Clinical efficacy of oros(r) hydromorphone in patients suffering from severe chronic pain: A study undertaken in routine clinical practice. *Wiener klinische Wochenschrift*, 123(17-18):531–535.

[236] Tassain, V., Attal, N., Fletcher, D., Brasseur, L., Degieux, P., Chauvin, M., and Bouhassira, D. (2003). Long term effects of oral sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain. *Pain*, 104(1-2):389–400.

[237] Taylor, Webster, L. R., Chun, S. Y., Reinking, J., Stegman, M., and Shoemaker, S. (2007). Impact of breakthrough pain on quality of life in patients with chronic, noncancer pain: patient perceptions and effect of treatment with oral transmucosal fentanyl citrate (otfc, actiq). *Pain medicine (Malden, Mass.)*, 8(1526–2375 (Print), 3):281–288.

[238] Tessaro, L., Bandieri, E., Costa, G., Fornasier, G., Iorno, V., Pizza, C., Pastacaldi, G., and Micheletto, G. (2010). Use of oxycodone controlled-release immediately after nsaids: a new approach to obtain good pain control. *European review for medical and pharmacological sciences*, 14(2):113–121.

[239] Überall, M. A. and Müller-Schwefe, G. H. H. (2015). Safety and efficacy of oxycodone/naloxone vs. oxycodone vs. morphine for the treatment of chronic low back pain: results of a 12 week prospective, randomized, open-label blinded endpoint streamlined study with prolonged-release preparations. *Current medical research and opinion*, 31(7):1413–1429.

[240] van Seventer, R., Smit, J. M., Schipper, R. M., Wicks, M. A., and Zuurmond, W. W. (2003). Comparison of tts-fentanyl with sustained-release oral morphine in the treatment of patients not using opioids for mild-to-moderate pain. *Current medical research and opinion*, 19(6):457–469.

[241] Vorsanger, G., Xiang, J., Jordan, D., and Farrell, J. (2007). Post hoc analysis of a randomized, double-blind, placebo-controlled efficacy and tolerability study of tramadol extended release for the treatment of osteoarthritis pain in geriatric patients. *Clinical therapeutics*, 29 Suppl:2520–2535.

[242] Wallace, M., Skowronski, R., Khanna, S., Tudor, I. C., and Thipphawong, J. (2007). Efficacy and safety evaluation of once-daily oros hydromorphone in patients with chronic low back pain: a pilot open-label study (do-127). *Current medical research and opinion*, 23(5):981–989.

[243] Wallace, M. and Thipphawong, J. (2010). Open-label study on the long-term efficacy, safety, and impact on quality of life of oros hydromorphone er in patients with chronic low back pain. *Pain medicine (Malden, Mass.)*, 11(10):1477–1488.

[244] Watson, C. P. and Babul, N. (1998). Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology*, 50(6):1837–1841.

[245] Weil, A. J., Nicholson, B., and Sasaki, J. (2009). Factors affecting dosing regimens of morphine sulfate extended-release (kadian) capsules. *Journal of opioid management*, 5(1):39–45.

[246] Wong, J. O., Chiu, G. L., Tsao, C. J., and Chang, C. L. (1997). Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain. *Acta anaesthesiologica Sinica*, 35(1):25–32.

[247] Yarlas, A., Miller, K., Wen, W., Dain, B., Lynch, S. Y., Pergolizzi, J. V., Raffa, R. B., and Ripa, S. R. (2013). A randomized, placebo-controlled study of the impact of the 7-day buprenorphine transdermal system on health-related quality of life in opioid-naive patients with moderate-to-severe chronic low back pain. *The journal of pain : official journal of the American Pain Society*, 14(1):14–23.

[248] Yarlas, A., Miller, K., Wen, W., Lynch, S. Y., Munera, C., Dain, B., Pergolizzi, JR, J. V., Raffa, R., and Ripa, S. R. (2016). A subgroup analysis found no diminished response to buprenorphine transdermal system treatment for chronic low back pain patients classified with depression. *Pain practice : the official journal of World Institute of Pain*, 16(4):473–485.

[249] Zimmermann, M. and Waap, I. (2005). Individual aspects of the quality of life of patients with chronic pain. observational study of treatment with fentanyl-tts. *MMW Fortschritte der Medizin*, 147 Suppl 1:33–40.

[250] Zin, C. S., Nissen, L. M., O'Callaghan, J. P., Duffull, S. B., Smith, M. T., and Moore, B. J. (2010). A randomized, controlled trial of oxycodone versus placebo in patients with postherpetic neuralgia and painful diabetic neuropathy treated with pregabalin. *The journal of pain : official journal of the American Pain Society*, 11(5):462–471.

Appendix A

Various completive tables and figures

Table A.1 Criteria for risk of bias assessment

Risk of bias domain	Criteria for evaluation
Random sequence generation (selection bias)	If the method of randomization reported is adequate, this domain is rated as low risk. Examples are: computer-generated randomization list, stratified randomization etc.. Inadequate methods, like randomization based on day of enrollment or birth date, are rated as high risk. However, if there are no information on the specific randomization method, this domain is considered unclear.
Allocation concealment (selection bias)	If the method of allocation reported is adequate, this domain is rated low risk. Adequate methods are for example the use of sealed, opaque envelopes or the allocation by interactive voice response system (IVRS). Methods in which the order of allocation seems predictable are considered high risk. If the method is not reported, this domain is considered unclear.

Risk of bias domain	Criteria for evaluation
Blinding of participants and care personnel (performance bias)	If the method of blinding of participants and personnel is adequate and well reported this domain is considered low risk. Information on appearance of active drug and placebo and method of administration are essential for valuation of this domain. If it is likely that the active drug is distinguishable from the placebo, this domain is considered high risk. Otherwise, if there are not enough information on the blinding strategy, this domain is considered unclear.
Blinding of outcome assessment and investigators (detection bias)	The first criterion is fulfilled, if the person, who assesses the outcome is reported and remains blinded. This is the case, if, for example, the patients themselves make the rating of HRQL and remain blinded. Obviously, this domain can interfere with the performance bias domain. The second criterion asks if the main investigators remain blinded, until the statistical analysis is made. If this is also reported, then this domain is considered low risk.
Incomplete outcome data (attrition bias)	Studies were considered high risk, if only patients, who completed the study were included into efficacy analysis or if only a per-protocol analysis was made. Studies ($\geq$ 3 months duration) and short-term studies were also considered high risk, if the percentage of drop-outs exceeded 20% in short-term studies ($<$ 3 months $\hat{=}$ 12 weeks duration) or 30% in long-term studies ($\geq$ 3 months duration). If for imputation of missing values of HRQL measures, the last-observation-carried-forward approach was used, the study was considered unclear risk. An intention-to-treat analysis was considered as low risk criterion.
Selective reporting (reporting bias)	If all outcomes were reported sufficiently, this domain is rated low risk. If it is only reported that an outcome is "non-significant" without stating its values or showing grapically, this domain is considered a high risk. In the case, that a HRQL measure is only reported partially, this domain may be considered as unclear.

Risk of bias domain	Criteria for evaluation
Other bias	This domain rates specific risks of the studies included. Special study designs, such as “enriched design” or “withdrawal study”, may considered as a high risk. If there are no specific issues, this domain is rated as low risk.

Table A.2 Search history of PubMed/Medline search. RCT filter of the Cochrane Collaboration is implemented at #19

Search	Query
#1	Search narcotics[MeSH Terms]
#2	Search opioid analgesics[MeSH Terms]
#3	Search ((alfentanil OR amidone OR buprenorphine OR butorphanol OR codeine OR dextromoramide dextropropoxyphene OR dezocine OR diamorphine OR dihydrocodeine OR diphenoxylate OR dipipanone OR dolantine OR fentanyl OR hydrocodone OR hydromorphone OR ketobemidone OR levorphanol OR meperidine OR meptazinol OR methadone OR morphine OR nalbuphine OR oxycodone OR oxymorphone OR *morphone OR papaveretum OR pentazocine OR pethidine OR phenazocine OR propoxyphene OR remifentanil OR sufentanil OR tapentadol OR tilidine OR tramadol))
#4	Search opioid*
#5	Search opioid
#6	Search opiate
#7	Search #1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	Search chronic pain[MeSH Terms]
#9	Search chronic* pain
#10	Search chronic pain
#11	Search long*term pain
#12	Search (((back pain OR central pain OR complex regional pain OR neuropath* pain OR neuropathic pain OR post*stroke pain OR malignant pain OR musculosc* pain OR myofasc* pain OR neck pain OR phantom limb pain OR spinal cord pain OR cancer pain OR non-cancer pain OR maligne pain OR benigne pain) AND (chronic* OR long*term OR chronic)))
#13	Search #8 OR #9 OR #10 OR #11 OR #12
#14	Search quality of life[MeSH Terms]
#15	Search ((life quality OR health level OR wellbeing OR daily activity OR functional ability OR functionality))
#16	Search #14 OR #15
#17	Search #7 AND #13 AND #16
#18	Search (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT (animals [mh] NOT humans [mh]))
#19	Search #17 AND #18

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

doi:10.1371/journal.pmed.1000097.t001

Fig. A.1 PRISMA statement, taken from [55]

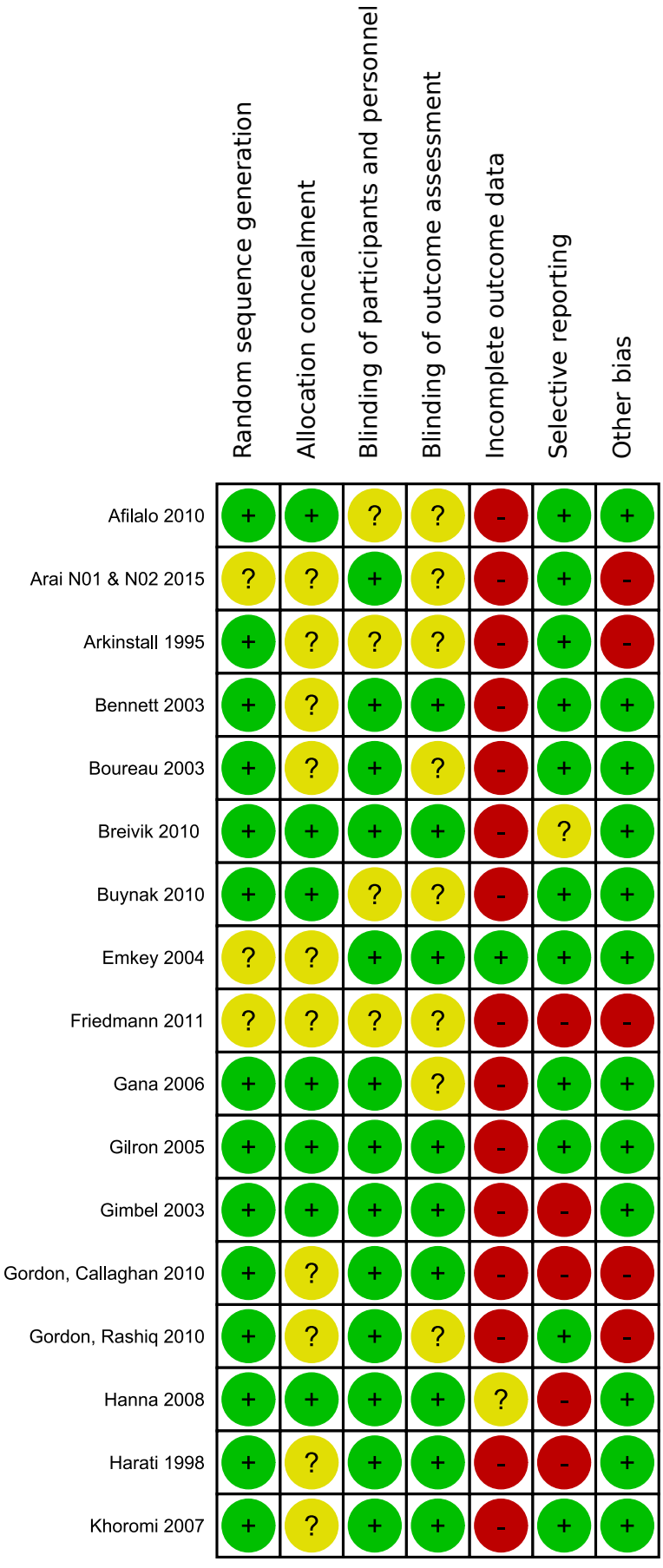

Fig. A.2 Summary of the risk of bias assessment of included studies: Afilalo 2010 - Khoromi 2007. The studies Arai N01 and Arai N02 are summarized into one item, because they are also reported together in one article.

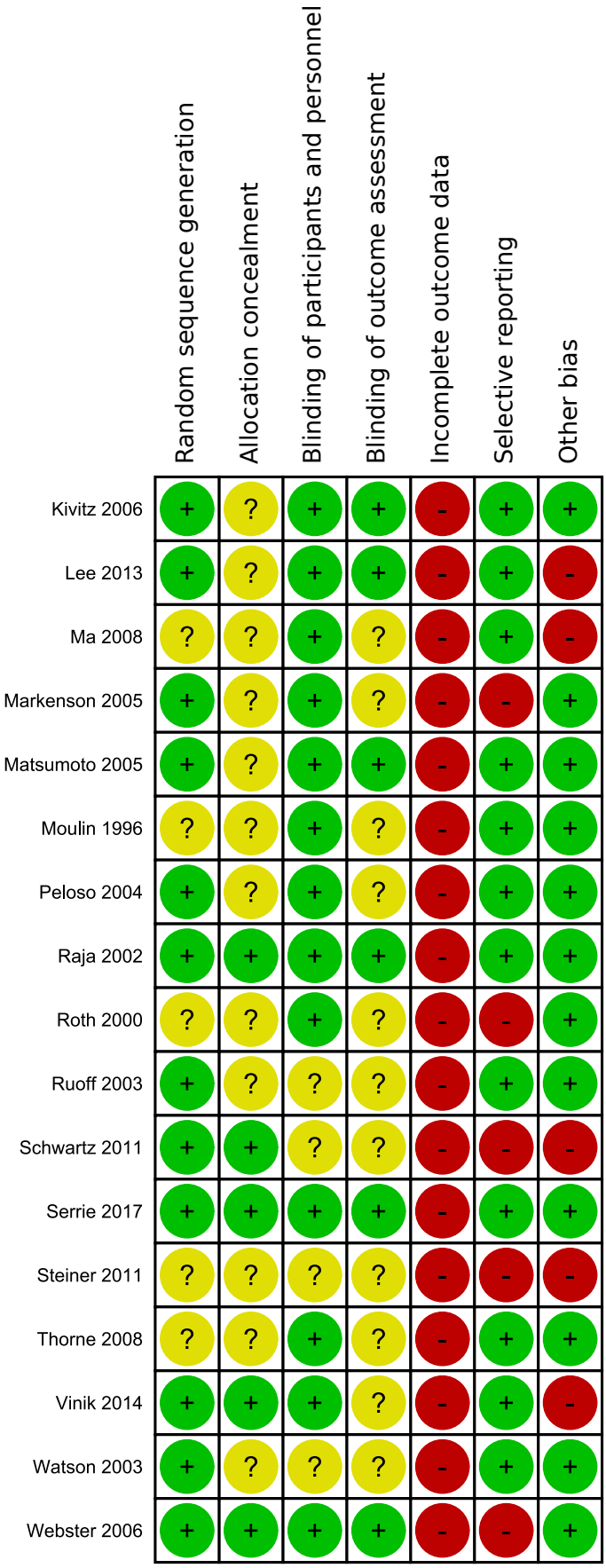

Fig. A.3 Summary of the risk of bias assessment of included studies: Kivitz 2006 - Webster 2006.

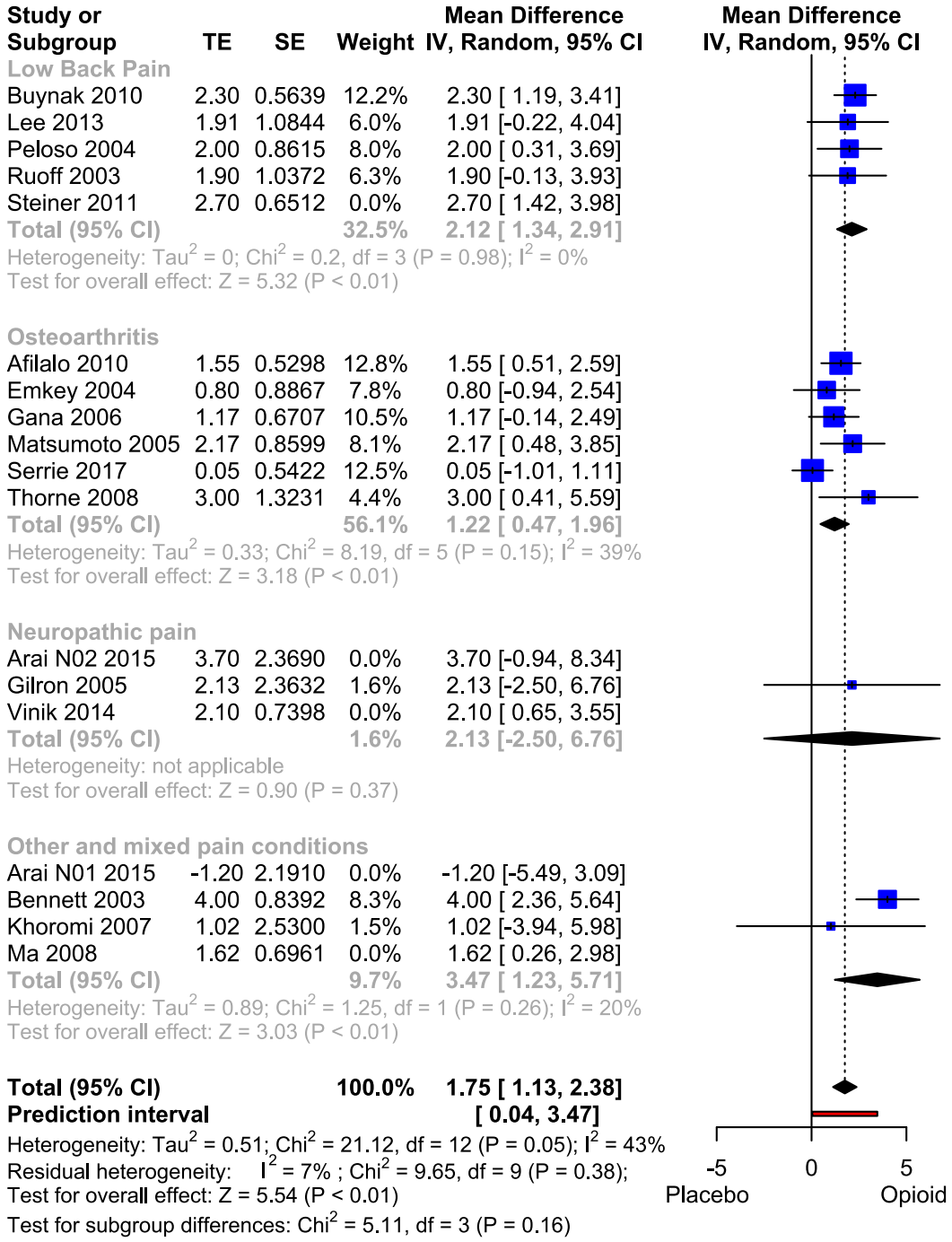

Fig. A.4 Sensitivity analysis of PCS is shown. Studies using an design favoring the opioid treatment were excluded. In comparison to the full-set analysis, the analysis results in a slightly lower mean difference (MD: 1.75, $p < 0.01$).

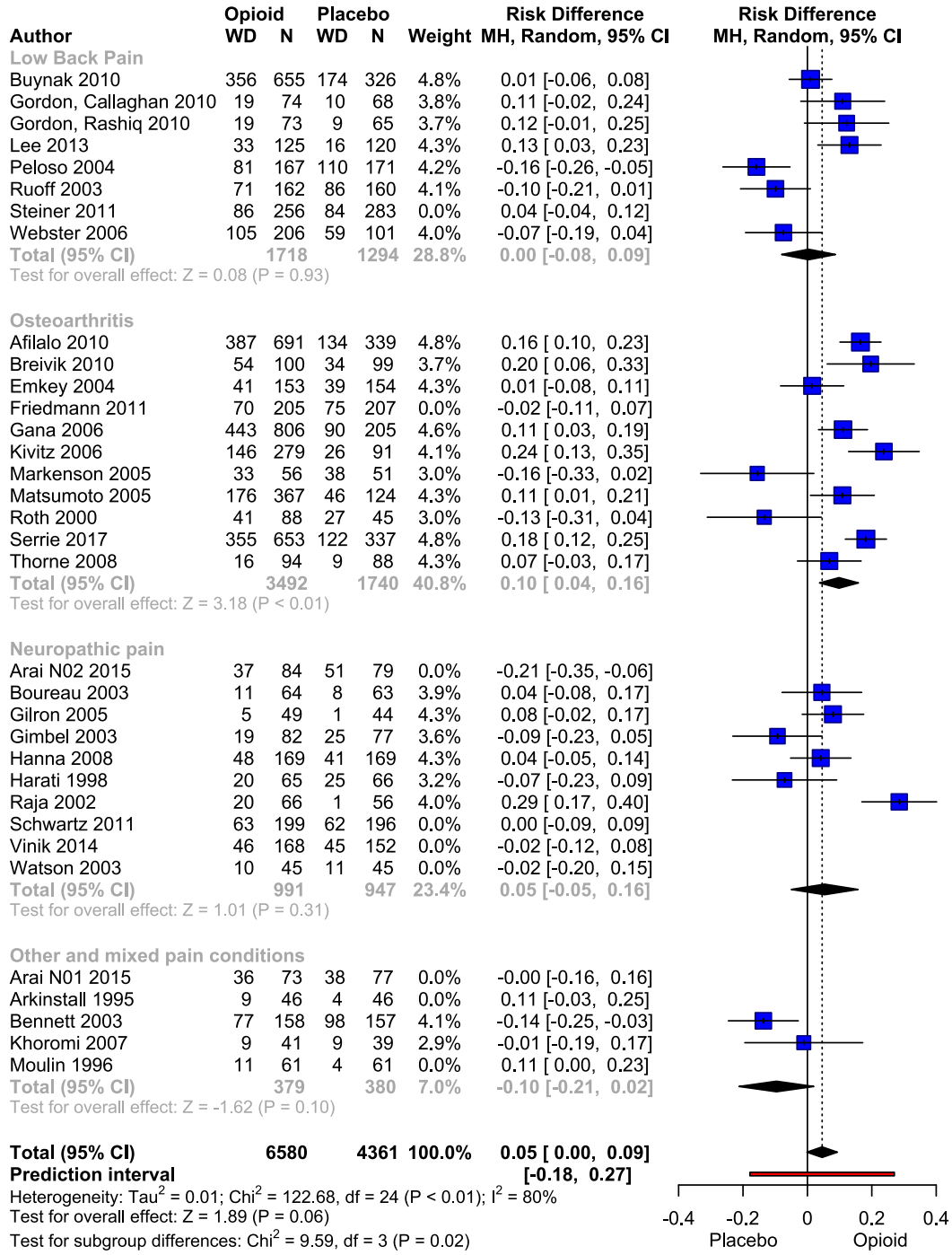

Fig. A.5 Example of a sensitivity analysis of the meta-analysis of study withdrawals. In the depicted analysis the studies Arkinstall 1995, Moulin 1996 and Watson 2003 were excluded because they did not report how many patients in fact attended the two phases of crossover study. Using the number of all patients randomized at the beginning of the crossover study does overestimate a treatment effect on the withdrawal rate. The studies Arai N01 & N02 2015, Friedmann 2011, Schwartz 2011, Steiner 2011 and Vinik 2014 used a enriched study design, which systematically favors opioid therapy. However, compared to the metaanalysis of all studies there is neither in the overall result (RD: 0.05, p=0.06) nor in the subgroup analysis a significant change in risk difference.

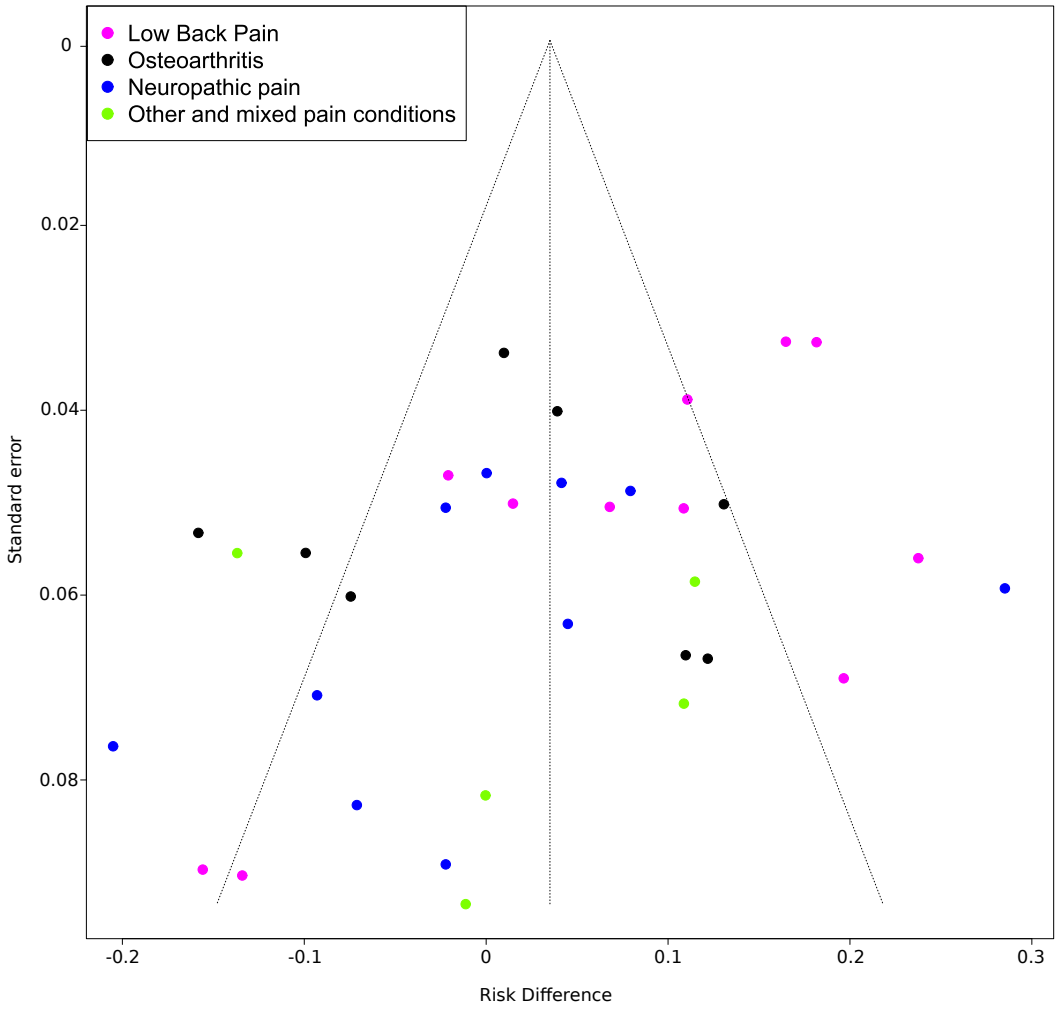

Fig. A.6 The funnel plot shows the standard error of the studies against the risk difference for premature study withdrawal. A positive risk difference indicates a higher risk in the opioid group. The mean effect of 0.04 and the 95% confindence interval are marked by a dotted line. The single studies are colour-coded by the underlying cause of chronic pain. The funnelplot shows a significant heterogeinity and an overrepresentation of smaller studies with a negative risk difference, favoring the opioid treatment. This is possible to be an indicator for publication bias, but may also be caused by inter-study heterogeinity

Appendix B

Characteristics and risk of bias of included studies

Table B.1 Afilalo et al., 2010 [102]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter Tapentadol ER vs. Oxycodone CR vs. Placebo in osteoarthritis of the knee **Duration:** 15 weeks
Participants	**Patients randomized:** 1030; intention-to-treat (ITT; intake of at least 1 dose of medication) population: 1023. ITT-population and LOCF method were used for efficacy analysis. **Pain diagnosis:** osteoarthritis of the knee **Inclusion criteria:** at least 40 years of age, osteoarthritis of the knee (ACR functional capacity class I-III), pain at reference joint requiring the use of analgesics (non-opioids or opioids at doses equivalent to $\leq$ 160 mg oralmorphine/day) for at least 3 months prior to screening. **Exclusion criteria:** clinical instabil medical or psychiatric disease, requirement of painful procedures (e.g.surgery), history of substance abuse, seizure disorder, HIV infection, stroke, malignancy (last 2 years), hepatitis B or C infection, hypertension ($> 160/95$ mmHg), renal or hepatic disorders, creatinine clearance < 60 ml/min, ALT or AST concentrations > 3 times the upper limit, hypersensitivity to study medication, anatomical deformities or infectious or autoimmune diseases affecting the knee, fibromyalgia, gout.
Interventions	**Screening phase:** 14 days.

Table B.1, Afilalo et al., 2010 [102] , continued from previous page.

	Washout period: 3-7 days, discontinuation of all analgesic medication. If patients had a pain intensity score of ≥ 5 on numerical rating scale (0-10) they continued to double-blind phase.
	Double-blind phase: 15 weeks, randomization to tapentadol ER b.i.d. vs. oxycodone HCL CR b.i.d. vs. placebo b.i.d. 1. Titration phase: 3 weeks, starting dose: tapentadol ER 50 mg b.i.d. and oxycodone HCl CR 10 mg b.i.d., after 3 days titration to minimum dose of: tapentadol ER 100 mg b.i.d. and oxycodone HCl CR 20 mg b.i.d. Increasement was possible at 3-day intervals to a maximum dose of tapentadol 250 mg b.i.d. and oxycodone 50 mg b.i.d. 2. Maintenance phase: 12 weeks, patients remain on stable doses. Dose adjustments were possible if necessary. Rescue medication: paracetamol ≤ 1 g/day, up to 3 consecutive days.
Outcome	**Quality of Life:** EQ-5D, SF-36
	Other measurements: pain intensity (NRS, 0-10), patient global impression of change, patient assessment of constipation symptoms, clinical opiate withdrawal scale, subjective opiate withdrawal scale.
Notes	**Funding:** study was funded and supported by Johnson & Johnson Pharmaceutical Research & Development and Grünenthal GmbH. Six study authors are Johnson & Johnson employees, two authors are employees of Grünenthal GmbH. Study was registered as NCT00421928 (ClinicalTrials.gov). Missing data was imputed by last-observation-carried-forward (LOCF) method. Study is also included in pooled analyses Afilalo, Morlion 2013 and Lange 2017.

Risk of Bias, Afilalo et al., 2010 [102]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"Randomization was based on a computer-generated randomization list, balanced using permuted blocks, and stratified by study site."
Allocation concealment	Low risk	An interactive voice response system (IVRS) was used for implementing randomization.
Blinding of participants and personnel	Unclear risk	"Placebo tablets and capsules (one for each active treatment) were used to maintain blinded treatments." It is not futher described if these tablets and capsules were identical in appearance, and why tablets and capsules are used at the same time.

Afilalo et al., 2010 [102], continued from previous page

Bias	Judgement	Support for judgement
Blinding of outcome assessment	Unclear risk	"The blinding was not broken until all patients had completed the trial, except in the case of a suspected unexpected serious adverse reaction or if emergency treatment required knowledge of a patient's treatment status." But this domain is rated unclear, as the blinding of participants is also considered unclear.
Incomplete outcome reporting	High risk	High withdrawal rate in the oxycodone group (224/342; 65,5%) in comparison to tapentadol (163/344; 47.7%) and placebo (134/337; 39,8%). LOCF method was used for imputing missing values (i. e. for QoL measurements).
Selective reporting	Low risk	All outcomes reported
Other bias	Low risk	No further signs of bias.

Table B.2 Arai et al., 2015 [103]

Study characteristics	
Methods	**Type:** RCT, withdrawal design (enriched enrollment), parallel-group, multicenter. Fentanyl TDS vs. placebo in Nociceptive and Neuropathic Pain. **Duration:** 12 weeks
Participants	**Patients enrolled:** 476 (open-label phase), patients randomized: 313, full-analysis set (all subjects, which received $\geq$ 1 dose of study drug with efficacy data in double-blind phase): 313. **Pain diagnosis:** osteoarthritis/low back pain [N01] or post-herpetic neuralgia/complex regional pain syndrome (CRPS)/chronic postoperative pain [N02]. **Inclusion criteria:** osteoarthritis or low back pain (study N01), post-herpetic neuralgia or CRPS or chronic postoperative pain (study N02) for $\geq$ 12 weeks. No intake of opioid medication, except for acute pain or as antitussive. Pain intensity of $\geq$ 50 mm (VAS, 0-100 mm) for 24 h prior to study entry. **Exclusion criteria:** low back pain with severe neuropathic component or due to compression fracture, psychogenic pain, respiratory disfunction, asthma, bradyarrythmia, liver or renal dysfunction, malignancy, alcohol, substance, neuropsychiatric disorders, impaired consciousness. Hypersensitivity to fentanyl or history of 1-day patch treatment.

Table B.2, Arai et al., 2015 [103] , continued from previous page.

Interventions	**Screening period:** 3-14 days. Patients with mean pain intensity of $\geq$ 50 mm (VAS) for at last 3 days, treated with nonopioid medication at a stable dose and requiring opioid medication could continue to next phase. **Open-label titration phase:** 10-29 days, treatment with fentanyl 1-day patch, starting dose: 12.5 µg/h, maximum dose: 50 µg/h. Patients, with mean VAS score $\leq$ 45 mm, an improvement of $>$ 15 mm, constant fentanyl dose for last 3 days and use of rescue medication $\leq$ 2/day could continue to double-blind phase. **Double-blind phase:** 12 weeks, randomization to fentanyl TDS vs. placebo. Patients in the placebo group, were tapered off in a blinded fashion. Different discontinuation criteria were defined like worsening of pain of $\geq$ 15 mm or use of rescue medication $\geq$ 3/day. Rescue medication: oral morphine, at a dose of 5 mg per fentanyl 12.5 µg/h.
Outcome	**Quality of Life:** SF-36 **Other measurements:** number of days from start of double-blinde phase to withdrawal due to insufficient analgesia, pain intensity (VAS, 0-100 mm), BPI (self-reported pain), physician's and subject's overall assessments.
Notes	**Funding:** study was funded by Janssen Pharmaceutical KK. Five study authors were employees of Janssen Pharmaceutical KK. The publication includes two studies registered as NCT01008618 (N01) and NCT01008533 (N02) on clinicaltrials.gov. Enriched design (withdrawal design) is used.

Risk of Bias, Arai et al., 2015 [103]

Bias	Judgement	Support for judgement
Random sequence	Unclear risk	Not reported
Allocation concealment	Unclear risk	Not reported
Blinding of participants and personnel	Low risk	Use of "matching placebo" is reported.
Blinding of outcome assessment	Unclear risk	Not reported
Incomplete outcome reporting	High risk	151 of 313 patients (48,2%) completed the double-blind phase. Moreover, under certain criteria discontinuation of patients from study was promoted. This leads to high risk of bias.

Arai et al., 2015 [103] , continued from previous page

Bias	Judgement	Support for judgement
Selective reporting	Low risk	All outcomes were reported.
Other bias	High risk	Withdrawal design/enriched design. 476 patients entered open-label phase, but only patients, who had a certain benefit and tolerated the opioid well, continued to the double-blind phase.

Table B.3 Arkinstall et al., 1995 [104]

Study characteristics	
Methods	**Type:** RCT, crossover, multicenter Oxycodone CR vs. Placebo in chronic non-malignant pain. **Duration:** 1 week
Participants	**Patients randomized:** 46, efficacy analysis population (patients who completed entire phase I and II): 30 **Pain diagnosis:** non-malignant pain **Inclusion criteria:** adult patient with history of chronic non-malignant pain. **Exclusion criteria:** hypersensitivity to opioid analgesics, intolerance to codeine or acetaminophen, concurrent use of other opioid analgesics during study, cephalalgia, intractable nausea or vomiting, history of drug or alcohol abuse.
Interventions	**Screening phase:** $\geq$ 3 days, intake of combined acetaminophen/codeine 300 mg/30 mg tablets for pain treatment. Depending on used daily dose of acetaminophen/codeine tablets, the dose of CR oxycodone during double-blind phase was calculated:patients who took 4-6 tablets of acetaminophen/codeine during prospective period were randomized to CR codeine 100 mg b.i.d., patients who took 7-9 tablets to CR codeine 150 mg b.i.d. and patients who took 10-12 tablets to CR codeine 200 mg b.i.d. during double-blind phase. **Double-blind phase:** 1 week, randomization to CR codeine b.i.d. vs. placebo b.i.d.. Minimum dose: 100 mg b.i.d.., maximum dose: 200 mg b.i.d.. After 1 week in phase I patients crossed over to the alternative treatment. No washout-period was in between the different phases. Rescue medication: acetaminophen/codeine 300 mg/ 30 mg 1-2 tablets every 4 hours.
Outcome	**Quality of Life:** Pain Disability Index **Other measurements:** pain intensity (VAS, 0-100 mm and 5-point categorical scale, 0-4), patients and investigators preference for treatment.

Table B.3, Arkinstall et al., 1995 [104] , continued from previous page.

Notes	**Funding:** supported by Purdue Frederick, Pickering, Ontario. Patients, who completed study, could continue drug therapy in an open-label extension.

Risk of Bias, Arkinstall et al., 1995 [104]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"A random treatment allocation list was generated by computer for each center [...]."
Allocation concealment	Unclear risk	"Designated pharmacist" administered the treatment allocation. The exact method of allocation concealment is not reported.
Blinding of participants and personnel	Unclear risk	Not reported.
Blinding of outcome assessment	Unclear risk	Not sufficiently reported.
Incomplete outcome reporting	High risk	All reasons for withdrawals are reported. 30/45 (66.7%) patients completed study, 9 patients discontinued while receiving CR codeine and 4 while receiving placebo. Only the completers (30) were analysed in efficacy analysis.
Selective reporting	Low risk	All outcomes reported
Other bias	High risk	No washout-period was in between treatmentsm which is important, because of a relative short treatment period.

Table B.4 Bennett et al., 2003 [105]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter. Tramadol/Acetaminophen vs. Placebo in fibromyalgia. **Duration:** 13 weeks
Participants	**Patients randomized:** 315, intention-to-treat (intake of at least one study dose and at least one post-randomization efficacy measurement): 313. **Pain diagnosis:** fibromyalgia. **Inclusion criteria:** 18 to 75 years of age, moderate pain intensity ($\geq 40/100\,\text{mm}$) due to fibromyalgia, fulfilling of ACR criteria for fibromyalgia. For women: contraception, no pregnancy.

Table B.4, Bennett et al., 2003 [105] , continued from previous page.

	Exclusion criteria: previous failure of tramadol therapy, use of tramadol during 30 days prior to study entry, more severe pain due to other cause than fibromyalgia. Use of certain drugs (antidepressants other than SSRI, antieplieptic drugs for pain or treatments (acupuncture) was prohibited in certain time periods prior to study entry.
Interventions	**Screening phase:** 3 weeks, medical examination were performed, complete washout of analgesics. **Double-blind phase:** randomization to tramadol/acetaminophen 37.5 mg/325 mg vs. placebo, titration over 10 days to maximum daily dose: tramadol/acetaminophen 300 mg/2600 mg (8 tablets/day).
Outcome	**Quality of Life:** SF-36 **Disease-specific QoL/functionality:** fibromyalgia impact profile **Other measurements:** cumulative time to discontinuation due to lack of efficacy, pain (VAS, 0-100 mm), pain relief (NRS, -1 - 4), sleep questionnaire.
Notes	**Funding:** supported by a grant from Ortho-McNeil Pharmaceutical. Two study authors were employees of Ortho-McNeil Pharamceutical, one study author was employee of Johnson & Johnson Pharmaceutical Research. HRQL outcome of this study is also reported and analyzed in the post-hoc analysis Bennett et al, 2005. [106]

Risk of Bias, Bennett et al., 2003 [105]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"Subjects were assigned sequentially in 1:1 fashion at eachsite using a randomized list of medication codes."
Allocation concealment	Unclear risk	Not sufficiently reported.
Blinding of participants and personnel	Low risk	Use of "matching" placebo.
Blinding of outcome assessment	Low risk	"Treatment assignments were not revealed to study subjects, investigators, clinical staff, or study monitors until all subjects had completed therapy and the database had been finalized." Patients assessed their outcome via completing standardized questionnaires.

Bennett et al., 2003 [105] , continued from previous page

Bias	Judgement	Support for judgement
Incomplete outcome reporting	High risk	All reasons for withdrawals were reported. 175/315 individuals (55.5%) discontinued prematurely.
Selective reporting	Low risk	All outcomes reported.
Other bias	Low risk	No further signs of bias.

Table B.5 Boureau et al., 2003 [107]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter Tramadol vs. Placebo in Post-Herpetic Neuralgia **Duration:** 6 weeks
Participants	**Patients randomized:** 127; intention-to-treat (ITT; at least one dose of medication and one VAS measurement at day 43) population: 125; per-protocol-population (PPP; defined as ITT-population without major protocol deviation, used for QoL efficacy analysis): 108 (n=53 tramadol, 55 placebo) **Pain diagnosis:** post-herpetic neuralgia (PHN) **Inclusion criteria:** age: 18-85 years of age, suffering from PHN from at least 3 months to a maximum of 1 year and a pain intensity on VAS $\geq$ 40 (VAS 0-100 mm) **Exclusion criteria:** depression, immune-depression, seizures, substance-abuse, cerebral tumour or cranial traumatism, severe hepatic, renal, cardiac or respiratory disease, hypersensitivity to opioids, pregnant or lactating women. Moreover there are several restrictions regarding treatments with different drugs, like MAO-inhibitors or antidepressants. Treatment with MAO-Hemmer 15 days prior, antidepressants, anticonvulsants, opioid analgesics or local/general anaesthetics 7 days prior to inclusion visit. Treatment which interferes with study design: neurological surgery, anaesthetic blocks, local treatments of pain, antidepressants, anticonvulsants, anti-vitamin K, enzymatic inductors, psychoactive agents, central and peripheral analgesics (except acetaminophen to max. 3 g/day).
Interventions	**Double-blind phase:** randomization to tramadol hydrochloride (100 mg) vs. placebo up to maximum dose of 4x100 mg/day (age $\leq$ 75) or 3x100 mg/day (age $\geq$ 75). Rescue medication: acetaminophen, maximum dose: 3 g/day.
Outcome	**Quality of Life:** "Nottingham Scale"

Table B.5, Boureau et al., 2003 [107] , continued from previous page.

	Other measurements: pain intensity past 24 hours (VAS and 5-point VRS), global improvement of pain (percentage of pain relief), use of rescue medication.
Notes	**Funding:** not further mentioned. However, one researcher is employee of Aventis. "Nottingham Scale" means likely Nottingham Health Profile. It's not reported how this Scale is been valuated (reference values: 0-100 or 0-38 are possible). Numerical differences at baseline in score of Nottingham Scale (tramadol: 10.6 [7.2], placebo: 12.4 [7.0]).

Risk of Bias, Boureau et al., 2003 [107]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"Patients [were] randomly assigned to one of the two parallel treatment groups in accordance with a computer-generated four-block centralized randomization list [...]."
Allocation concealment	Unclear risk	Not sufficiently reported.
Blinding of participants and personnel	Low risk	"Both treatments were identical with regard to appearance."
Blinding of outcome assessment	Unclear risk	Not reported.
Incomplete outcome reporting	High risk	11/64 patients in tramadol group (17.2%) and 8/63 in placebo group (12.7%) dropped out from study prematurely. Per-protocol population is used for efficacy analysis of quality of life outcomes.
Selective reporting	Low risk	All outcome reported.
Other bias	Low risk	No further signs of bias.

Table B.6 Breivik et al., 2010 [108]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter Buprenorphine TDS vs. Placebo in Osteoarthritis Pain **Duration:** 24 weeks (6 months)
Participants	**Patients randomized:** 199; intention to-treat (ITT; all subjects enrolled) population: 199; per-protocol population: 175 (only relevant for analysis of change in pain on WOMAC)

Table B.6, Breivik et al., 2010 [108] , continued from previous page.

	Pain diagnosis: osteoarthritis pain of the hip or knee
	Inclusion criteria: clinical diagnosed osteoarthritis, pain from joint at least 1 year prior to study, radiographic evidence of osteoarthritis hip/knee II-IV after Kellgren and Lawrence Scale. Patients, experiencing at least moderate pain when walking, had to take NSAIDs or coxibs for pain for $\geq$ 1 month prior to study and continue this treatment at stable dose. Treatment with low-dose opioids or trancutaneous nerve stimulation (TENS) had to be discontinued.
	Exclusion criteria: treatment with strong opioids (morphine, oxycodone, fentanyl, methadone) or treatment with weak opioids for $>$ 3 weeks to study entry, other chronic diseases requiring frequent analgetic therapy, contraindication to treatment with opioids, history of substance abuse, use of antidepressants, antiepileptics, steroids, hypnotics, unstable cardiac disease, long-QT-syndrome, treatment with IA or III anti-arrhythmics.
Interventions	**Screening phase:** screening visit 5 to 9 days prior to baseline visit, characterization of pain, compliance and tolerance to current analgetic regimen, checking of inclusion/exclusion criteria. Stable dose of NSAIDs or coxibs is allowed.
	Double-blind phase: 24 weeks, randomization to 7-day buprenorphine patch + stable dose of NSAIDs und coxibe vs. 7-day placebo Patch + stable dose NSAIDS und Coxibe; starting dose of BTDS: 5 µg/h titrated, possible doses: 10 µg/h or 20 µg/h. Rescue medication: acetaminophen, maximum daily dose: 4 g/day.
Outcome	**Quality of Life:** EQ-5D (exploratory endpoint)
	Functionality: WOMAC
	Other measurements: change in pain intensity (WOMAC), daily pain intensity on movement (NRS, 0-11), daily rescue medication, number of nights woken because of pain, patients global impression of change (PGIC), general health state (VAS, 0-100), abuse/diversion interview of investigator.
Notes	**Funding:** sponsored by Mundipharma.
	Problems with recruiting patients, who were taking NSAIDs regularly, led to an adjusted sample size (224 to 200). Therefore, and due to high withdrawal rate (44.2%), the statistical power of this study is low.

Risk of Bias, Breivik et al., 2010 [108]

Bias	Judgement	Support for judgement
Random sequence	Low risk	Block randomization, use of a "validated computer system that automates the random assignment of subject to randomisation numbers".
Allocation concealment	Low risk	Block size of treatment allocation was unknown to investigators, randomization schedule was inaccessible to personnel and patients.
Blinding of participants and personnel	Low risk	Patches were "identical in appearance, packed in a labelled foil pouch, containing coded treatment group identification. The medication codes were not available until the completion of the study [...]."
Blinding of outcome assessment	Low risk	Investigators and outcome assessment blinded (see above). Patients assessed their outcome via completing standardized questionnaires.
Incomplete outcome reporting	High risk	High withdrawal rate (44,2%), but equally distributed through study groups. Reasons for withdrawals in the vast majority of cases reported (lack of 16 patients, whose reasons for withdrawals are not properly described). ITT population is used for efficacy analysis of quality of life measurements.
Selective reporting	Unclear risk	EQ-5D only analyzed as categorical data. Data not shown, no statistical analysis performed. Other outcomes are sufficiently reported.
Other bias	Low risk	No further signs of bias.

Table B.7 Buynak et al., 2010 [109]

Study characteristics	
Methods	**Type:** RCT, double-blind, multicenter. Tapentadol vs. Oxycodone vs. Placebo in Chronic Low Back Pain **Duration:** 15 weeks
Participants	**Patients randomized:** 981 (pla/tap/oxy: 326/321/334); safety population (received at least one study dose): 965; intention-to-treat (ITT; patients who received at least one study dose, same as safety population): 958 (pla/tap/oxy: 317/315/326). Seven patients were excluded from ITT due major audit findings, so finally ITT population consists of 951 individuals. **Pain diagnosis:** low back pain.

Table B.7, Buynak et al., 2010 [109] , continued from previous page.

	Inclusion criteria: $\geq$ 18 years of age, history of low back pain and intake of analgesics for $\geq$ 3 months prior study, maximum opioid intake 160 mg morphine/day. **Exclusion criteria:** clinical significant psychiatric or medical diseases, surgery in low back area 3 months prior to screening, history of substance abuse, HIV, hepatitis B/C, malignancy (preceding 2 years), uncontrolled hypertension, cardiovascular disorders (ischemic diseases etc.), severe renal/hepatic impairments, gout, fibromyalgia.
Interventions	**Screening phase:** 3-7 days; washout of all previous analgesics, if pain intensity $\geq$ 5 on NRS (0-10) patients continue to next phase. **Double-blind phase:** 15 weeks, randomization to tapentadol ER vs. oxycodone HCl CR vs. Placebo; Titration (2 weeks): starting dose: tapentadol 50 mg b.i.d.; oxycodone 10 mg b.i.d.; titration in 3 day intervals (titrations steps: tapentadol: 50 mg; oxycodone 10 mg) up to maximum dose of 250 mg b.i.d. (tap.) or 50 mg b.i.d. (oxy.). Downward titration possible. Minimum dose: tapentadol: 100 mg b.i.d., oxycodone: 20 mg b.i.d.. Maintenance phase (12 weeks). Rescue medication: acetaminophen, 3 g/day
Outcome	**Quality of Life:** SF-36, EQ-5D, BPI. **Other measurements:** pain intensity (NRS 0-10), percentage of patients who responded with $\geq$ 30% and $\geq$ 50% reduction of pain intensity, patients global impression of change, sleep questionnaire, clinical opiate withdrawal scale, patient assessment of constipation syndrome.
Notes	**Funding:** study was funded by Johnson & Johnson Pharmaceutical Research & Development, L. L. C. and Grünenthal GmbH. Five study authors were employees and shareholders of Johnson & Johnson, three study authors were employees or former employees of Grünenthal GmbH. Patients who completed study could continue treatment in open-label extension. LOCF-method was used for imputing missing values in statistical analyses of outcome. Sensitivity analysis was only done for primary outcome (pain intensity), not for QoL-measurements.

Risk of Bias, Buynak et al., 2010 [109]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"Randomization [...] was based on computer-generated randomization list, balanced by randomly permuted blocks[...]."
Allocation concealment	Low risk	Interactive voice response system was used
Blinding of participants and personnel	Unclear risk	"Placebo tablets and capsules (one for each active treatment) were used to maintain blinded treatments." It is not futher described if these tablets and capsules were identical in appearance, and why tablets and capsules are used at the same time.
Blinding of outcome assessment	Unclear risk	"Investigators were not provided with the randomization code[...]." and "the blind was not broken until all patients completed the trial and the database was locked." But this domain is rated unclear, as the blinding of participants is also considered unclear.
Incomplete outcome reporting	High risk	Only 47.6% (pla.), 40.5% (tap.) and 52.2% (oxy.) of patients completed study. Reasons for withdrawals fully reported. LOCF was used (without sensitiviy analysis for QoL measures).
Selective reporting	Low risk	All outcomes are reported
Other bias	Low risk	No further signs of bias.

Table B.8 Emkey et al., 2004 [110]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter Tramadol/Acetaminophen vs. Placebo in osteoarthritis **Duration:** 13 weeks (91 days)
Participants	**Patients randomized:** 307, intention-to-treat (ITT; intake of $\geq$ 1 dose of study medication and $\geq$ 1 post-baseline measurement available) population: 306 **Pain diagnosis:** osteoarthritis. **Inclusion criteria:** osteoarthritis of the hip/knee for $>$ 1 year (with radiographic evidence), moderate pain intensity of $\geq$ 50 mm (VAS, 0-100 mm). Intake of a stable dosis of celecoxib ($\geq$ 200 mg/day) or rofecoxib ($\geq$ 25 mg/day) for $\geq$ 2 weeks. Women: contraception, negative pregnancy test.

Table B.8, Emkey et al., 2004 [110] , continued from previous page.

	Exclusion criteria: history of rheumatoid arthritis, ankylosing spondylitis, active gout, pseudogout, major trauma to the target joint or avascular necrosis in target joint within 6 months, previous failure of tramadol therapy, major psychiatric disorder, history of substance abuse. Use of antidepressants, cyclobenzaprine, antiepileptic drugs within 3 weeks prior to double-blind phase, short-acting analgesics, topiac medication and anaesthetics, muscle relaxants within $<$ 5 half-lives of the specific drug prior to study entry. Other interventions (intraarticular injection of steroids or physical therapy) within certain time periods prior to double-blinde phase.
Interventions	**Screening phase:** 3 weeks, washout of all non-COX2 analgesics. **Double-blind phase:** 13 weeks, randomization to tramadol/acetaminophen vs. placebo. Starting dose: 1 tablet/day $\hat{=}$ tramadol/acetaminophen 37.5 mg/325 mg, maximum dose: 8 tablets/day $\hat{=}$ tramadol/acetaminophen 300 mg/2600 mg.
Outcome	**Quality of Life:** SF-36 **Functionality/disease-specific QoL:** WOMAC **Other measurements:** pain intensity (VAS, 0-100 mm), pain relief rating score (5-point ordinal scale), overall medication assessment by physician/patient, proportion of patients who dropped out due to lack of efficacy, distribution of time to discontinuation due to lack of efficacy.
Notes	**Funding:** supported by Ortho-McNeil Pharmaceutical, New Jersey, USA. Four Study authors were employees of Ortho-McNeil Pharmaceutical, USA. All patients, which were included in analysis, took COX2-inhibitors as constant medication. Use of fixed acetaminophen/tramadol combination.

Risk of Bias, Emkey et al., 2004 [110]

Bias	Judgement	Support for judgement
Random sequence	Unclear risk	Not reported.
Allocation concealment	Unclear risk	Not reported.
Blinding of participants and personnel	Low risk	Use of “matching placebo” is reported.

Emkey et al., 2004 [110] , continued from previous page

Bias	Judgement	Support for judgement
Blinding of outcome assessment	Low risk	"All subjects, investigators,and clinical personnel were blinded to treatment assignments until the trialwas complete and the database had been finalized." It is assumed that patients fullfil standardized questionnaires by themselves.
Incomplete outcome reporting	Low risk	All withdrawals were reported and equally distributed between study groups. 227 of 307 patients (73,9%) completed full study.
Selective reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No further signs of bias.

Table B.9 Friedmann et al., 2011 [111]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter Extended-Release vs. Placebo in osteoarthritis **Duration:** 12 weeks
Participants	**Patients randomized:** 412 (entered double-blind phase); Patients, who entered open-label treatment period: 558 (enriched enrollment) **Pain diagnosis:** osteoarthritic pain of the knee **Inclusion criteria:** 40-75 years of age, osteoarthritis pain (hip/knee) for $\geq$ 3 months, radiographic evidence according to the American College of Rheumatology. Regular (4 days/week) intake of at least one of the following drugs: NSAIDs, COX-2-Hemmer, tramadol, opioids. **Exclusion criteria:** 80 mg oxycodone/d for $\geq$ 4d/wk one week prior to screening visit, intraarticular injection of hyaluronic acid 6 months prior to screening visit, epidural or intrathecal analgesic infusion 1 month prior to screening visit, positive urine drug screen (opiates, cannabinoids, etc.), medication of high doses of sedatives, hypnotics, tranquilizers and phenothiazines.
Interventions	**Screening/washout phase:** 4-10 days, all analgesics were discontinued (except acetaminophen up to 3000 mg/d, some opioids had to be tapered off first). If pain intensity $\geq$ 5 (NRS 0-10), IVRS diary compliance $\geq$ 75% and patients met all other inclusion criteria, they continued to next phase.

Table B.9, Friedmann et al., 2011 [111] , continued from previous page.

	Open-label titration phase: 14 days, starting dose oxycodone ER: 5 mg bid, titrated up to 20 mg b.i.d. Patients who tolerated medication and had a IVRS diary compliance $\geq$ 75% continued to double-blind treatment period (enriched enrollment). **Double-blind phase:** randomization to oxyocodone ER 20 mg b.i.d. vs. placebo. Placebo patients were titrated down over a 2-week period, during first 4 weeks, than maintenance for 8 weeks. Maximum dose: 20 mg b.i.d., minimum dose: 5 mg b.i.d. After double-blind period, patients were tapered off in a blinded fashion.
Outcome	**Quality of Life:** SF-12 **Functionality:** WOMAC **Other measurements:** change in daily pain intensity, quality of analgesia, global assessment of study medication, clinical and laboratory evaluations
Notes	**Funding:** funded by King Pharmaceuticals (Pfizer), one researcher was Principal Investigator for Pain Therapeutics, the other two researchers were employees of Pain Therapeutics. Enriched enrollment is used: only patients included who tolerated 20 mg oxycodone ER b.i.d. Last-oberservation-carried-forward method for some outcomes used, except WOMAC, SF-12 and AUC.

Risk of Bias, Friedmann et al., 2011 [111]

Bias	Judgement	Support for judgement
Random sequence	Unclear risk	Not reported.
Allocation concealment	Unclear risk	Not reported.
Blinding of participants and personnel	Unclear risk	Not reported.
Blinding of outcome assessment	Unclear risk	IVRS used, but as the blinding of participants is considered unclear, this domain is also considered unclear.
Incomplete outcome reporting	High risk	Reasons for withdrawals (placebo: n=75/207, 36,2%; oxycodone ER: n=70/205, 34,1%) sufficiently reported and evenly distributed throughout the study groups. Number of patients included in statistical analysis of quality of life assessment (WOMAC, SF-12) was not sufficiently reported (i. e. number of patients included in intention-to-treat population, no sensitivity analysis was made).

Friedmann et al., 2011 [111] , continued from previous page

Bias	Judgement	Support for judgement
Selective reporting	High risk	Not all outcomes are sufficiently reported (i.e. SF-12 or WOMAC)
Other bias	High risk	Enriched enrolled design was used, so that only patients who tolerated medication were included into trial.

Table B.10 Gana et al., 2006 [112]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter Extended-release Tramadol vs. Placebo in Osteoarthritic Pain **Duration:** 12 weeks
Participants	**Patients randomized:** 1020; intention-to-treat (ITT, patients who took at least one dose of stud medication, LOCF): 1011 **Pain diagnosis:** osteoarthritis of hip/knee **Inclusion criteria:** radiographically confirmed osteoarthritis of hip/knee (ACR Class I-III) and intake of acetaminophen, NSAID's, COX-2-inhibitor or opioid for $\geq$ 75 of 90 previous days **Exclusion criteria:** other uncontrolled medical conditions, another form of arthritis/joint disease on index joint, chronic pain syndrome or fibromyalgia, contraindication to tramadol, history of substance abuse during past 6 months, any condition which could influence absorption of tramadol ER.
Interventions	**Screening phase:** 2-7 days, discontinuation of all prior analgesics, if pain intensity on VAS (0-100 mm): $\geq$ 40 mm, patients continued to next phase. **Double-blind phase:** 12 weeks; randomization to 5 treatment groups: tramadol 400 mg once daily vs. tramadol 300 mg o.d. vs. tramadol 200 mg o.d. vs. tramadol 100 mg o.d. vs. placebo. Starting dose: 100 mg tramadol/day, titration to 200/300/400 mg on day 5/10/15 depending on study group. Rescue medication: acetaminophen, maximum dose: 2000 mg/day for 3 consecutive days. After double-blind treatment discontinuation of tramadol ER, without tapering.
Outcome	**Quality of Life:** SF-36 **Functionality:** WOMAC **Other measurements:** pain intensity during last 48 h, daily pain intensity, subject and physician global assessment of disease activity, sleep-related questions, overall sleep quality.

Table B.10, Gana et al., 2006 [112] , continued from previous page.

Notes	**Funding:** supported by Biovail Laboratories International SRL. Last-observation-carried-forward method for imputing missing post-baseline efficacy data.

Risk of Bias, Gana et al., 2006 [112]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"Before study enrollment, a randomization schedule was generated with permuted blocks of 10 subjects."
Allocation concealment	Low risk	Interactive voice-response system was used.
Blinding of participants and personnel	Low risk	"[...] tablets were similar in appearance and size."
Blinding of outcome assessment	Unclear risk	Not sufficiently reported.
Incomplete outcome reporting	High risk	Reasons for withdrawals are sufficiently reported. Withdrawals evenly distributed throughout study groups, 558 of 1011 completed study (55.2%). ITT-population evaluated, but last-observation-carried-forward method used to impute missing values.
Selective reporting	Low risk	All outcomes reported.
Other bias	Low risk	No further signs of bias.

Table B.11 Gilron et al., 2005 [113]

Study characteristics	
Methods	**Type:** RCT, 4-period crossover, active placebo, single-center Morphine vs. Gabapentin vs. Combination vs. Active Placebo (lorazepam) in Neuropathic Pain **Duration:** 5 weeks for each arm
Participants	**Patients randomized:** 57, efficacy analysis population (subjects, who completed $\geq$ 2 treatment periods): 44. **Pain diagnosis:** neuropathic pain (diabetic polyneuropathy (1) or postherpetic neuralgia (2))

Table B.11, Gilron et al., 2005 [113] , continued from previous page.

	Inclusion criteria: (1) diabetic neuropathy: distal symmetric sensory polyneuropathy with decrease response to pinprick, temperature or vibration in both feet or bilaterally decreased/absent ankle-jerk reflexes or (2) postherpetic neuralgia: eruption of herpes zoster not more recently than 6 months before study begin. (1)+(2): daily moderate pain at least 3 months, 18-89 years of age, ALAS or ASAT $<$ 1.2x the reference level, creatinine $<$ 1.5x reference level, sufficient language skills **Exclusion criteria:** hypersensitivity to study drugs, another painful interfering condition, myocardial infarction, unstable angina, congestive heart failure, central neurologic disorder, mood disorder, history of substance abuse, lactation and pregnancy.
Interventions	**Double-blind phase:** randomization to 4 groups: a) sustained-release morphine, maximum dose: 120 mg b) gabapentin, max.: 3200 mg c) SR morphine/gabapentin max.: 60 mg/2400 mg d) active placebo: lorazepam max.: 1.6 mg. Among subjects older than 60 years and/or weighing less than 60 kg,, theceiling doses were adapted. Week 1-3: titration of drugs to maximum dose or maximal tolerated dose; week 4: maintainence at maximum tolerated dose; week 5: 4-day tapering and 3-day complete washout phase. Then switching to another phase, according Latin-square design. Nonopioid drugs were permitted, at stable dose. Docusate sodium was provided as prophylaxis against constipation (100 to 300 mg/day).
Outcome	**Quality of Life:** SF-36, BPI **Other measurements:** mean intensity of pain (NRS, 0-10), Short-Form McGill Pain Questionnaire, Beck Depression Inventory (BDI), Mini-Mental State Examination, global pain relief, "blinding" questionnaire (guessing received therapy).
Notes	**Funding:** funded by the Candian Institutes of Health Research (CIHR). First and last-author reported paid activities for Pfizer and/or Aventis-Pharma. “Blinding” questionnaire showed higher number of patients guessing correctly the placebo group (66 %) than the active treatment groups ((a): 44%, (b): 42%, (c): 25%). Also the research nurse guessed more correct placebo treatments (71%) compared to the active treatments ((a): 33%, (b): 43%, (c): 53%).

Risk of Bias, Gilron et al., 2005 [113]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"use of balanced Latin-square crossover design"
Allocation concealment	Low risk	"pharmacist [...] prepared a concealed allocation schedule randomly assigning the four sequences, in blocks of four, to a consecutive series of numbers. On enrollment, each patient was assigned to the next consecutive number [...]."
Blinding of participants and personnel	Low risk	Use of identical appearing capsules (blue - morphin or placebo, gray - gabapentin or placebo).
Blinding of outcome assessment	Low risk	Patients and research nurses, which assessed the outcome, were blinded.
Incomplete outcome reporting	High risk	Withdrawals evenly distributed, but the reasons not sufficiently reported. 16/57 patients (28%) withdrew throughout the study.
Selective reporting	Low risk	All outcomes reported.
Other bias	Low risk	No further signs of bias.

Table B.12 Gimbel et al., 2003 [114]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter.
	Controlled-Release Oxycodone vs. Placebo in Painful Diabetic Neuropathy.
	Duration: 6 weeks
Participants	**Patients randomized:** 159 (oxy/plac: 82/77), intention-to-treat (at least one dose of study medication) population: 159, per-protocol population (ITT without protocol violation): 146
	Pain diagnosis: diabetic polyneuropathy
	Inclusion criteria: distal symmetrical polyneuropathy. Symptoms were assigned using the Einstein Focused Neurologic Assessment (evaluation of sensory function, distal muscle strength and reflexes). History of stable diabetes mellitus (HbA1c $\geq$ 11%) and of pain in both feet ($\geq$ 5 on NRS 0-10) for $\geq$ 3 months, at least moderate pain during absence of any opioid analgesic therapy within 3 days prior to study begin.

Table B.12, Gimbel et al., 2003 [114] , continued from previous page.

	Exclusion criteria: unstable/poorly controlled diabetes, chronic pain unrelated to diabetic neuropathy. History of substance or alcohol abuse, serum creatinine $\geq$ 2.5mg/dl, hepatic dysfunction $\geq$ 3times upper limit of normal, history of active cancer, hypersensitivity to oxycodone or opioids, rapidly escalating pain within the previous month. Treatment with long-acting opioid formulation and $>$ 3 times/week intake of short-acting opioids. Autonomic neuropathy or gastrointestinal dysfunction, need for elective surgery, pregnant or breast-feeding women.
Interventions	**Screening phase:** 3-7 days, general examination, blood tests, discontinuation of all other opioid therapies. Assessment of daily pain, if pain $\geq$ 5 on NRS (0-10) patients continued to next phase. **Double-blind phase:** randomization to CR Oxycodone vs. placebo, starting dose: 10 mg/b.i.d., maximum dose: 60 mg/b.i.d., upward titration was possible every 3 days by one 10 mg-tablet in the morning or evening. Coanalgesics like NSAIDs or acetaminophen, taken at stable dose for $\geq$ 3 weeks prior enrollment, were allowed. Opioid analgesics other than study medication were prohibited. **Tapering phase:** optional one-week tapering phase.
Outcome	**Quality of Life:** SF-36, BPI, Sickness Impact Profile **Other measurements:** average daily pain intensity (11-point scale, 0-10) at different time points, current and worst pain intensity, satisfaction with pain medication (NRS), scale for sleep quality (NRS), scales for current and worst pain (NRS), Rand Mental Health Inventory, time to mild pain, number and proportion of days with mild pain.
Notes	**Funding:** supported by Purdue Pharma L.P. One study author is employee of Purdue Pharma L.P. LOCF method was used for imputing missing data.

Risk of Bias, Gimbel et al., 2003 [114]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"[...] subjects were assigned to treatment using a randomization schedule with permuted blocks of size 4 which was generated by the sponsor with SAS software."

Gimbel et al., 2003 [114] , continued from previous page

Bias	Judgement	Support for judgement
Allocation concealment	Low risk	The study staff, who assigned the randomization treatment was unaware of the randomization schedule. The randomization schedule was sealed.
Blinding of participants and personnel	Low risk	"Subjects received CR oxycodone or an identical placebo tablet [...]."
Blinding of outcome assessment	Low risk	Staff and patients were blinded, procedure is described sufficiently.
Incomplete outcome reporting	High risk	Only 115 of 159 patients completed study (72%); withdrawals (n=44) evenly distributed throughout study groups (25 in placebo group, 19 in oxycodone group). LOCF method was used for imputing missing data.
Selective reporting	High risk	Not all outcomes are sufficiently reported (i. e. SF-36, Sickness Impact Profile).
Other bias	Low risk	No further sings of bias.

Table B.13 Gordon, Callaghan et al., 2010 [115]

Study characteristics	
Methods	**Type:** RCT, crossover, multicenter. Buprenorphine transdermal system (BTDS) vs. Placebo for Chronic Low Back Pain **Duration:** 4 weeks each arm
Participants	**Patients randomized:** 78, intention-to-treat population (ITT; all patients): 78, per-protocol population (PPP; completion of at least 2 consecutive weeks, no protocol violations): 52. For primary efficacy analysis of QoL measures PPP was used. **Pain diagnosis:** Chronic low back pain **Inclusion criteria:** $>$ 18 years of age, pain: $>$ 2 (ordinal scale 0-4) for $>$ 3 months and required $\geq$ 1 tablet/day of an opioid analgesic.

Table B.13, Gordon, Callaghan et al., 2010 [115] , continued from previous page.

	Exclusion criteria: history of pain refractory to opioids, hypersensitivity to opioids/acetaminophen. Other pain treatment (surgery etc), significant other source of pain. Substance abuse and major psychiatric disorders. Elevated liver enzymes, decreased serum potassium/magnesium levels, head injury, COPD, asthma, respiratory depression, atrial fibrillation, myocardial ischemia, heart failure, tachy- or bradycardia, long QT intervals (i. e.mean QTc interval $>$ 500 ms), peptic ulcer, inflammation of GI-tract, pregnancy.
Interventions	**Screening phase:** 2-7 day washout period, physical examination (i.e. assessment of nociceptive/neuropathic components of pain, ECG), laboratory tests. **Double-blind phase:** before being randomized to 7-day BTDS patches vs. placebo patches for 4 weeks, after completing one phase patients crossed over to alternative treatment. Initial dose: 10 µg/h, maximum dose: 40 µg/h BTDS. Rescue medication: acetaminophen, 325 mg tablets, 1 or 2 tablets every 4 to 6 hours.
Outcome	**Quality of Life:** SF-36, Pain Disability Index (PDI) Quebec Back Pain Disability Scale (QBPDS) **Other measurements:** pain intensity (VAS and 5-point ordinal scale), pain and sleep questionnaire, effectiveness of treatment (categorical scale), clinical benefit assessed by investigators, subjective opioid withdrawal scale, nausea and drowsiness (VAS 0-100 mm), patients treatment preference.
Notes	**Funding:** Purdue Pharma. Five study authors were employees of Purdue Pharma No washout phase between different treatments. Double-blind phase is followed by an 6-month open-label extension for patients who completed both phases.

Risk of Bias, Gordon, Callaghan et al., 2010 [115]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"A block-randomization procedure was used to generate the treatment allocations [...]. The randomization code was generated using PROC PLAN in SAS version [...]."
Allocation concealment	Unclear risk	"[...]for every 4 successive patients, 2 received BTDS in the first phase and 2 received BTDS in the second phase [...]." Not reported if deciphering was possible and which method was used.

Gordon, Callaghan et al., 2010 [115] , continued from previous page

Bias	Judgement	Support for judgement
Blinding of participants and personnel	Low risk	"patients [...] being randomized to receive BTDS or matching placebo patches." "Study monitors, investigators, coordinators, pharmacists, patients [...] remained blinded to treatment allocation[...]."
Blinding of outcome assessment	Low risk	"Study monitors, investigators, coordinators, pharmacists, patients [...] remained blinded to treatment allocation[...]." Moreover as patients assessed the outcome, blinding - most likely - has been maintained until outcome assessment.
Incomplete outcome reporting	High risk	29 of 78 patients withdrew prematurely (37%, 19 in BTDS group, 10 in Placebo). Reasons are fully reported, but number of withdrawals during BTDS therapy is nearly two times higher than during Placebo phase. Apparently for efficacy analysis of QoL-outcomes per-protocol population was used.
Selective reporting	High risk	Not all outcomes are sufficiently reported, lack of exact data (i. e. QoL measures).
Other bias	High risk	Crossover design, with no washout phase between studies. BTDS shows a long elimination time, possibly influencing subsequent treatment. Analysis on carryover-effects remains unclear.

Table B.14 Gordon, Rashiq et al., 2010 [116]

Study characteristics	
Methods	**Type:** RCT, double-blind, crossover Buprenorphine Transdermal System (BTDS) vs. Placebo for Chronic Low Back Pain **Duration:** 4 weeks each arm
Participants	**Patients randomized:** 79, Intention-to-treat (ITT) population: 79; Per-protocol-population (PPP; completed two consecutive weeks in each treatment arm, no major protocol violation): 53 **Pain diagnosis:** chronic low back pain **Inclusion criteria:** $>$ 18 years of age, low-back pain of at least moderate severity (2 on 5-point ordinal scala) and duration of mininum 6 weeks which was inadequately treated with nonopioids.

Table B.14, Gordon, Rashiq et al., 2010 [116] , continued from previous page.

	Exclusion criteria: expected BTDS dose exceeds maximum study dose, hypersensitivity to opioids and acetaminophen, refractory to opioids. Severe organ dysfunction, head injury, seizures, COPD, asthma, respiratory depression, cor pulmonale, heart failure, peptic ulcer disease, gastrointestinal inflammation, elevated liver function tests. History of substance abuse, major psychiatric disorders.
Interventions	**Double-blind phase:** randomization to 7-day BTDS vs. placebo 4 weeks, after completing one phase patients crossed over to alternative treatment. Initial dose: 5 µg/h, maximum dose: 20 µg/h. Rescue medication: acetaminophen/codeine (300 mg/30 mg) tablets, 1 or 2 tablets every 4-6 h. Other nonopioid analgesics at stable dose were allowed.
Outcome	**Quality of Life:** SF-36, Pain Disability Index (PDI) **Functionality:** Quebec Back Pain Disability Scale **Other measurements:** pain intensity (VAS and 5-point ordinal scale), recorded twice daily. Pain and sleep questionnaire, patients level of activity (VAS), effectiveness of treatment assessed by patient/investigator, overall treatment preference. Nausea and drowsiness (VAS)
Notes	**Funding:** funded by Purdue Pharma. Five study authors were associated with Purdue Pharma or Astellas Pharma. "For patients who withdrew from the study, the final week of treatment was considered to be the last week [...]." This is a version of last-observation-carried-forward method for imputing missing values. Patients, who completed double-blind study could enter a 6-month open-label treatment with BTDS. Physical component score was significant lower at the end of an open-label extention phase compared to end of double-blinded phase.

Risk of Bias, Gordon, Rashiq et al., 2010 [116]

Bias	Judgement	Support for judgement
Random sequence	Low risk	Block randomization procedure with random code generated bei PROC PLAN.
Allocation concealment	Unclear risk	"For every four successive patients, two received active BTDS in the first phase and two received active BTDS in the second phase." Not reported, if deciphering was possible and which method was used.

Gordon, Rashiq et al., 2010 [116] , continued from previous page

Bias	Judgement	Support for judgement
Blinding of participants and personnel	Low risk	Matching placebo were used.
Blinding of outcome assessment	Unclear risk	Patients assessed their outcome and were blinded. But no statement regarding blinding of investigators and study personnel is made.
Incomplete outcome reporting	High risk	All dropouts are sufficiently reported (28/79, 35.4%), but two-times higher drop-out rate in BTDS, than in placebo (n=18 in BTDS, 9 in Placebo treatment). Imputation of missing values with method likely to LOCF is used. Apparently for efficacy analysis of QoL outcomes per-protocol population was used.
Selective reporting	Low risk	All outcomes are reported sufficiently.
Other bias	High risk	Crossover design, with no washout phase between studies. BTDS shows a long elimination time, possibly influencing subsequent treatment. However carryover analysis showed "no significant" carryover-effect.

Table B.15 Hanna et al., 2008 [117]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter Oxycodone prolonged-release vs. Placebo in Diabetic Neuropathy **Duration:** 12 weeks
Participants	**Patients randomized:** 338 (Oxy/Plac: 169/169). Full analysis population (FAP; at least on edose of study medication and one primary efficacy measurement): 328 (Oxy/Plac: 163/165). Per-Protocol population (PPP; FAP with no protocol violations): 302 (at least one dose of medication + one post-baseline measurement). **Pain diagnosis:** diabetic neuropathy **Inclusion criteria:** $\geq$ 3 months pain due to diabetic neuropathy, stable dose of gabapentin for at least 1 month at maximum tolerated dose. Michigan Neuropathy Screening Instrument score $\geq$ 2.5, moderate to severe pain "right now" ($\geq$ 5 on NRS, 0-10).

Table B.15, Hanna et al., 2008 [117] , continued from previous page.

	Exclusion criteria: HbA1c $>$ 11%, use of long-acting opioid during last month prior to screening, former use of oxycodone/gabapentin combination
Interventions	**Screening phase:** 5-14 days before study begin.
	Double-blind phase: 12 weeks, randomization to Oxycodone prolonged release b. i. d. vs. Placebo. Initial dose: 5 mg b.i.d. Stepwise dose titration (each step is one dose level) was allowed during double-blind phase. Rescue medication: paracetamol 1g. NSAIDs and tricyclic antidepressants were allowed at stable doses.
	Follow-up: 30 days after last dose of study medication.
Outcome	**Quality of Life:** SF-BPI, EuroQol EQ-5D
	Other measurements: Box Scale-11 pain scores, use of escape medication, subjects global assessment of pain, sleep disturbance/sleep quality. Short-form McGill Pain-Questionnaire, subject resource utilisation.
Notes	**Funding:** Mundipharma Research Limited. One researcher also was employee of Mundipharma Research Limited. Last-observation-carried-forward was used for impuation of BS-12 pain scores, escape medication use and sleep assessments. All included Patients were taking Gabapentin at a stable dosis during study.

Risk of Bias, Hanna et al., 2008 [117]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"Treatment allocation was in balanced blocks of 4 and was stratified by country."
Allocation concealment	Low risk	Interactice voice response system was used for allocation concealment.
Blinding of participants and personnel	Low risk	Use of "matching" placebo.
Blinding of outcome assessment	Low risk	Outcome assessment was made by patients themselves. "Patients and all personnel involved in the study, including investigators, site personnel and sponsor's staff, were blinded to the medication codes until the time of unblinding."

Hanna et al., 2008 [117] , continued from previous page

Bias	Judgement	Support for judgement
Incomplete outcome reporting	Unclear risk	249 patients (73,6%) completed study, but withdrawals distributed equally throughout study groups. It is not reported on how many patients, analysis of QoL variables was made. In QoL analysis no LOCF is used, but only "available data" is analyzed.
Selective reporting	High risk	Exploratory variables (i.e. QoL measurements) were not sufficiently reported (no exact values).
Other bias	Low risk	No further signs of bias.

Table B.16 Harati et al., 1998 [118]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter, outpatient Tramadol vs. Placebo for Diabetic Neuropathy **Duration:** 6 weeks (42 days)
Participants	**Patients randomized:** 131, intention-to-treat population: 127, safety analysis population: 131. **Pain diagnosis:** diabetic neuropathy **Inclusion criteria:** at least 18 years of age, distal symmetric diabetic neuropathy, total glycosylated hemoglobin of $< 14\%$. Pain in lower extremities for at least 3 months, moderate pain (2) on Likert scale (0-4) without analgetic therapy. **Exclusion criteria:** contraindication to tramadol, neuropathy caused by other diseases: alcoholism, toxic exposure etc.. Pain more severe than neuropathic pain, severe depression, creatinine clearence < 30 ml/min, clinically significant medical conditions, use of narcotic analgesics or mexiletine, amputations, open ulcera or Charcot joints.
Interventions	**Screening phase:** discontinuation of short-acting analgesics 7 days before study entry, tricyclic drugs/anticonvulsants 21 days before entry. Clinical laboratory tests were performed and medical history was obtained.

Table B.16, Harati et al., 1998 [118] , continued from previous page.

	Double-blind phase: 42 days, randomization to tramadol vs. placebo, administered in divided doses q.i.d. Initial dose 50 mg/day, minimum dose: 100 mg/day, maximum dose: 400 mg/day. Increment every 3 days by 50 mg/day up to 200 mg/day at day 10-14, from day 14-28 increasing dose up to maximum dose. After day 28 dosage could not be reduced. Alternative schedule was permitted, if patients experienced inadequate pain relief.
Outcome	**Quality of Life:** MOS (Stuart and Ware, Medical outcome study, 6 dimensions of health + 2 sleep problem indices) **Other measurements:** pain intensity score (5-point Likert scale: 0-4), pain relief score (6-point Likert scale: -1-4)
Notes	**Funding:** supported by a grant from Ortho-McNeil Pharmaceutical, Raritan, NJ. Two study authors were employees of Ortho-McNeil Pharmaceutical, Raritan, NJ. 117 patients chose to continue treatment with tapentadol in open-label follow-up trial.

Risk of Bias, Harati et al., 1998 [118]

Bias	Judgement	Support for judgement
Random sequence	Low risk	A computer generated random code was used
Allocation concealment	Unclear risk	"A Physician Drug Assignment/Inventory Record listing the double-blind code numbers was supplied to each investigator. The investigator entered the eligible patients in numerical order, thereby assigning the patient to one of the two treatment groups." But is it not stated, if it is possible for the investigator to foresee if two patients were assigned to the same group.
Blinding of participants and personnel	Low risk	Identical appearing "blue opaque size 0 capsules containing either tramadol 50 mg or placebo"
Blinding of outcome assessment	Low risk	"Identification of the test preparation assigned to a subject could be revealed only for emergency purposes by cutting the label along the line and opening it. [...] When that occurred, the time, date and reason for the unmasking was described on the appropriate case record form page."

Harati et al., 1998 [118] , continued from previous page

Bias	Judgement	Support for judgement
Incomplete outcome reporting	High risk	High withdrawal rate (37.4%) but evenly distributed throughout study groups (tramadol: 20/65, placebo: 25/66). Reasons for withdrawals are fully reported. 4 patients had no postbaseline efficacy assessment, and were lost to efficacy analysis.
Selective reporting	High risk	Outcomes of quality of life measurements are not fully reported (missing values).
Other bias	Low risk	No further signs of bias.

Table B.17 Khoromi et al., 2007 [119]

Study characteristics	
Methods	**Type:** RCT, active-placebo, single-center, 4-periods crossover study. Morphine vs. Nortriptyline vs. Combination vs. Active Placebo in Neuropathic Pain **Duration:** 9 weeks each period
Participants	**Patients randomized:** 55; efficacy analysis population (completed at least 2 treatment periods): 34 **Pain diagnosis:** Lumbar radiculopathy/sciatica **Inclusion criteria:** 18 to 65 years of age; lumbar radiculopathy/sciatica: pain in at least one buttock or leg for ≥ 3 months or ≥ 5 days a week. Additional characteristics regarding at least one of the following characteristics: sharp shooting pain below the knee, sensory loss in L5/S1, electromyographic and imaging evidence for root denervation/compression, decreased/absent ankle reflexes, pain evoked by straight leg rising or weakness of muscles below the knee. Average leg pain minimum 4/10 for past month on NRS (0-10), no change of concomitant analgetic medication during study. **Exclusion criteria:** serious illnesses (Unstable angina, advanced diabetes, cancer), medicated prostatic disease, pregnancy or lactation, history of depression or substance abuse, narrow angle glaucoma, seizure disorder, fibromyalgia, polyneuropathy, hypersensitivity to study drugs, multisomatoform disorder, greater pain in other regions than legs/low back, evidence for multisomatoform disorder, unwillingness to discontinue other opioids than study medication.

Table B.17, Khoromi et al., 2007 [119] , continued from previous page.

Interventions	**Screening phase:** MRI of lumbosacral spine was analyzed by two blinded neuroradiologist, classifying visible evidence of root compression. Laboratory examinations of the blood (sedimentation rate, rheumatoid factor etc.) were also performed. **Double-blind phase:** randomization into 4 groups: a) SR morphine, maximum daily dose: 90 mg b) nortriptyline, max.: 100 mg c) SR morphine/nortriptyline, max.: 90 mg/100 mg d) active placebo: Benztropine, max.: 1 mg. Week 1-5: starting dose: 15 mg morphine, 25 mg nortryptiline. Intake of blue morphine/placebo capsules was possible at morning and at bed time, intake of red nortriptyline/placebo capsules was possible only at bed time. Uptitration to maximum tolerated dose in steps of 15 mg (morphine) or 25 mg (nortriptyline) each week. Week 6-7: maintenance of maximum tolerated dose. Week 8-9: 10 days of tapering off study medication, then 4 days of staying drug free before starting next period. If pain level dropped below 4 on NRS (0-10) patient had to wait until pain level increased to $\geq$ 4. Rescue medication: acetaminophen and anti-inflammatory medication. To prevent constipation tablets of docusate sodium (50 mg) and sennosides (8.6 mg) were provided.
Outcome	**Quality of Life:** SF-36 **Functionality/disease-specific QoL:** Oswestry low back pain disability index **Other measurements:** daily average pain back/leg/overall pain (NRS, 0-10), global pain relief, Beck Depression Inventory, "blinding questionnaire"
Notes	**Funding:** supported bei National Institut of Dental and Craniofacial Research.

Risk of Bias, Khoromi et al., 2007 [119]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"Patients were assigned by random numbers within blocks of four to one of tour treatment sequences specified by Latin square"
Allocation concealment	Unclear risk	Not reported.

Khoromi et al., 2007 [119] , continued from previous page

Bias	Judgement	Support for judgement
Blinding of participants and personnel	Low risk	Usage of identical appearing capsules described (blue pill: morphin or placebo, pink pill: nortriptyline or placebo).
Blinding of outcome assessment	Low risk	Outcome assessment performed by patients and study nurses. "Patients and research staff were blinded to the randomization order." "Blinding questionnaire" showed 50% correct guesses for Placebo (statistically expected: 25%), 35% for morphine. However, results of "blinding questionnaire" were not considered for rating of this item.
Incomplete outcome reporting	High risk	High drop-out rate (27/55, 49.1%), but sufficiently described and evenly distributed throughout study groups (placebo: n=9, morphine: n=9). Efficacy analysis population contained only 34 patients, who completed at least two treatment periods. It was not exactly reported on how many patients QoL-analysis (i. e. SF-36) was made.
Selective reporting	Low risk	All outcomes are described sufficiently.
Other bias	Low risk	No further signs of bias.

Table B.18 Kivitz et al., 2006 [120]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter. Oxymorphone vs. Placebo in Osteoarthritis pain of the hip or knee **Duration:** 2 weeks
Participants	**Patients randomized:** 370 , intention-to-treat (ITT; intake of $\geq$ 1 dose of study medication and baseline and $\geq$ 1 postbaseline VAS score) population: 357 **Pain diagnosis:** osteoarthritis pain of hip/knee. **Inclusion criteria:** at least 18 years of age, osteoarthritis of the knee/hip (symptoms + radiographical evidence II-IV on Kellgren/Lawrence scale). Paracetamol/NSAIDs/Opioids had to be taken regularly 90 days before screening visit, in the case of nonopioid medication, investigators had to judge analgesic response as suboptimal. Premenopausal women: sexual abstinence or adequate contraception.

Table B.18, Kivitz et al., 2006 [120] , continued from previous page.

	Exclusion criteria: gout, pseudogout, inflammatory arthritis, Paget's disease, chronic pain syndrome, fibromyalgia, another major joint disease. History of seizure, alcohol or substance abuse, need for surgical treatment, former treatment with corticosteroide during 2 months and intra-articular viscosuplementation during 3 (nonindex joint) or 6 (index joint) months prior to study. Difficulty in swallowing medication.
Interventions	**Screening phase:** First baseline assessment, then 2-7 day washout period: discontinuation of all analgesic medicaments except ASS $\leq 375 mg/day$. If pain $> 40 mm$ (VAS, 0-100) patients continued to double-blind phase. **Double-blind phase:** 2 weeks, randomization to 4 groups: a) oxymorphone ER 10 mg 2-wk b.i.d, maximum daily dose: 20mg/day n:95, completed:61 b) oxymorphone ER 20mg b.i.d. 1st wk., 40 mg b.i.d. 2nd wk. (n:93, completed:35) c) oxymorphone ER 20mg b.i.d. 1st wk., 50mg b.i.d. 2nd wk. (n:91, completed:37) d) placebo 2 wks., n:91, completed:65. No concomitant or rescue analgesia was allowed.
Outcome	**Quality of Life:** SF-36 (physical health component summary - PCS) **Functionality:** WOMAC **Other measurements:** pain intensity (VAS, 100 mm), chronic pain sleep inventory, electrocardiogram, adverse events, clinical laboratory parameters.
Notes	**Funding:** supported by Endo Pharmaceuticals Inc., Pennsylvania and Penwest Pharmaceuticals Co., Connecticut. One study author is employee of Endo Pharamceuticals, one study author is employee of PharmaStats. Last-observation-carried-forward method is used for imputing missing values. Short duration as double-blind phase of study lasts only two weeks.

Risk of Bias, Kivitz et al., 2006 [120]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"A computer-generated randomization schedule was used to assign them [the patients] to 1 of 4 groups."
Allocation concealment	Unclear risk	Not sufficiently reported.
Blinding of participants and personnel	Low risk	"Study medications were overencapsulated in gelatin capsules so they were visually indistinguishable, and they were administered in a double-dummy fashion to maintain blinding."
Blinding of outcome assessment	Low risk	The investigators and patients remain blinded. The method used is described sufficiently. It is assumed that patients assessed by themselves via standardized questionnaires
Incomplete outcome reporting	High risk	Only 198 (53,5%) Patients completed study. More patients completed in Oxymorphone 10 mg b.i.d. (n=61, 64,2%) and Placebo group with (n=65, 71,4%) than in Oxymorphone 40 mg b.i.d. (n=35, 37,6%) and 50 mg b.i.d. group (n=37, 40,0%). Moreover last-observation-carried-forward method is used to impute missing values.
Selective reporting	Low risk	All outcomes are sufficiently reported.
Other bias	Low risk	No further signs of bias.

Table B.19 Lee et al., 2013 [121]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter. Tramadol Extended-Release/Acetaminophen vs. Placebo in Chronic Low Back Pain **Duration:** 4 weeks
Participants	**Patients randomized:** 248, intention-to-treat (ITT; at least one dose of study medication) population: 245, full analysis population (FAS, $\geq$ 1 dose of study medication and at least "one measurement of change in average pain intensity from baseline"): 175. Per-protocol population (PPP, completed study per-protocol): 151. For quality of life analysis (SF-36) 170 patients were included. **Pain diagnosis:** chronic low back pain.

Table B.19, Lee et al., 2013 [121] , continued from previous page.

	Inclusion criteria: 25-75 years of age, at least moderate chronic low back pain $\geq 4\,cm$ (VAS, 10cm) despite regular use of NSAIDs and COX-Inhibitors for ≥ 3 months before screening. NSAIDs and COX-Inhibitors had to be taken at stable dose 7 days before study entry and maintained during double-blind period. **Exclusion criteria:** discontinuation of tramadol or tramadol/acetaminophen due to adverse events. Ingestion of: opioid analgesics within 30 days, acetaminophen within 7 days, antidepressants, anticonvulsants, cyclobenzaprine within 3 weeks prior to study begin. Tumor or infection on the meninges/spinal cord, severe pain in other area than low back, neurologic deficit on the legs, painful fibromyalgia, complex regional pain syndrome, acute spinal cord compression, cauda equina syndrome, proximal diabetic neuropathy, infection, back surgery within 3 months or steroid injection within 4 weeks of screening.
Interventions	**Screening phase:** 7 days, medical examination and assessment of medical history. Stable dose of NSAID's/COX-2-Inhibitors was administered. If pain intensity of last 48 hours was $\geq 4\,cm$ on VAS (0-10 cm) patients proceed to double-blind phase. **Double-blind phase:** randomization to ER tramadol hydrochloride/acetaminophen 75 mg/650 mg vs. placebo. Day 1-3: 1 tablet/day; day 4-7: 1 tablet b.i.d.; day 8-29: maintenance at stable dose; maximum dose: 2 tablets b.i.d, that is tramadol/acetaminophen: 300 mg/2600 mg per day. NSAID's/COX-2-Inhibitors were maintained at stable dose, other pain therapy (drug or physical therapy) was not allowed.
Outcome	**Quality of Life:** Korean Short-Form-36 (K-SF-36) **Functionality/disease-specific QoL:** Korean Oswestry Disability Index (K-ODI) **Other measurements:** pain intensity (VAS, 10 cm), pain relief (6-point scale), control of chronic low back pain during ingestion of test drug (patient and investigator, 5-point scale).
Notes	**Funding:** supported and funded by Janssen Korea, Ltd. First efficacy analysis of primary outcome was not significant. After 100% source data verification the composition of the full analysis population (FAS) was changed. Different patients were in- and excluded from the analysis. The second analysis of the "corrected" FAS showed significant results. FAS population is smaller than population of patients, who completed study (175 vs. 196). Study was registered as NCT01112267 (ClinicalTrials.gov).

Risk of Bias, Lee et al., 2013 [121]

Bias	Judgement	Support for judgement
Random sequence	Low risk	Use of a "computer-generated,stratified randomization plan prepared by the sponsor [...]."
Allocation concealment	Unclear risk	Methods of allocation concealment were not sufficiently described.
Blinding of participants and personnel	Low risk	"Both tablets [placebo and interventional drug] were identical in appearance."
Blinding of outcome assessment	Low risk	Outcome appears to be assessed by the patients themselves at the assessment centers. "Blinding was maintained until all patients completed the study and the database was closed."
Incomplete outcome reporting	High risk	Withdrawals in opioid group two times higher than in placebo group. (n=33/125 vs. n=16/120; 26,4% vs. 13,3%) Moreover the reasons for withdrawals of the people, who are included in FAS are not reported. FAS population is smaller than population of patients, who completed study (175 vs. 196).
Selective reporting	Low risk	All outcomes are reported.
Other bias	High risk	After first analysis, which showed no significant improvement of opioid therapy in pain intensity measurement, database was changed. Second analysis with "corrected" FAS population showed significant changes.

Table B.20 Ma et al., 2008 [122]

Study characteristics	
Methods	**Type:** RCT, parallel-group and multicenter. Oxycodone CR vs. Placebo in Chronic Neck Pain with Acute Pain Flares **Duration:** 2-4 weeks
Participants	**Patients randomized:** 116. No withdrawals reported. Statistical analysis is made on a strongly decreasing number of subjects during the study at different time points (see Intervention, Notes). **Pain diagnosis:** chronic neck pain with acute pain flares

Table B.20, Ma et al., 2008 [122] , continued from previous page.

	Inclusion criteria: 40 to 70 years of age, chronic refractory neck pain for $>$ 6 months and MRI/CT suggesting degenerative disease or neck injury, acute pain flares $>$ 3 times/day with $>$ 30 min/episode with pain intensity of $>$ 4 (VAS, 0-10) for three days. No response to NSAIDs, weight $>$ 40 kg, no history of alcohol and drug abuse, no severe liver/renal disease, no use of opioid within 2 weeks prior study entry. **Exclusion criteria:** unbearable side effects from opioid medication and patients who required "sudden change" in oxycodone CR doses.
Interventions	**Double-blind phase:** placebo vs. oxycodone CR 5-10 mg b.i.d., starting dose depending on pain intensity measured prior to study entry. Dose could be increased or decreased by a maximum of 50%. Discontinuation was possible if following criteria were fulfilled: I) oxycodone CR intake of at least 1 week II) frequency of acute pain flares $<$ 3 times/day and pain intensity $<$ 2 (VAS, 0-10) III) significant improvement of QoL and QoS. Rescue medication: acetaminophen 325-650 mg every 4-6 hrs.
Outcome	**Quality of Life:** performance status score (PS), patient satisfaction scale (PSS), SF-36. **Other measurements:** frequence of acute pain flares, pain intensity (VAS, 0-10), quality of sleep.
Notes	**Funding:** funded by Shanghai Sixth People's Hospital Clinical Research grant. Patient could discontinue the study at different times (see Interventions). This leads to a strongly decreasing number of subjects during the study.

Risk of Bias, Ma et al., 2008 [122]

Bias	Judgement	Support for judgement
Random sequence	Unclear risk	Not reported.
Allocation concealment	Unclear risk	Not reported.
Blinding of participants and personnel	Low risk	Identical tablets of placebo and Oxycodone-CR.
Blinding of outcome assessment	Unclear risk	Not reported.

Ma et al., 2008 [122] , continued from previous page

Bias	Judgement	Support for judgement
Incomplete outcome reporting	High risk	Many dropouts or patients who discontinuated the study, due to study design, which allows premature discontinuation under certain criteria of success. So i.e. only 12 patients from 116 enrolled completed 4 weeks of double-blind treatment. Moreover, withdrawals due to AEs or lack of efficacy are not reported.
Selective reporting	Low risk	All outcomes are reported.
Other bias	High risk	The study design allows premature discontinuation in the case of a positive effect of therapy on QoL and pain intensity. Therefore short and transient positive effects could be judged as successful, without evaluating them until the end of the study. This may arise additional bias to this study.

Table B.21 Markenson et al., 2005 [123]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter. CR Oxycodone vs. Placebo in Osteoarthritis pain. **Duration:** 90 days $\hat{=}$ 13 weeks
Participants	**Patients randomized:** 109, intention-to-treat (ITT; at least intake of one dose of study medication) population: 107. **Pain diagnosis:** osteoarthritis. **Inclusion criteria:** complaints of pain of at least 1 month before study entry and average pain intensity in week before study entry $\geq$ 5 (NRS, 0-10) or $\geq$ 3 for patients taking opioids. Patients were taking NSAIDs or APAP for at least 2 weeks before study entry or NSAID intolerant (therefore not taking NSAIDS) or taking opioids with an equivalent dosis of $\leq$ 60 mg/day of Oxycodone. **Exclusion criteria:** hypersensitivity to opioids. Unstable coexisting disease, active cancer, pregnancy, substance abuse, receiving of steroid injections within 6 weeks prior to study entry.
Interventions	**Screening phase:** assessment of demographic information and medical history. Medical examination and assessment of osteoarthritis symptoms. If patients meet inclusion criteria, they proceed to double-blind phase.

Table B.21, Markenson et al., 2005 [123] , continued from previous page.

	Double-blind phase: CR oxycodone (OxyContin) 10 mg vs. placebo. Titration to stable dose, defined as pain intensity $\leq$ 4 (0-10, NRS) during 48 hrs. Maximum dose: 60 mg b.i.d. (120 mg/day). NSAIDs and APAP were allowed at stable doses.
Outcome	**Quality of Life:** BPI, PGI (Patient generated index)
	Functionality: WOMAC
	Other measurements: patient-reported satisfaction and acceptability with pain medication, time to stable dosing, percentage of patients achieving stable dosing within 30 days, daily dose throughout the study, pain intensity.
Notes	**Funding:** financial support by Puedue Pharma. Two author are employees of Purdue Pharma, the other two authors received financial support by Purdue Pharma, Stamford, CT. Last-observation-carried-forward was used for imputing missing efficacy values in ITT population. Evaluation of PGI is questionable. Sponsor is chosing the "primary activity" from 5 areas, which is then evaluated. Neither the criteria, which lead to the Sponsor's decision are mentioned, nor the reasons why the analysis did not include all areas. Considering this method of analysis, the PGI reflects does not reflect a multidimensional approach to QoL anymore.

Risk of Bias, Markenson et al., 2005 [123]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"computer generated randomization code..."
Allocation concealment	Unclear risk	Not reported.
Blinding of participants and personnel	Low risk	"Patients [...] were randomly assigned in double blind fashion to receive either 10-mg tablets of CR oxycodone [...] or matching placebo."
Blinding of outcome assessment	Unclear risk	Not reported.
Incomplete outcome reporting	High risk	Placebo group completed: 13/51 (4% lost due to AE, 67% due to ineffective treatment). Oxycodone group completed: 23/56 (36% lost due to AE, 16% due to AE's). ITT-analysis was performed, but LOCF-method was used to impute missing measurement values.
Selective reporting	High risk	All outcomes sufficiently reported, except evaluation of PGI. Sponsor is choosing the "primary activity" in PGI prior to unblinding. Only this measure is then evaluated.

Markenson et al., 2005 [123] , continued from previous page

Bias	Judgement	Support for judgement
Other bias	Low risk	No further signs of bias.

Table B.22 Matsumoto et al., 2005 [124]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter. Oxymorphone ER vs. Oxycodone CR vs. Placebo in Osteoarthritis pain **Duration:** 4 weeks
Participants	**Patients randomized:** 491, whereas 489 patients received $\geq$ 1 dose of study medication. Intention-to-treat (ITT; received at least 1 dose of study medication and had a baseline and at least 1 postbaseline measurement) population: 467. **Pain diagnosis:** osteoarthritis. **Inclusion criteria:** $>$ 40 years of age, knee/hip symptoms and radiographic evidence of OA, $\geq$ 2 grade of Kellgren-Lawrence scale, intake of acetaminophen, COX2-Inhibitor or opioid for at least 75 of 90 days before screening visit with suboptimal response. Contraception and negative serum pregnancy test 7 days before first dose of study medication. **Exclusion criteria:** inflammatory arthritis, gout, morbus Paget, chronic pain syndrome, fibromyalgia. Weight of $<$ 100 pounds, history of substance or drug abuse, opioid intolerance, any need of surgical procedure on index joint.
Interventions	**Screening phase:** 2-7 days, washout period: discontinuation of all analgesic medicaments. The patients proceed to double-blind phase if they had a pain intensity of $\geq$ 40 mm on VAS (0-100mm). **Double-blind phase:** 4 weeks, randomization into 4 groups: a) Oxymorphone ER 40 mg b.i.d.: 1.-2. week: 20 mg b.i.d., 3.-4. week: 40 mg b.i.d.; randomized: n=121. b) Oxymorphone ER 20 mg b.i.d.: 1.-4. week: 20 mg b.i.d., n=121. c) Oxycodone CR 20 mg b.i.d.: 1.-2. week: 10 mg b.i.d., 3.-4. week: 20 mg b.i.d. n=125. d) Placebo, n=125. No rescue medication provided.
Outcome	**Quality of Life:** SF-36

Table B.22, Matsumoto et al., 2005 [124] , continued from previous page.

	Functionality: WOMAC
	Other measurements: pain intensity (VAS, 100mm), patients and physicians global assessment of therapy, patients sleep assessment, several safety assessments.
Notes	**Funding:** supported by Endo Pharmaceuticals Inc., Pennsylvania, and Penwest Pharmaceuticals, Danbury, Connecticut. One study author was employee of TheraQuest Biosciences, another study author was employee of Endo Pharmaceuticals Inc. Last-observation-carried-forward method was used for imputing missing outcome values in ITT-population.

Risk of Bias, Matsumoto et al., 2005

Bias	Judgement	Support for judgement
Random sequence	Low risk	"The list of randomization numbers was based on a computergenerated randomization schedule."
Allocation concealment	Unclear risk	Method of allocation concealment is not sufficiently reported.
Blinding of participants and personnel	Low risk	"Active study medication tablets were overencapsulated and visually indistinguishable from each other and from the placebo tablets."
Blinding of outcome assessment	Low risk	"Study enrollees, study personnel, and investigators were blinded to the identity of the treatments. The statisticians who analyzed the data remained blinded to the identity of the treatmentsuntil all data were entered into the database and the database was locked." It is assumed that patients assessed their outcomes by themselves via standardized questionnaires.
Incomplete outcome reporting	High risk	222 Patients discontinued study (45,21%). 68 patients discontinued in Oxymorphone 40mg group (56,2%), 58 patients in Oxymorphone 20 mg group (47,9%) and 50 patients in Oxycodone 20 mg group (40,0%) vs. 46 patients in Placebo (37,1%). Last-observation-carried-forward method was used to impute missing values for efficacy analysis.
Selective reporting	Low risk	All outcomes are reported sufficiently.
Other bias	Low risk	No further signs of bias.

Table B.23 Moulin et al., 1996 [125]

Study characteristics	
Methods	**Type:** RCT, crossover, active-placebo. Morphin sustained-release vs. Benztropine (active placebo) in Chronic Non-Cancer Pain **Duration:** each arm 11 weeks.
Participants	**Patients randomized:** 61, analysis population: 46 (completed at least one week of treatment in each arm). Patients, who completed the two treatment arms: 43. **Pain diagnosis:** chronic non-cancer pain. **Inclusion criteria:** 18-70 years old, stable non-malignant pain of at least 6 month duration, average weekly pain $\geq$ 5 (VAS 0-10) at week before study enrollment. Regional myofascial, rheumatical, musculoskeletal pain, no analgetic response to NSAIDs or tricyclic antidepressants, effective birth control. **Exclusion criteria:** history of substance abuse, history of psychosis or major depression, neuropathic pain syndromes, congestive heart failure, myocardial infarction one year before study, hypersensitivity to morphine/codeine, history of asthma, epilepsy or hepatic or renal disease, isolated headache syndromes, former use of opioids (oxycodone, morphine, hydromorphone) except codeine.
Interventions	**Double-blind phase:** 11 weeks. a) Titration phase: 3 weeks, titration of morphine SR: 15/30/60 mg b.i.d. vs. active placebo: benztropine 0,25/0,5/1 mg b.i.d.. Maximum dose: morphine: 60 mg b.i.d. $\hat{=}$ 120 mg/day , benztropine: 1 mg b.i.d. $\hat{=}$ 2 mg/day. b) Evaluation phase: 6 weeks, maintenance at highest tolerated dose. c) Washout phase: 2 weeks, decreasing doses of medicaments, last week maintenance at lowest study dose. Patients were regularly visited by a psychologist and offered additional therapy, in the sense of a multidimensional therapy concept. Rescue medication: acetaminophen 500 mg, maximum dose: 1 tablet/4 hours. After completion of double-blind phase, patients switched to the opposite treatment arm.
Outcome	**Quality of Life:** Sickness Impact Profile (SIP), Pain Disability Index (PDI) **Other measurements:** pain intensity (VAS, 0-10 cm), McGill Pain Questionnaire, Symptom Check List-90, Profile of Mood States (POMS), “drug liking index”, “blinding questionnaire”.

Table B.23, Moulin et al., 1996 [125] , continued from previous page.

Notes	**Funding:** supported by Medical Research Council of Canada and Purdue Frederick. Carryover effect for mean pain intensity was found in patients with morphine as first treatment.

Risk of Bias, Moulin et al., 1996 [125]

Bias	Judgement	Support for judgement
Random sequence	Unclear risk	Not reported.
Allocation concealment	Unclear risk	Not reported.
Blinding of participants and personnel	Low risk	"Matching placebos" were used.
Blinding of outcome assessment	Unclear risk	Not reported. 67,4% of the investigators identified morphine patients, according to results of blinding questionnaire.
Incomplete outcome reporting	High risk	Reasons for withdrawals were not reported fully. 61 patients were randomized, but only 46 were included in the efficacy analysis (75.4%). 43 patients completed study (70.5%).
Selective reporting	Low risk	All outcomes are reported.
Other bias	Low risk	No further signs of bias.

Table B.24 Peloso et al., 2004 [126]

Study characteristics	
Methods	**Type:** RCT, parallel-group, double-blind, placebo-controlled and multicenter Tramadol/Acetaminophen Combination vs. Placebo in Chronic Low Back Pain **Duration:** 13 weeks (91 days)
Participants	**Patients randomized:** 338; intention-to-treat (ITT; intake of $\geq$ 1 dose of study medication and $\geq$ 1 postbaseline measurement) population: 336; safety population (intake of $\geq$ 1 dose of study medication and $\geq$ 1 safety measurement): 336. **Pain diagnosis:** chronic low back pain **Inclusion criteria:** $\geq$ 8 years of age, pain due to chronic low back pain, requiring medication for at least 3 months prior to study entry. Good general health, for female patients: postmenopausal or adequate contraception.

Table B.24, Peloso et al., 2004 [126] , continued from previous page.

	Exclusion criteria: contraindication or hypersensitivity to tramadol, use of sedative hypnotics, short-acting analgesics, topical medication/anaesthetics, intake of muscle relaxans for period of less than 5 half-lives of the medication prior to study entry, use of medications reducing the seizure threshold within 3 weeks prior to study entry, use of opioids within 6 weeks prior to study entry, treatment with tramadol 30 days prior to study entry. History of seizure, unstable medical disease, renal or hepatic dysfunction, substance abuse, inflammatory disease, other diseases or pain that may interfere with CLBP, neurological deficits in the lower extremities, tumors, infections of spinal cord, meninges, symptomatic disk herniation, severe spinal stenosis, spondylolisthesis $\geq$ grade 2, acute vertebral fracture with surgical treatment.
Interventions	**Washout/screening phase:** up to 21 days, discontinuation of all pain medications. Patients with pain $\geq$ 40 on VAS (0-100 mm) proceeded to double-blind phase. **Double-blind phase:** 91 days, randomization to tramadol/acetaminophen 37,5 mg/325 mg vs. placebo. Day 1-10: titration from 1 tablet/day up to 1 tablet q.i.d., maximum daily dose: 2 tablets q.i.d. $\hat{=}$ tramadol/acetaminophen: 300 mg/2600 mg; minimum daily dose: 3 tablets $\hat{=}$ tramadol/acetaminophen: 112,5 mg/975 mg. Rescue medication: acetaminophen, maximum dose: 1000 mg/day
Outcome	**Quality of Life:** SF-36 **Functionality/Disease-specific QoL:** Roland Disability Questionnaire (RDQ) **Other measurements:** pain last 48 hours on VAS (0-100 mm), pain relief, present pain intensity, Short-form McGill Pain questionnaire, patient/investigator overall rating of therapeutic effect.
Notes	**Funding:** supported by Ortho-McNeil Pharmaeutical, Raritan, New Jersey, USA. One study author is employee of Ortho Biotech, another one of Ortho-McNeil, Pharmaceutical. Tramadol is here given in fixed combination with acetaminophen.

Risk of Bias, Peloso et al., 2004 [126]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"Patients were randomized in a 1:1 fashion to tramadol/acetaminophen or placebo, using a centrally prepared randomization scheme carried out in blocks of 8."
Allocation concealment	Unclear risk	Not reported.
Blinding of participants and personnel	Low risk	"identical-appearing tablets" were used.
Blinding of outcome assessment	Unclear risk	It is assumed that the patients themselves collect the outcome data by completing questionnaires. However, there is no statement regarding the blinding of the investigators and physicians.
Incomplete outcome reporting	High risk	High withdrawal rate (placebo: 64.3 %, tramadol/acetaminophen: 48.5 %), reasons fully described. ITT-population is analyzed.
Selective reporting	Low risk	All outcomes reported.
Other bias	Low risk	No further signs of bias.

Table B.25 Raja et al., 2002 [127]

Study characteristics	
Methods	**Type:** RCT, crossover.
	Morphine or Methadone vs. Nortriptyline or Desipramine vs. Placebo in Post-Herpetic Neuralgia (PHN) **Duration:** 8 weeks
Participants	**Patients randomized:** 76; patients, who completed all three treatment periods: 44. 26 patients were treated with the alternative opioid. **Pain diagnosis:** post-herpetic neuralgia (PHN)
	Inclusion criteria: $>$ 18 years of age, persisting pain for $\geq$ 3 months after healing of cutaneous lesions, pain intensity of $\geq$ 4 on NRS (0-10) during last week before study entry. **Exclusion criteria:** history of substance abuse, allergy to opioid or tricyclic antidepressiva (TCA), myocardial infarction in the previous 3 months, cardiac conduction defects, severe pulmonary disease, angle-closure glaucoma, pregnancy, dementia, encephalopathy, HIV-positivity, life expectancy $<$ 6 months.
Interventions	**Screening phase:** initial interview, physical and neurologic examination. All pain medication used for PHN had to be discontinued for at least one week prior study.

Table B.25, Raja et al., 2002 [127] , continued from previous page.

	Double-blind phase: 2 weeks, three different treatment arms: nortriptyline (10 mg/capsule) vs. morphine (MS contin 15 mg/capsule) vs. placebo. Patients who could not tolerate morphine or nortriptyline were offered alternative drugs (for morphine: methadone: 5 mg/capsule, for nortryptyline: desipramine 10 mg/capsule). One treatment period consisted of three phases: I) Titration phase was flexible and lasted approx. 4 weeks (range 1-9 weeks). Dose could be increased twice weekly. Starting dose: 1 tablet/day, maximum dose 16 tablets/day (morphine: 240 mg/day, nortriptyline: 160 mg/day). II) Maintenance phase, 2 weeks, at maximum tolerated dose. III) Tapering phase, 2-3 weeks. Rescue medication: acetaminophen and NSAR. Also active treatment of side effects was allowed (i. e. senna or lactulose for constipation, prochlorperazine or ondansetrone for nausea). Each patient runs through the three different treatment arms with one week break before crossing over to the next treatment.
Outcome	**Quality of Life:** two dimensions of multidimensional pain inventory (MPI): interference and general activity. **Other measurements:** pain intensity (NRS, 0-10), pain relief (NRS, 0-100%), symbol substitution (from Wechsler Adult Intelligence Scale), Hopkins verbal learning test, grooved pegboard task (manual dexterity and psychomotor speed), sleep item (from MPI), Beck depression inventory, different scale from profile of mood states, global preference of treatment.
Notes	**Funding:** supported by National Institute of Health grant no. NS 32386 and GCRC grant no. RR0052.

Risk of Bias, Raja et al., 2002 [127]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"The randomization sequence was computer generated [...]."
Allocation concealment	Low risk	"The randomization sequence [...] was provided in sealed envelopes to the pharmacist and the monitoring committee."
Blinding of participants and personnel	Low risk	Identical gel capsules were used for different treatment arms.

Raja et al., 2002 [127] , continued from previous page

Bias	Judgement	Support for judgement
Blinding of outcome assessment	Low risk	It is plausible stated, that investigators remain blinded until the end of study. Outcome is assessed by the patients themselves.
Incomplete outcome reporting	High risk	After opioid period signficant more patients dropped out (n=20) than after placebo (n=1, $p< 0.01$). Reasons are fully reported. The efficacy analysis of the pain outcome - and probably the QoL analysis - were performed on 64 patients (opioids) and 56 patients (placebo).
Selective reporting	Low risk	All outcomes are reported.
Other bias	Low risk	No further signs of bias.

Table B.26 Roth et al., 2000 [128]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter. Oxycodone CR vs. Placebo in Osteoarthritis-related Pain. **Duration:** 14 days
Participants	**Patients randomized:** 133, analysis population for pain (intake of $\geq$ 4 doses of study medication and recording $\geq$ 2 pain intensity evaluation): 109, last-observation-carried-forward method is used. For efficacy analysis of other outcomes (i. e. QoL) the full study population (133) is analyzed. **Pain diagnosis:** osteoarthritis **Inclusion criteria:** adult patients, for 3 months $\geq$ 2 of the following signs of osteoarthritis: pain aggravated by motion, limitation of the range of motion, stiffness, bony tenderness o2n pressure, bony swelling, joint fluid analysis consistent with osteoarthritis and $\geq$ 1 radiographic finding: i. e. osteophytes, joint space narrowing or subchondral bony sclerosis. **Exclusion criteria:** severe organ dysfunction, history of drug or alcohol abuse.
Interventions	**Double-blind phase:** randomization to placebo vs. CR oxycodone 10 mg b.i.d. vs. CR oxycodone 20 mg b.i.d.. Dose titration and use of rescue medication was not allowed. NSAIDs-intake could be continued, if dose had been stable for 1 month prior study entry. Patients could continue therapy in an open-label 6-month extension.

Table B.26, Roth et al., 2000 [128] , continued from previous page.

Outcome	**Quality of Life:** brief pain inventory (BPI), activity and lifestyle questionnaire (modified Stanford Health Assessment Questionnaire, 4-point categorical scale). **Other measurements:** pain intensity (4-point categorical scale), quality of sleep.
Notes	**Funding:** sponsored by Purdue Pharma LP, Norwalk, Connecticut. One study author is employee of Purdue Phara LP. Last-observation-carried-forward method is used for analysis of pain measurement.

Risk of Bias, Roth et al., 2000 [128]

Bias	Judgement	Support for judgement
Random sequence	Unclear risk	Not reported.
Allocation concealment	Unclear risk	Not reported.
Blinding of participants and personnel	Low risk	"Identical placebo or [...] oxycodone tablets" were used.
Blinding of outcome assessment	Unclear risk	Not reported.
Incomplete outcome reporting	High risk	High withdrawal rate (52,6%), but evenly distributed throughout study groups. LOCF method is used for imputing pain intensity values. If this method is also used for imputing QoL-values remains unclear.
Selective reporting	High risk	Not all outcomes are sufficiently reported (i. e. activity and lifestyle questionnaire, lack of exact data).
Other bias	Low risk	No further signs of bias.

Table B.27 Ruoff et al., 2003 [129]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter. Tramadol/Acetaminophen vs. Placebo in Chronic Low Back Pain **Duration:** 13 weeks
Participants	**Patients randomized:** 322, intention-to-treat (intake of $\geq$ 1 dose of study medication and $\geq$ 1 post-baseline assessment): 318 **Pain diagnosis:** chronic low back pain

Table B.27, Ruoff et al., 2003 [129] , continued from previous page.

	Inclusion criteria: 25-75 years of age, general good health, lower back pain with requirement of daily medication for $\geq$ 3 months before entry. Women: postmenopausal or practicing of adequate form of contraception. **Exclusion criteria:** contraindications to opioids or acetaminophen, major psychiatric disorders, history of suicide. Previously discontinued tramadol therapy, intake of tramadol 30 days prior study entry, intake of antidepressants, cyclobenzaprine, antiepileptic drugs for pain, acupuncture within 3 weeks of double-blind phase.
Interventions	**Screening phase:** 3 weeks, washout of all analgesics, patients with pain intensity of $\geq$ 40 mm (VAS) continued to double-blind phase. **Double-blind phase:** randomization to tramadol/acetaminophen vs. placebo. Starting dose: 1 tablet (tramadol/acetaminophen 37.5 mg/325 mg), maximum daily dose: 8 tablets $\hat{=}$ tramadol/acetaminophen 300 mg/2600 mg. Rescue medication: acetaminophen, maximum dose: 2000 mg/day, only allowed during first 6 days of double-blind phase.
Outcome	**Quality of Life:** SF-36 **Disease-specific QoL/functionality:** roland disability questionnaire **Other measurements:** pain intensity (VAS, 0-100 mm), pain relief rating scale, short-form McGill pain questionnaire, incidence of discontinuation due to insufficient pain relief.
Notes	**Funding:** not reported. 4 authors were employees of Ortho-McNeil Pharmaceutical. Use of fixed tramadol/acetminophen combination

Risk of Bias, Ruoff et al., 2003 [129]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"Randomization was performed using SAS version 8 (SAS Institute Inc., Cary, North Carolina). Blockrandomization was by site."
Allocation concealment	Unclear risk	Not sufficiently reported.
Blinding of participants and personnel	Unclear risk	Not sufficiently reported.

Ruoff et al., 2003 [129] , continued from previous page

Bias	Judgement	Support for judgement
Blinding of outcome assessment	Unclear risk	"Patients, investigators, clinical staff, and study monitors remained blinded to treatment assignments until therapy was complete and the database was finalized." It is assumed that patients assessed the outcome by themselves, but as the "blinding of participants"-item is rated unclear, this item is also assigned as unclear risk of bias.
Incomplete outcome reporting	High risk	Withdrawals were fully reported. 157 patients (48.8%) dropped out prematurely. Number of patients analyzed for QoL outcome differs from ITT population (288 vs. 318).
Selective reporting	Low risk	All outcomes were reported.
Other bias	Low risk	No further signs of bias.

Table B.28 Schwartz et al., 2011 [130]

Study characteristics	
Methods	**Type:** RCT, parallel-group, enriched design (withdrawal study) Tapentadol ER vs. Placebo in Diabetic Peripher Neuropathy (NCT00455520) **Duration:** 12 weeks
Participants	**Patients enrolled:** 591 (open-label period), received study drug: 588; randomized in double-blind phase: 395, ITT-population ($\geq$ 1 dose of study medication in double-blind period): 389, (plac/tap: 193/196) **Pain diagnosis:** diabetic peripher neuropathy (DPN) **Inclusion criteria:** $\geq$ 18 years of age, diabetes type 1 or 2 and chronic DPN $\geq$ 6 months, if their HbA1C $\leq$ 11 for $\geq$ 3 months. Use of analgetics for $\geq$ 3 months and dissatisfaction with current treatment (if patients taking opioids maximum equivalent dose morphine $\leq$ 160 mg/day).

Table B.28, Schwartz et al., 2011 [130] , continued from previous page.

	Exclusion criteria: participation in another trial within 30 days before study entry, history of alcohol or drug abuse. Condition which could confound pain assessment (e.g. fibromyalgia, rheumatoid arthritis), significant pulmonary, gastrointestinal, endocrine or psychiatric disease interfering with study assessment, moderate or severe hepatic impairment, severe renal impairment, seizure disorder or epilepsy, traumatic brain injury, stroke or TIA. Brain neoplasm, malignancy within past 2 years, extensive diabetic foot ulcers or amputation, charcot disease. Use of neuroleptics, SNRI, anticonvulsants, antiparkinsonian drugs during study. Use of other analgesic except study drug was permitted.
Interventions	**Washout phase:** 3-14 day washout, discontinuation of all analgesic medication. **Evaluation phase:** 3 days, pain intensity measurement; if average pain intensity ("pre-titration") $\geq$ 5 on NRS (0-10) patients continue to open-label titration phase. 21 days, titration within range of 100-250 mg b.i.d. tapentadol ER; titration steps: 50 mg every 30 days, starting dose: 50 mg b.i.d. minimum dose: 100 mg b.i.d.. Rescue medication: acetaminophen ($\leq$ 2000 mg/day). Titration period was followed by measuring of pain intensity ("baseline"). If patients improve $\geq$ 1 in pain intensity (NRS) vs. baseline, they continued to double-blind phase. **Double-blind phase:** 12 weeks, randomization to tapentadol ER vs. Placebo. In Placebo group: first three days tapentadol ER 100mg b.i.d., then switching to placebo; in both groups: use of supplemental tapentadol ER 25 mg b.i.d. permitted. Follow up: follow-up visit 4 days after end of double-blind phase, 2 weeks later phone call.
Outcome	**Quality of Life:** EQ-5D, BPI (ClinicalTrials.gov and Schwartz et al. 2015), SF-36 (Schwartz et al. 2015). Report of quality of life measurements only in pooled analysis (Schwartz et al. 2015) and in database ClinicalTrials.gov. **Other measurements:** pain intensity (NRS, 0-10), percentage of improvement in pain intensity (responder rates), patient's global impression of change (PGIC), clinical opiate withdrawal scale (COWS), subjective opiate withdrawal scale (SOWS).
Notes	**Funding:** study was funded by Johnson & Johnson Pharmaceutical Research, L. L. C. and Grünenthal GmbH. Five study authors were employees of Johnson & Johnson, one study author was employee of Grünenthal GmbH.

Table B.28, Schwartz et al., 2011 [130] , continued from previous page.

	Enriched design/withdrawal design was used. Not all outcomes were described in publication, compared to the National Library of Medicine (NLM) database ClinicalTrials.gov (NCT00455520) and to pooled analysis of two tapentadol studies in Schwartz, Etropolski, et al., 2015, Clinical drug investigation.

Risk of Bias, Schwartz et al., 2011 [130]

Bias	Judgement	Support for judgement
Random sequence	Low risk	Block randomization is used
Allocation concealment	Low risk	Interactive voice response system (IVRS) is used
Blinding of participants and personnel	Unclear risk	Not reported.
Blinding of outcome assessment	Unclear risk	Patients and investigators were not provided with randomization codes. Because blinding of patients is rated as unclear, this dimension is rated unclear, too.
Incomplete outcome reporting	High risk	Withdrawals evenly distributed (Plac/Tap: 30.1%/30.6%). Reasons were fully reported. It remains unclear, which imputation method is used for QoL values, as last-observation-carried-forward method is used for "primary efficacy analysis".
Selective reporting	High risk	Not all results are reported, which are mentioned in pooled analysis (Schwartz et al. 2015) and in database ClinicalTrials.gov. In these publications the results are also incomplete.
Other bias	High risk	Withdrawal study/enriched design. 501 patients entered open-label phase but only 395 proceed to double-blind phase.

Table B.29 Serrie et al., 2017 [131]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter.
	Tapentadol vs. Oxycodone vs. Placebo in Osteoarthritis of the knee
	Duration: 15 weeks
Participants	**Patients randomized:** 990, intention-to-treat (intake of $\geq$ 1 study dose): 987.

Table B.29, Serrie et al., 2017 [131] , continued from previous page.

	Pain diagnosis: osteoarthritis of the knee.
	Inclusion criteria: $\geq$ 40 years of age, knee osteoarthritis according to diagnosis criteria of American College of Rheumatology, functional capacity class I-III, requirement of analgesia for $\geq$ 3 months (if opioids: $\leq$ 160 mg/day morphine equivalent dose).
	Exclusion criteria: istory of substance abuse, active hepatitis b/c, stroke, traumatic brain injury, malignancy, transient ischemic attack, severe renal or hepatic impairment, hypersensitivity to study medication, clinically significant medical or psychiatric illnesses, requirement of painful medical interventions during study, participation in former tapentadol study or any other study within 30 days prior to study begin. Intake of corticosteroids, neuroleptics, monoamine oxidase inhibitors, SNRI, tricyclic antidepressants, antiepileptics, antiparkinsonian drugs was prohibited.
Interventions	**Screening phase:** $\leq$ 14 days.
	Washout period: 3-7 days, discontinuation of all analgesic medication. If patients had a pain intensity score of $\geq$ 5 on numerical rating scale (0-10) they continued to double-blind phase.
	Double-blind phase: 15 weeks, randomization to tapentadol PR b.i.d. vs. oxycodone HCL CR b.i.d. vs. placebo b.i.d. 1. Titration phase: 3 weeks, starting dose: tapentadol PR 50 mg b.i.d. and oxycodone HCl CR 10 mg b.i.d., then after 3 days titration to minimum dose of: tapentadol PR 100 mg b.i.d. and oxycodone HCl CR 20 mg b.i.d. Increasement was possible at 3-day intervals to a maximum dose of tapentadol 250 mg b.i.d. and oxycodone 50 mg b.i.d. 2. Maintenance phase: 12 weeks, patients remain on stable doses. Dose adjustments were possible if necessary. Rescue medication: paracetamol $\leq$ 1 g/day, up to 3 consecutive days.
Outcome	**Quality of Life:** EQ-5D, SF-36
	Functionality/disease-specific QoL: WOMAC
	Other measurements: pain intensity (NRS, 0-10), patient global impression of change (PGIC), patient assessment of constipation symptoms (PAC-SYM), clinical opiate withdrawal scale (COWS), subjective opiate withdrawal scale (SOWS), sleep questionnaire, responder analysis of patients with $\geq$ 30% or $\geq$ 50% improvement of pain intensity.

Table B.29, Serrie et al., 2017 [131] , continued from previous page.

Notes	**Funding:** study was sponsored by Grünenthal GmbH. A collaborator was Johnson & Johnson Pharmaceutical Research & Development, L. L. C.. LOCF method is used for imputing missing values (EQ-5D, SF-36). Study is registered as NCT 00486811 at ClinicalTrials.gov. Study is also included in pooled analyses Afilalo, Morlion 2013 and Lange 2017. Data of withdrawals and study completers published online on ClinicalTrials.gov at 2007 differ slightly from data in this publication.

Risk of Bias, Serrie et al., 2017 [131]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"Randomization followed a computer-generated randomization list balanced by randomly permuted blocks and stratified by study site [. . .]."
Allocation concealment	Low risk	"[. . .] Implementation was [made] through an interactive voice response system."
Blinding of participants and personnel	Low risk	"Active medication was packed in blister cards together with placebo medication matching the medication for the respective other active groups and at each administration active and placebo medication were taken together."
Blinding of outcome assessment	Low risk	"During the double-blind study period, treatment assignments were masked from investigators and patients. Treatment allocations were not made available until all patients had completed the study except inemergency situations." Patients assessed the outcome by themselves via standardized questionnaires.
Incomplete outcome reporting	High risk	Reasons for withdrawals are reported, but differ between treatment groups. While on placebo 122/337 subjects (36,2%) withdrew prematurely, there were 214/333 subjects (64,3%) on oxycodone. 513 of 990 patients (51,8%) completed the full study.
Selective reporting	Low risk	All outcomes are reported.
Other bias	Low risk	No further signs of bias.

Table B.30 Steiner et al., 2011 and Yarlas et al., 2013 [132] [247]

Study characteristics	
Methods	**Type:** RCT, parallel-group, withdrawal study Buprenorphine Transdermal System vs. Placebo for Chronic Low Back Pain **Duration:** 12 weeks
Participants	**Patients enrolled:** 1027 (open-label period), patients randomized: 541, full-analysis population (received $\geq$ 1 dose double-blind study drug): 369, randomized safety population ($\geq$ 1 safety measurement): 539 **Pain diagnosis:** Chronic low back pain **Inclusion criteria:** $\geq$ 18 years of age, moderate to severe low back pain for $\geq$ 3 months prior study entry lasting for several hours daily. Opioid naive, no benefit from or no tolerance of non-opioid therapy, non-malignant pain causes (e.g. intervertebral disc disease, spinal stenosis etc.) **Exclusion criteria:** radicular symptoms, acute spinal cord compression, acute compression fracture, seronegative spondyloarthropathy, acute nerve root compression, cauda equina compression, fibromyalgia, reflex sympathetic dystrophy, diabetic amyotrophy, meningitis, discitis, gout, pseudogout, psoriatic arthritis, active Lyme disease, rheumatoid arthritis, trochanteric bursitis, ischial tuberosity bursitis, neuropathic conditions, back pain due to secondary infection, tumor or postherpetic neuralgia. Surgery to threat back pain within six months prior to study entry. QTc $\geq$ 480 ms, treatment with IA oder III antiarrhythmic agents.
Interventions	**Screening period:** 6-10 days, patients had to score pain intensity value of $\geq$ 5 (NRS, 0-10) in first screening visit, then pain medication for low back pain was discontinued. If following pain intensity measurements were $\geq$ 5 for two consecutive days patients could proceed to next phase.

Table B.30, Steiner et al., 2011 and Yarlas et al., 2013 [132] [247] , continued from previous page.

	Run-in period: 13-27 days, enriched enrollment, all patients were titrated first to 7-day buprenorphine transdermal system (BTDS) 5 µg/hour and later 10 µg/hour for 10 ± 2 days. If patients tolerate and respond to BTDS ($\geq$ 2 point reduction and a score of $\leq$ 4 in "average pain over the last 24 hours") they were randomized to BTDS 10 µg/hour vs. placebo. If no sufficient response was achieved, patients were uptitrated to BTDS 20 µg/hour for another 10 ± 2 days. If they tolerated this dose and achieved claimed pain reduction they were randomized to BTDS 20 µg/hour vs. placebo. Patients who could not tolerate the mentioned BTDS doses had to discontinue the study and were not randomized to double-blind phase. **Double-blind phase:** 84 days, randomization to either BTDS 10 µg/hour vs. placebo or BTDS 20 µg/hour vs. placebo. Switching between dose of BTDS 10 and 20 µg/hour during double-blind phase was allowed. Supplementary analgesia (first six days): immediate-release oxycodone 5 mg, maximum dose: 10 mg/day. Supplementary analgesia (week 2-12): acetaminophen 500 mg, maximum dose: 2 g/day or ibuprofen 200 mg, maximum dose: 800 mg/day.
Outcome	**Quality of Life:** SF-36v2, BPI **Functionality/disease-specific QoL:** Oswestry Disability Index (ODI) **Other measurements:** average pain last 24 hours (NRS, 0-10), medical outcome sleep scale (MOS), use of oxycodone supplemental analgetics. Patients global impression of change (PGIC), daily "pain right now" score, time from randomization to discontinuation.
Notes	**Funding:** sponsored by Purdue Pharma L.P.. 6 study authors (Steiner 2011) are employees of Purdue Pharma L.P.. Enriched enrollment is used: only patients who tolerated and showed analgetic response to BTDS entered double-blind phase. Registered in ClinicalTrials.gov (NCT00490919).

Risk of Bias, Steiner et al., 2011, Yarlas et al., 2013 [247] [132]

Bias	Judgement	Support for judgement
Random sequence	Unclear risk	Not reported.
Allocation concealment	Unclear risk	Not reported.
Blinding of participants and personnel	Unclear risk	Method is not reported.

Steiner et al., 2011, Yarlas et al., 2013 [247] [132] , continued from previous page

Bias	Judgement	Support for judgement
Blinding of outcome assessment	Unclear risk	Not reported.
Incomplete outcome reporting	High risk	Reasons for dropouts (BTDS: 86/256 $\hat{=}$ 34%, placebo: 84/283 $\hat{=}$ 30%) were reported. Only the QoL scores at the study endpoint were included in efficacy analysis, without imputing results (only data of 361 individuals is included in analysis, compared to 541 of full-analysis population).
Selective reporting	High risk	QoL outcomes are not reported sufficiently. Exact data is often missing.
Other bias	High risk	Enriched enrollment is used in study design. 1027 patients entered open-label period, but only 541 were randomized.

Table B.31 Thorne et al., 2008 [133]

Study characteristics	
Methods	**Type:** RCT, crossover Tramadol CR vs. Placebo in Osteoarthritis Pain **Duration:** 4 weeks
Participants	**Patients randomized:** 100, intention-to-treat (full analysis set) population: 100, per protocol population (at least 2 weeks in each treatment phase): 77 **Pain diagnosis:** osteoarthritis **Inclusion criteria:** $\geq$ 18 years of age, diagnosed with osteoarthritis (clinical symptoms and radiographic evidence in hip or knee) and requiring therapy with acetaminophen, NSAIDs or combination of non-opioids and opioids for at least 3 months. **Exclusion criteria:** opioid intolerance, tramadol or acetaminophen, history of drug abuse, other form of joint disease or joint replacement, renal or hepatic impairment, several gastrointestinal disease (peptic ulcera etc.), high risk for development of respiratory depression, seizure. Intake of carbamazepine, MAO-inhibitors, SSRI, tricyclic antidepressants, cyclobenzaprine, neuroleptics, warfarin, digoxin.
Interventions	**Screening phase:** 2-7 days, patients were withdrawn from all analgesics, except acetaminophen. If their pain level after the screening period is $\geq$ 2 (0-4, ordinal scale), patients continued to double-blind phase.

Table B.31, Thorne et al., 2008 [133], continued from previous page.

	Double-blind phase: 4 weeks, randomization to CR tramadol vs. placebo. Starting dose: 150 mg/day, maximum dose: 400 mg/day. After completion of first double-blind phase, patients switched to opposite treatment arm for another 4 weeks. Rescue medication: acetaminophen 326-650 mg every 4-6 hours.
Outcome	**Quality of Life:** SF-36, PDI Disease-specific QoL/functionality: WOMAC **Other measurements:** pain intensity (5-point scale, VAS 0-100), pain and sleep questionnaire, effectiveness of treatment (patient, investigator), overall treatment phase preference (patient, investigator), clinical benefit (patients).
Notes	**Funding:** supported by a research grant of Purdue Pharma. Four study authors were employees of Purdue Pharma, Ontario. Patients, who completed study, could continue drug therapy in a six-month open-label extension.

Risk of Bias, Thorne et al., 2008 [133]

Bias	Judgement	Support for judgement
Random sequence	Unclear risk	Not reported.
Allocation concealment	Unclear risk	Not reported.
Blinding of participants and personnel	Low risk	Use of "matching placebo tablets."
Blinding of outcome assessment	Unclear risk	Not sufficiently reported.
Incomplete outcome reporting	High risk	All withdrawals were reported. However only 77 of 100 patients (per-protocol population) were included in QoL analysis. 75 subjects (75%) completed the two treatments.
Selective reporting	Low risk	All outcomes reported
Other bias	Low risk	No washout phase before switching treatment phase. However no carryover effect was found and CR tramadol elimination time is short compared to study duration.

Table B.32 Vinik et al., 2014 [135]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter withdrawal study (enriched enrollment) Tapentadol ER vs. placebo in diabetic peripher neuropathy **Duration:** 12 weeks
Participants	**Patients enrolled:** 459 (open-label period), randomized in double-blind phase: 320; intention-to-treat (ITT; at least one dose of medication in double-blind period) population: 318. **Pain diagnosis:** diabetic peripheral neuropathy (DPN). **Inclusion criteria:** $\geq$ 18 years of age, diabetes type 1 or 2, chronic DPN for $\geq$ 6 months and pain at screening. Diabetic therapy for $\geq$ 3 months (diet, oral hypoglycemic or insulin therapy), use of analgetics for $\geq$ 3 months (in case of opioids: maximum equivalent dose of morphine: 160 mg/day). **Exclusion criteria:** history of alcohol or drug abuse, condition which could interfere with pain assessment (e.g. fibromyalgia, rheumatoid arthritis, ankylosing spondylitis), a significant pulmonary, gastrointestinal, endocrine or psychiatric disease interfering with study assessment, moderate to severe hepatic impairment, severe renal impairment, seizure disorder or epilepsy, traumatic brain injury, stroke or TIA. Brain neoplasm, malignancy within past 2 years, extensive diabetic foot ulcers or amputation, charcot disease.
Interventions	**Screening/washout phase:** 21 days. 13 days screening phase followed by a 5-day washout period, with discontinuing of all pain analgesics. The last 3 days, pain intensity was evaluated. If patients had a average pain intensity score of $\geq$ 5 on NRS (0-10) they continued to open-label titration phase. **Open-label phase:** 3 weeks, titration to optimal dose of tapentadol, first 3 days: starting dose: 50 mg b.i.d., minimum dose: 100 mg b.i.d., maximum dose: 500 mg/day (250 mg b.i.d.). Additional drugs: acetaminophen, maximum dose: 2000 mg/day. Patients who tolerated tapentadol well and had $\geq$ 1 point improvement in pain intensity on NRS in the last 3 days compared to pretitration evaluation period, continued to double-blind period.

Table B.32, Vinik et al., 2014 [135] , continued from previous page.

	Double-blind phase: 2 weeks, randomization to tapentadol vs. placebo. Tapentadol group: continue intake of the optimal dose from titration period. Placebo group: downtitration to 100 mg tapentadol b.i.d. for 3 days, then placebo. Supplemental/rescue analgesia: tapentadol 25 mg (day 1-4: 2x/day, from day 5: 1x/day). Use of neuroleptics, SNRI, anticonvulsants, antiparkinsonian drugs were prohibited during whole study.
Outcome	**Quality of Life:** SF-36, brief pain inventory-short form (BPI-SF), EQ-5D. **Other measurements:** pain intensity (NRS, 0-10), proportions of patients with $\geq$ 30 or $\geq$ 50% improvement in pain intensity, patients global impression of change (PGIC), subscales of neuropathic pain symptom inventory (NPSI), clinical opioid withdrawal scale (COWS).
Notes	**Funding:** the study was supported and funded by Janssen Research and Grünenthal GmbH. Five study authors are employees of Janssen Research, one of Grünenthal GmbH. In this study enriched enrollment is used. So only patients, who tolerated well tapentadol and had improvement in pain intensity score, continued to double-blind period (withdrawal study). For BPI score the exact values for change from start of open-label phase to end of double-blind phase are reported. In other QoL-measurements (EQ-5D, SF-36) the change from starting point of double-blind period to end of double-blind period was analyzed. LOCF method is used for imputing missing values of primary outcome (pain intensity). Study is registered as NCT01041859 (ClinicalTrials.gov).

Risk of Bias, Vinik et al., 2014 [135]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"Patients were randomized to treatment based on a computer-generated schedule using an interactive voice response system."
Allocation concealment	Low risk	Use of interactive voice response system.
Blinding of participants and personnel	Low risk	"Tapentadol ER and placebo were identical in appearance and packaging."
Blinding of outcome assessment	Unclear risk	Not sufficiently reported, no statement regarding blinding of investigators.

Vinik et al., 2014 [135] , continued from previous page

Bias	Judgement	Support for judgement
Incomplete outcome reporting	High risk	Withdrawals evenly distributed throughout double-blind groups: placebo-group: 30% (45/152); tapentadol ER-group: 28% (46/166). But the efficacy analysis was performed only on 277 patients (SF-36) or on 284 patients (BPI) of 320 patients in the double-blind phase. For EQ-5D score the number of subjects is not reported.
Selective reporting	Low risk	All outcomes are reported.
Other bias	High risk	Enriched design, 459 patients were enrolled in open-label phase, but only 320 proceed to double-blind phase.

Table B.33 Watson et al., 2003 [136]

Study characteristics	
Methods	**Type:** RCT, crossover, active-placebo. Controlled-released Oxycodone vs. Active Placebo for Painful Diabetic Neuropathy **Duration:** each arm 4 weeks
Participants	**Patients randomized:** 45, safety population ($\geq$ 1 dose of study medication): 43. Intention-to-treat (ITT; completed $\geq$ 1 assessment in phase I) population: 42, efficacy analysis (completed $\geq$ 1 week of treatment and evaluation in each phase) population: 36. **Pain diagnosis:** diabetic neuropathy **Inclusion criteria:** adult patients, painful symmetrical distal sensor neuropathy: moderate pain ($\geq$ 2 on 5-point categorical scale), pain duration at least 3 months, one or more symptoms of diabetic neuropathy (paresthesie, dysesthesia, hyperesthesia, hyperalgesia, allodynia), reduced sensation, strength, tendon reflexes. Diabetes mellitus had to be in stable glycemic control. **Exclusion criteria:** intolerance to oxycodone, history of drug or alcohol abuse, significant pain of alternate etiology.
Interventions	**Screening phase:** 2-7 days, discontinuation of all opioid analgesics.

Table B.33, Watson et al., 2003 [136] , continued from previous page.

	Double-blind phase: 4 weeks, randomization to oxycodone CR 10 mg tablets b.i.d. vs. benztropine (active placebo) 0.25, 0.5, 0.75 or 1 mg tablets b.i.d.. Starting dose: oxycodone/placebo: 10 mg b.i.d./0.25 mg b.i.d., maximum dose: oxycodone/placebo: 40 mg b.i.d./1 mg b.i.d.. After 4 weeks or earlier if patients had inadequate pain relief with highest tolerated medication dose they crossed-over to the alternate therapy (phase I to phase II). No washout-period was in between the different phases. Intake of antidepressants, anticonvulsants or non-opioid analgesics could be continued at stable doses. Rescue pain medication: acetaminophen 325-650 mg every 4-6 hours.
Outcome	**Quality of Life:** PDI, SF-36
	Other measurements: pain intensity (VAS: 100 mm and 5-point categorical scale: 0-4), pain relief (6-point categorical scale: 0-5), pain and sleep questionnaire, patients and investigators evaluation of effectivity of pain medication and their treatment preference, patients rating of satisfaction with pain relief, blinding-test for patients and investigators.
Notes	**Funding:** supported by Purdue Pharma.
	Patients who received benefit from therapy could continue treatment with CR Oxycodone in an open-label manner for up to 12 months.

Risk of Bias, Watson et al., 2003 [136]

Bias	Judgement	Support for judgement
Random sequence	Low risk	"Computer-generated random code in blocks of four"
Allocation concealment	Unclear risk	"Patients were given consecutive numbers after screening to ensure balanced treatment assignment at both centres." Not sufficiently reported. Blinding-test shows that 88% of patients and investigators correctly identified treatment.
Blinding of participants and personnel	Unclear risk	Not sufficiently reported.
Blinding of outcome assessment	Unclear risk	Not reported.

Watson et al., 2003 [136] , continued from previous page

Bias	Judgement	Support for judgement
Incomplete outcome reporting	High risk	All reasons for withdrawals are described. 21 of 45 randomized patients (46.7%) withdrew prematurely from study. Withdrawals were evenly distributed throughout study groups. Efficacy analysis population (n=36) is used for efficacy analysis, but "ITT population results were similar to the evaluable population for all other efficacy measurements."
Selective reporting	Low risk	All outcomes are reported.
Other bias	Low risk	No washout-period was in between two treatment phases. However elimination time of CR oxycodone is short compared to study duration.

Table B.34 Webster et al., 2006 [137]

Study characteristics	
Methods	**Type:** RCT, parallel-group, multicenter. Oxycodone vs. Oxycodone/Ultralow-dose Naltrexone (Oxytrex) vs. Placebo in Chronic Low Back Pain. **Duration:** 13-18 (12 weeks maintenance).
Participants	**Patients randomized:** 719, intention-to-treat (intake of $\geq$ 1 study medication and $\geq$ post-baseline pain intensity value): 709. **Pain diagnosis:** chronic low back pain. **Inclusion criteria:** 18-70 years of age, low back pain for $\geq$ 3 months with requirement of analgesics. Patients had to be opioid-free for $\geq$ 72 h prior to screening. **Exclusion criteria:** secondary low back pain due to primary disease (i. e. fibromyalgia, fracture, autoimmune disease), positive urine drug screen, history of drug abuse, pregnancy, hypersensitivity to study medication, severe hepatic, renal or pulmonary impairment, unstable cardiac disease, unstable malignancy, corticosteroid therapy. Intraspinal analgesic infusion or spinal cord stimulator within 1 month, major surgery within 3 months and open or percutaneous lumbosacral intervention within 4 months prior to study entry.

Table B.34, Webster et al., 2006 [137] , continued from previous page.

Interventions	**Screening phase:** 4-10 days, washout of all analgesics, except acetaminophen. If patients had a pain intensity score of $\geq$ 5 at screening visit, during last three days of washout and at conclusion of washout period (baseline value), they could continue to randomization. **Double-blind phase:** randomization to oxycodone q.i.d. vs. oxytrex q.i.d. vs. oxytrex b.i.d. vs. placebo in a 2:2:2:1 ratio. 1. Titration phase: 1-6 weeks, starting dose oxycodone: 2.5 mg q.i.d. (10 mg/day), maximum dose: 20 mg q.i.d. (80 mg/day). Patients were titrated until their pain intensity was $\leq$ 2, side effects could be tolerated or to maximum dose. Maintenance phase: 12 weeks, patients remained on their final dose. No other analgesics were allowed.
Outcome	**Quality of Life:** SF-12 **Disease-specific QoL/functionality:** Oswestry disability index (ODI) **Other measurements:** pain intensity (NRS, 0-10), global assessment of study drug, assessment of quality of analgesia, rating of adverse events, short opiate withdrawal scale (SOWS).
Notes	**Funding:** not reported. One study author is afiliated to Lifetree Clinical Research, Utah, five study authors were employees of Pain Therapeutics, California. LOCF method is used to impute missing pain intensity value.

Risk of Bias, Webster et al., 2006 [137]

Bias	Judgement	Support for judgement
Random sequence	Low risk	Investigators describe the use of stratification ("Randomization was stratified by gender.").
Allocation concealment	Low risk	"[...] patients were randomized via a central call-in system [...]."
Blinding of participants and personnel	Low risk	"All study medications were identical in appearance [...]"
Blinding of outcome assessment	Low risk	"[...] Patients, site personnel, and study monitors were blinded to treatment assignments." Patients assessed their outcome via completing standardized questionnaires.
Incomplete outcome reporting	High risk	Reasons for withdrawals were reported. 391 (54%) subjects did not complete the study. LOCF method is used for imputing missing pain intensity values. It is not reported, if missing values for QoL were also imputed.

Webster et al., 2006 [137] , continued from previous page

Bias	Judgement	Support for judgement
Selective reporting	High risk	QoL outcome is not sufficiently reported.
Other bias	Low risk	No further signs of bias.

Appendix C

Overview of excluded studies

Table C.1 Characteristics of excluded studies

Study name	Reasons for exclusion
Ahmedzai et al., 2012 [139]	Comparison of oxycodone/naloxone vs. oxycodone PR. Not placebo-controlled.
Allan et al., 2001 [140]	Comparison of transdermal fentanyl vs. oral morphine. Not placebo-controlled.
Allan et al., 2005 [141]	Comparison of Morphine vs. Fentanyl. Not placebo-controlled.
Am Ionescu et al., 2016 [142]	No QoL assessment.
Amato et al., 2017 [143]	No RCT. Fixed Oxycodone/Naloxone combination.
Babul et al., 2004 [144]	Only Osteoarthritis-specific functionality (WOMAC) is assessed.
Banerjee et al., 2016 [145]	No placebo-controlled RCT.
Binsfeld et al., 2010 [146]	Comparison of OROS Hydromorphone vs. ER Oxycodone. Not placebo-controlled.
Böhme 2002 [147]	No adequate measurement of quality of life. Only duration of sleep "uninterrupted by pain" is measured.
Boureau, Saudubray et al., 1992 [148]	Comparison of CR Morphine suspension vs. CR Morphine tablets.
Brema et al., 1996 [149]	Comparison of Tramadol vs. Buprenorphine. Study not blinded and not placebo-controlled.
Ceniti et al., 2016 [150]	No placebo-controlled RCT. Fixed Oxycodone/Naloxone combination.
Chindalore et al., 2005 [151]	Results of SF-12 were not reported for Oxycodone vs. Placebo.

Table C.1, continued from previous page

Study name	Reasons for exclusion
Chu et al., 2012 [152]	Only disease-specific quality of life is assessed (Roland Morris Disability Index).
Cowan et al., 2005 [153]	Study is about opioid cessation/abstinence in patients with long-term opioid use. Strong methodical difference in contrast to other included studies.
de Hoogd et al., 2018 [154]	No placebo-controlled RCT.
Dellemijn et al., 1998 [155]	Open-label, uncontrolled trial.
Derry et al., 2018 [Derry et al.]	Referring to Arai et al., 2015. No RCT.
Dupoiron et al., 2017 [157]	Not placebo-controlled.
Etropolski, et al., 2014 [158]	Post-hoc safety analysis of studies yet included.
EUCTR2007-001313-42-DE, 2007 [159]	No placebo-controlled RCT.
EUCTR2009-010423-58-DE, 2009 [160]	No placebo-controlled RCT.
EUCTR2009-010425-39-DE, 2009 [161]	No placebo-controlled RCT.
EUCTR2009-010427-12-PL, 2009 [162]	No placebo-controlled RCT.
EUCTR2009-010428-25-NL, 2009 [163]	No placebo-controlled RCT.
EUCTR2010-019998-14-DE, 2010 [164]	No placebo-controlled RCT.
EUCTR2012-002943-11-AT, 2013 [165]	No placebo-controlled RCT.
EUCTR2014-004718-27-PL, 2016 [166]	No placebo-controlled RCT.
EUCTR2014-004851-30-NL, 2016 [167]	No placebo-controlled RCT. Pediatric patients.
EUCTR2014-004897-40-DE, 2017 [168]	No placebo-controlled RCT. Pediatric patients.
Ferreira et al., 2020 [169]	Inclusion condition is chronic breathlessness, not chronic pain.
Ferrell et al., 1989 [170]	Comparison of CR Morphine vs. short-acting analgesia [opioids].
Franco et al., 2002 [171]	No placebo-controlled RCT.
Frank et al., 2008 [172]	Comparison of Morphine vs. Nabilone. Not placebo-controlled.
Fredheim et al., 2006 [173]	Uncontrolled trial. Switching from morphine to methadone.

Table C.1, continued from previous page

Study name	Reasons for exclusion
Gammaitoni et al., 2003 [174]	Open-label, uncontrolled trial.
Gatti et al., 2010 [175]	Open-label, uncontrolled trial.
Griffin et al., 2015 [176]	No interventional study/RCT, rather cross-sectional design.
Grond et al., 1997 [177]	Open-label, uncontrolled trial.
Hale et al., 2007 [178]	Comparison of OROS Hydromorphone vs. ER Oxycodone. Not placebo-controlled.
Hanna, Thippawong et al., 2008 [179]	Comparison of OROS Hydromorphone vs. Morphine. Not placebo-controlled.
Herbst et al., 1992 [180]	Uncontrolled, open-label study of fentanyl.
Hesselbarth et al., 2014 [181]	No RCT, not placebo-controlled. Parallel-group, obervational study.
James et al., 2010 [182]	Comparison of transdermal Buprenorphine vs. sublingual Buprenorphine. Not placebo-controlled.
Jamison et al., 1998 [183]	Open-label study, no double-blind treatment. No adequate results of QoL assessment.
Jensen et al., 2006 [184]	No RCT. Observational design.
Julius et al., 2017 [185]	No placebo-controlled RCT
Kamboj et al., 2014 [186]	No QoL-assessment
Kaplan et al., 1996 [187]	Open-label, uncontrolled trial.
Karlsson et al., 2009 [188]	Comparison of transdermal buprenorphine vs. PR Tramadol. Not placebo-controlled.
Krocker et al., 2008 [189]	Pseudo-randomization. Not double-blind.
Lange et al., 2017 [191]	Post-hoc analysis of studies included.
Lange et al., 2010 [190]	Post-hoc analysis of studies included.
Leppert et al., 2019 [192]	No placebo-controlled RCT.
Liguori et al., 2010 [193]	Open-label, uncontrolled trial.
Likar et al., 2007 [194]	Comparison of 4-day vs. 3-day application of transdermal Buprenorphine. QoL not adequately reported.
Milligan et al., 2001 [196]	Open-label, uncontrolled trial.
Miller et a., 2013 [195]	Unclear results, no data is presented. Most probably post-hoc analysis of Steiner 2011.
Müller et al., 2011 [197]	Open-label, uncontrolled trial.
Muriel et al., 2005 [198]	Open-label, uncontrolled trial.
Muriel et al., 2007 [199]	Uncontrolled postautorization study.
Mystakidou et al., 2003 [201]	Open-label, uncontrolled trial.

Table C.1, continued from previous page

Study name	Reasons for exclusion
Mystakidou et al., 2004 [200]	Open-label, uncontrolled trial.
NCT00399048, 2006 [202]	No placebo-controlled RCT.
NCT00495404, 2007 [203]	No placebo-controlled RCT. Behavioral therapy.
NCT00547885, 2007 [204]	No placebo-controlled RCT.
NCT00771758, 2008 [205]	Acute pain, no chronic pain assessment.
NCT01352741, 2011 [206]	No placebo-controlled RCT.
NCT01559454, 2012 [207]	No placebo-controlled RCT.
NCT01728246, 2012 [208]	No placebo-controlled RCT.
NCT01811186, 2013 [209]	No placebo-controlled RCT.
NCT01875848, 2013 [210]	No placebo-controlled RCT.
NCT02464813, 2015 [211]	No placebo-controlled RCT.
NCT03967327, 2019 [212]	No placebo-controlled RCT.
NCT04013529, 2019 [213]	No placebo-controlled RCT.
Nicholson, Ross, Sasaki et al., 2006 [214]	Comparison of ER Morphine vs. CR Oxycodone. Not placebo-controlled.
Nicholson, Ross, Weil et al., 2006 [215]	Open-label, uncontrolled trial.
Niemann et al., 2000 [216]	Open-label study. Comparison of transdermal Fentanyl vs. SR Morphine. Not placebo-controlled.
Niesters et al., 2014 [217]	No quality of life measurement.
Norrlid et al., 2015 [218]	No RCT.
Oliva et al., 2000 [219]	No placebo-controlled RCT.
Pace et al., 2007 [220]	Comparison of transdermal Buprenorphine vs. SR Morphine. Not placebo-controlled.
Parr et al., 1989 [221]	Opioid/Paracetamol combination is tested against diclofenac retard. No placebo control.
Pavelka et al., 2004 [222]	Open-label, uncontrolled trial.
Pedersen et al., 2014 [223]	Comparison of long-acting dihydrocodeine vs. short-acting dihydrocodeine.
Raffaeli et al., 2014 [224]	Open-label, uncontrolled trial.
Rauck et al., 2007 [225]	Comparison of ER Morphine vs. CR Oxycodone. Not placebo-controlled.
Rauck et al., 2009 [226]	No quality of life measurement.
Reimer et al., 2017 [227]	Retrospective analysis of open-label study.
Richarz et al., 2013 [228]	Open-label extension of Binsfeld 2010.
Roberto et al., 2016 [229]	No RCT.

Table C.1, continued from previous page

Study name	Reasons for exclusion
Rowbotham et al., 2003 [230]	Comparison between low-dose and high-dose opioid. No real placebo-control.
Sindrup et al., 1999 [231]	No quality of life assessment.
Soin et al., 2008 [232]	Retrospective study.
Sorge et al., 1997 [233]	No placebo-controlled RCT.
Steigerwald et al., 2012 [234]	Open-label, uncontrolled trial.
Stepanovic et al., 2011 [235]	Case series.
Tassain et al., 2003 [236]	Open-label, uncontrolled trial.
Taylor et al., 2007 [237]	No RCT.
Tessaro et al., 2010 [238]	Open-label, uncontrolled trial.
Überall et al., 2015 [239]	No placebo-controlled RCT.
van Seventer et al., 2003 [240]	No placebo-controlled RCT.
Vorsanger et al., 2007 [241]	Post-hoc analysis of patients $>$ 65 years of age with data from Gana 2007.
Wallace et al., 2007 [242]	Open-label, uncontrolled trial.
Wallace et al., 2010 [243]	Open-label, uncontrolled trial.
Watson, Babul et al., 1998 [244]	No adequate assessment of quality of life.
Weil et al., 2009 [245]	Open-label study. Comparison of different dosing regimen of ER Morphine. Not placebo-controlled.
Wong et al., 1997 [246]	Comparative study, morphine vs. fentanyl. Not placebo-controlled.
Yarlas et al., 2013 [247]	Open-label extension. No placebo-controlled RCT.
Yarlas et al., 2016 [248]	Subgroup analysis of Steiner et al., 2011 for depressed patients.
Zimmermann et al., 2005 [249]	Open-label, uncontrolled trial.
Zin et al., 2010 [250]	A combination of oxycodone with pregabalin is tested against pregabalin with placebo. Because of that it is not possible to determine the pure effect of oxycodone alone.

Danksagung

Zuallererst möchte ich mich bei Herrn Prof. Leopold Eberhart für die freundliche Überlassung des Promotionsthemas, die immer schnelle und unkomplizierte Hilfestellung, sowie das fortwährende Vertrauen in das Gelingen der Promotion bedanken.

Ich bedanke mich bei meinen Freund*innen für die schönen Stunden neben Promotion und Studium. Besonders möchte ich mich bei AleX bedanken für Unterstützung und tiefe Verbundenheit.

Meinen Eltern möchte ich danken für das was Sie mir im und fürs Leben mitgegeben haben.