Systematic review and meta-analysis on non-opioid analgesics in palliative medicine

Robert H. Schüchen[1,2*†], Martin Mücke[1,3,4*†], Milka Marinova[5], Dmitrij Kravchenko[6], Winfried Häuser[7], Lukas Radbruch[1,8†] & Rupert Conrad[6†]

[1]Department of Palliative Medicine, University Hospital of Bonn, Bonn, Germany, [2]Department of Internal Medicine II, DRK-Hospital Neuwied, Neuwied, Germany, [3]Center for Rare Diseases Bonn (ZSEB), University Hospital of Bonn, Bonn, Germany, [4]Department of General Practice and Family Medicine, University Hospital of Bonn, Bonn, Germany, [5]Department of Radiology, University Hospital of Bonn, Bonn, Germany, [6]Department of Psychosomatic Medicine and Psychotherapy, University Hospital of Bonn, Bonn, Germany, [7]Department of Psychosomatic Medicine and Psychotherapy, Technische Universität München, Munich, Germany, [8]Centre for Palliative Care, Malteser Hospital Bonn/Rhein-Sieg, Bonn, Germany

Abstract

Non-opioid analgesics are widely used for pain relief in palliative medicine. However, there is a lack of evidence-based recommendations addressing the efficacy, tolerability, and safety of non-opioids in this field. A comprehensive systematic review and meta-analysis on current evidence can provide a basis for sound recommendations in clinical practice. A database search for controlled trials on the use of non-opioids in adult palliative patients was performed in Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO, and EMBASE from inception to 18 February 2018. Endpoints were pain intensity, opioid-sparing effects, safety, and quality of life. Studies with similar patients, interventions, and outcomes were included in the meta-analyses. Our systematic search was able to only identify studies dealing with cancer pain. Of 5991 retrieved studies, 43 could be included (n = 2925 patients). There was no convincing evidence for satisfactory pain relief by acetaminophen alone or in combination with strong opioids. We found substantial evidence of moderate quality for a satisfactory pain relief in cancer by non-steroidal anti-inflammatory drugs (NSAIDs), flupirtine, and dipyrone compared with placebo or other analgesics. There was no evidence for a superiority of one specific non-opioid. There was moderate quality of evidence for a similar pain reduction by NSAIDs in the usual dosage range compared with up to 15 mg of morphine or opioids of equianalgesic potency. The combination of NSAID and step III opioids showed a beneficial effect, without a decreased tolerability. There is scarce evidence concerning the combination of NSAIDs with weak opioids. There are no randomized-controlled studies on the use of non-opioids in a wide range of end-stage diseases except for cancer. Non-steroidal anti-inflammatory drugs, flupirtine, and dipyrone can be recommended for the treatment of cancer pain either alone or in combination with strong opioids. The use of acetaminophen in the palliative setting cannot be recommended. Studies are not available for long-term use. There is a lack of evidence regarding pain treatment by non-opioids in specific cancer entities.

Keywords   NSAID; Non-opioid analgesics; Palliation; Cancer; Pain relief; Meta-analysis; Systematic review

Introduction

According to the World Health Organization (WHO) Global Atlas of Palliative Care, an estimated global number of over 19 million adults are in need of palliative care at the end of life.[1]

This estimation is based on the prevalence of pain as one of the most common and distressing symptoms in palliative care patients. The great majority of patients in need of palliative care suffered from cardiovascular diseases and cancer,[1–3] followed by chronic respiratory diseases, HIV, and diabetes. Pain can have a devastating impact on a patient's quality of life. Adequate assessment and management of pain is therefore a major challenge in palliative care. A vast amount of studies are aimed at optimizing opioid-based analgesic treatment by

analysing appropriate drug and dose selection as well as the treatment of opioid side effects.[4] Comparatively little research has focused on the effectiveness of non-opioid analgesics in this context. Systematic reviews from 1994,[5] 2005,[6] and 2017[7,8] analysed the evidence of non-opioid analgesics in cancer pain. However, the previous reviews did not analyse quality of life nor did they specifically focus on the aspect of palliative care treatment, which has a major impact on search strategy and inclusion of studies. Some links between pain intensity and health-related quality of life have been defined, which demonstrate that the stronger the intensity and the higher the frequency of pain, the lower the quality of life.[9–12] In a study by Løyland *et al.*, ~30% of health-related quality of life could be explained by chronic pain.[13] Even though non-opioid analgesics are thought to be helpful in the management of palliative patients, specifically in patients suffering from cancer pain,[14] their use is hampered by gastrointestinal, cardiovascular, and renal risks. An evidence-based assessment of the effectiveness of non-opioid analgesics is necessary in order to carefully weigh the benefits and risks in severely compromised palliative patients.[15,16] Our systematic review and meta-analysis aims at providing a clearer picture of the usefulness of non-opioid analgesics in these patients. On the basis of a comprehensive search strategy, we analysed the analgesic effectiveness, tolerability, safety, and the impact of quality of life of non-opioids in palliative medicine.

Materials and methods

Criteria for considering studies in this review

This review included studies comparing analgesic treatment with non-opioid analgesics [e.g. non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and dipyrone] at any dose, using any route of administration in palliative and supportive care settings, to other non-opioids, placebos, opioids, or combinations of non-opioids and opioids. Studies should include adult participants, diagnosed with any advanced or end-stage medical disease (e.g. cancer, HIV, heart disease, liver disease, and lung disease). We did not include patients with pain related directly to antineoplastic treatment (e.g. chemotherapy, radiotherapy, and surgical intervention). We included studies if they were randomized-controlled trials (RCTs) and double blinded with a parallel or crossover design. We excluded studies that investigated drugs completely withdrawn from the market as well as studies that were not published in English or German. *Table 1* presents an overview of inclusion criteria.

Types of outcome measures

Outcome measures were 'pain intensity'; 'pain intensity difference'; 'reduction of dosage'; 'withdrawal due to insufficient analgesia'; 'withdrawal due to adverse events' (tolerability); 'other specific adverse events' (safety), particularly somnolence, dizziness, and gastrointestinal symptoms; and 'health-related quality of life' as measured by different scales and questionnaires.

Search methods for identification of studies

The following databases were searched after developing an extensive search strategy without language restrictions from inception to 18 February 2018: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO, and EMBASE (Supporting Information, *Appendix* S1). We reviewed the bibliographies of any identified randomized trials and review articles to identify additional published or unpublished data.

Data collection

Selection of studies
We determined eligibility by reading the abstract of each study identified by our search. We eliminated studies that did not satisfy our inclusion criteria and acquired full copies of the remaining studies; decisions were made by two review authors (R. S. and M. M.). We did not make the studies anonymous in any way before assessment.

Data extraction and management
Two review authors (R. S. and M. M.) extracted data independently using a standard form. Information about the medical condition, study setting, inclusion and exclusion criteria, number and demographic and clinical characteristics of participants treated, drug and dosing regimen, co-therapies, study design (placebo or active control), study duration, analgesic outcome measures and results, and withdrawals and adverse events was extracted.

Table 1 Inclusion criteria

Study design	Participants
Randomized-controlled trials	Adult participants, >18 years
Double blinded	In palliative and supportive care settings
Non-opioid analgesics at any dose, using any application route (oral, intravenous, intramuscular, and as suppository)	Diagnosed with any advanced or end-stage medical disease (e.g. cancer, HIV, heart disease, liver disease, and lung disease)

Assessment of risk of bias and study quality

Two authors (R. S. and M. M.) independently assessed the risk of bias via the Cochrane risk of bias tool for each study using the aspects of bias recommended by the Cochrane Collaboration[17] with any disagreements resolved by a thorough evaluation involving other review authors (L. R., R. C., W. H., and D. K.). The 'Risk of bias' graph (Supporting Information, *Appendix* S2) presents the authors' judgments about seven relevant risk of bias categories shown as percentages across all included studies and the 'Risk of bias' summary (Supporting Information, *Appendix* S3) represents the review authors' judgment about each risk of bias item for each included study. Assessment of study quality was based on the risk of bias sum score across these seven categories (0–2 = high-quality studies, 3–5 = moderate-quality studies, and 6–7 = low-quality studies).

We assessed the following risk of bias for each study:

(i) Random sequence generation (checking for possible selection bias)

We assessed the method used to generate the allocation sequence as follows: low risk of bias (any accurately random process, e.g. random number table; computer random number generator) and unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies that were not randomized.

(ii) Allocation concealment (checking for possible selection bias)

The method that is used to conceal allocation was assessed as to whether intervention allocation could have been foreseen in advance of, or during enrolment, or changed after assignment. It was assessed as follows: low risk of bias [e.g. central allocation (phone, web, and pharmacy); sequentially numbered, sealed, opaque envelopes; sequentially numbered, identical drug container], unclear risk of bias (method not clearly stated), and high risk of bias where allocation was not concealed.

(iii) Blinding of participants and personnel (checking for possible performance and detection bias)

We assessed the methods used to blind study participants and personal from the knowledge of which intervention a participant received. We assessed the methods as follows: low risk of bias (study states that it was blinded and method used to achieve blinding is described, e.g. identical tablets; matched in appearance and smell; double-dummy technique) and unclear risk of bias (study states that it was blinded but without adequate description of how it was achieved). We excluded studies that were not blinded.

(iv) Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data)

We assessed the methods that are used to deal with incomplete data as follows: low risk of bias ($<$10% withdrawals and/or 'baseline observation carried forward' analysis used), unclear risk of bias ('last observation carried forward' analysis used), and high risk of bias ('completer' analysis used).

(v) Selective outcome reporting (checking for possible reporting bias)

We assessed if all outcomes of the study protocol were reported in the publications of the study. There is low risk of reporting bias if all the study's pre-specified outcomes that are of interest in the review have been reported in the pre-specified way. There is a high risk of bias if not all the study's pre-specified primary outcomes of interest in the review have been reported so that they cannot be entered in a meta-analysis. There is an unclear risk of bias if results were only commented but not clearly represented as tables or graphs.

(vi) Group similarity at baseline (selection bias)

Similarity of the study groups at baseline was assessed for the most important prognostic clinical and demographic indicators. There is low risk of bias if groups are similar at baseline for demographic factors, value of main outcome measure(s), baseline symptoms relevant to main outcomes, and important prognostic factors. There is high risk of bias if groups are not similar at baseline for demographic factors, value of main outcome measure(s), and important prognostic factors. There is an unclear risk of bias if clinical or demographic indicators were missing and if the study was done in crossover design and indicators were missing or similarity at baseline was deficient.

(vii) Study design bias

We assessed the study design for bias. Parallel trials and crossover trials with washout period were rated with low risk of bias. Crossover studies without washout period but with duration over at least 5 days per treatment or crossover single-dose trials with a time lag of $\geq$24 h were rated also with low risk of bias. Crossover trials without washout period and shorter time lag were rated with high risk of bias. Crossover trials without statement regarding washout period were rated with unclear risk of bias (a washout period in treatment of pain is hardly possible or ethical).

Statistical analysis

Data collection and analysis was done with the Review Manager provided by the Cochrane Collaboration.[18]

We used statistical significance and effect size (Cohen's *d*) for the evaluation of the studies. Because the effect size was rarely presented, it was calculated whenever possible from the mean, standard deviation, and sample size.

The number of 'withdrawals due to inadequate pain relief', 'withdrawals due to adverse events', and 'number of patients with adverse events' (if sufficiently available) was analysed by meta-analyses. The integration of dichotomous outcome data from crossover trials was done by pooling both periods.

We used dichotomous data to calculate risk differences (RDs) with 95% confidence intervals (CIs) using a fixed-effect model. The number needed to treat was calculated as the reciprocal of the absolute RD.[19] For unwanted effects, the number needed to harm was calculated in the same manner.

We used the following terms to describe the occurrence of adverse events. When significantly fewer adverse events occurred in the treatment condition, we used the term 'number needed to treat to prevent one event'. When the treatment condition was associated with significantly more adverse events, we used the term 'number needed to treat for an additional harmful event'.

Quality of evidence and strength of recommendation were assessed on the basis of Grading of Recommendations Assessment, Development, and Evaluation methodology. Treatment comparisons in the summary of findings table are given in one of four Grading of Recommendations Assessment, Development, and Evaluation scores reflecting the quality of the evidence—high-quality, moderate-quality, low-quality, or very-low-quality evidence.

Results

We screened 5991 publications, of which 43 met the inclusion criteria after full-text review (*Figure* 1).[20–62] We excluded 30 studies (Supporting Information, *Appendix* S4). Our search strategy identified no studies on any other palliative disease other than cancer.

A total of 2925 patients were included, of whom 2557 completed their trials. Of the included studies, 22 were implemented using a parallel design, while 21 applied a crossover design.

Only two studies[34,41] focused on a specific primary tumour (breast cancer). The remaining studies included a variety of primary tumours (e.g. lung, breast, colorectal region, prostate, liver, blood, or skin). Pain due to bone metastases was an inclusion criterion in six studies.[32–34,44,45,50] Approximately 50% of the studies did not specify the type and location of the pain; the remainder had various origins, for example, visceral, neuropathic, or bone. Pain intensity levels varied from

Figure 1 Flow chart selection process.
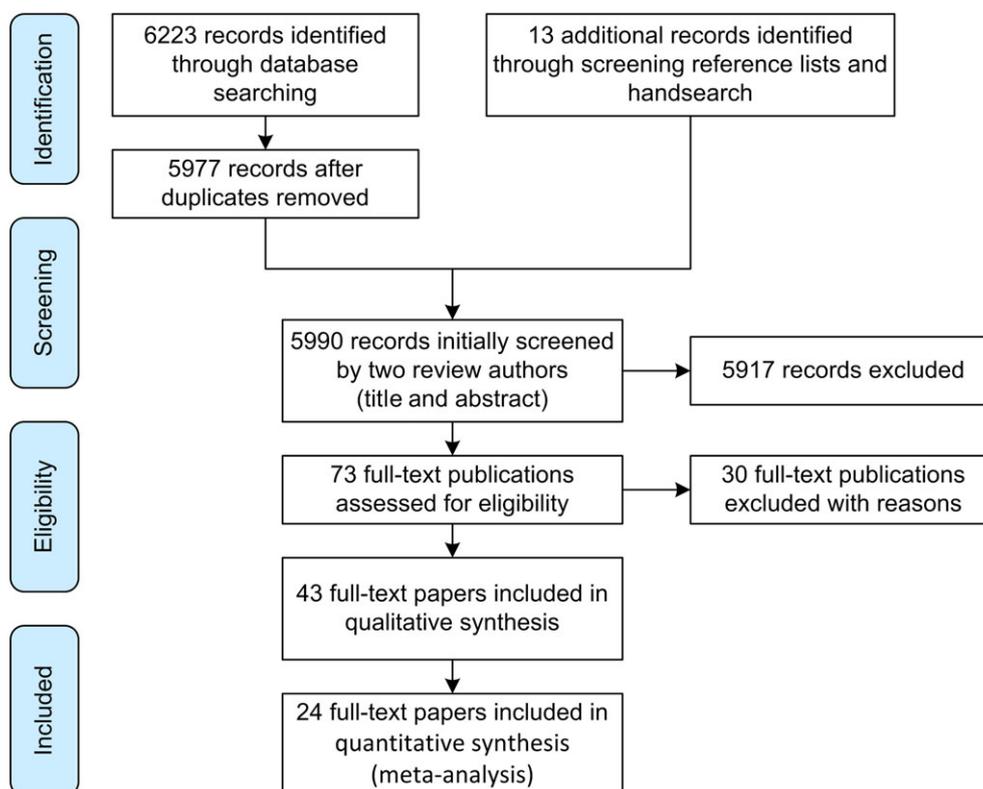
light to very intense and included patients undergoing high potent opioid therapy.

The duration of the studies ranged from single-dose trials (around 25% of the studies) to long-term treatment lasting up to 6 weeks (*Table* 2).[41]

Acetaminophen

In regard to tumour pain, Stambaugh[48] did not find a significant difference in pain reduction when comparing acetaminophen with placebo. Another study comparing various NSAIDs[61] did not perform inferential statistics; both studies showed a good tolerability.

A significant analgesic effect was achieved in two studies when acetaminophen was combined with weak opioids.[23,24] One of these studies,[23] only evaluated the combination preparation making it impossible to evaluate the effect of acetaminophen alone. In the other study,[24] differing doses were used (codeine 100/200/300 mg vs. codeine 60 mg + acetaminophen 600 mg), again making it difficult to draw meaningful conclusions about the single preparation use of acetaminophen.

A further four out of six studies, with a combined patient population of 141, were not able to show a further increase in analgesic effect when 650–1000 mg of acetaminophen (3–5 g/day) was combined with step III opioids.[20,25,30,56] Merely two studies,[48,53] comprising 50 patients, were able to show a positive effect. Stockler[53] reported a difference, albeit with minor significance, in one of two pain scales (verbal numeric scale: $P = 0.03$/visual analogue scale: $P = 0.09$). In another single-dose study,[48] a higher analgesic effect was discovered when acetaminophen was combined with butorphanol, compared with opioid monotherapy.

No differences in side effects were found when acetaminophen was combined with a strong opioid compared with a placebo.[20,25,30,53,56] A direct comparison of acetaminophen alone vs. butorphanol or acetaminophen + butorphanol showed that only the combined preparation delivered significantly superior analgesia compared with placebo.[48]

Dipyrone

Dipyrone is a worldwide commonly used analgesic thought to be particularly effective in post-surgical pain,[63,64] although it has been removed from the market in some countries (e.g. the USA and Great Britain) because of the occurrence of agranulocytosis. The real incidence of this side effect shows an estimated average risk, after 1 week of treatment, of 1.1 cases in 1 million.[65,66]

A monotherapy study[43] with 121 participants showed that both 1 and 2 g dosages of dipyrone (three times a day), over the course of 7 days, could lead to significant pain reduction compared with baseline. Moreover, the analgesic effect of 2 g of dipyrone (three times a day) was equal to 10 mg of morphine (six times a day). A crossover study[27] with 34 participants revealed that the addition of 500 mg of dipyrone

(four times a day) to 10 mg of morphine (six times a day) was superior to the opioid monotherapy ($P < 0.001$). In both studies, there were no dropouts because of insufficient analgesia or side effects. Dipyrone had fewer reported side effects compared with morphine,[43] although the difference was not significant.

Flupirtine

A dose of 100 mg flupirtine p.o. compared with a weak opioid was reviewed in two RCTs.[35,47] In one study,[35] 71 patients were tested in comparison with 50 mg of tramadol over the course of 4 weeks. The results showed a significant reduction in pain, with flupirtine even surpassing the reduction achieved by the opioid, albeit this difference being non-significant.

Another study[47] with 52 participants, comparing flupirtine with pentazocine over the course of 1 week, showed a significant advantage in analgesia ($P < 0.05$). It must be noted, however, that it was allowed to increase the initial dosages of the drugs, flupirtine (2 × 100 mg/day) and pentazocine (2 × 50 mg/day), to 600 mg/day and 300 mg/day, respectively. About 50% of each group took 100 mg of flupirtine three times a day or 50 mg of pentazocine three times a day, and approximately one-third of the patients in each group took the daily maximum dose. In the opioid group, more patients dropped out because of insufficient pain management, but no inferential statistics on this difference were reported. The meta-analysis (*Figure* 2; Supporting Information, *Appendix* S5) showed no significant difference in dropouts between weak opioids and flupirtine.

Flupirtine showed a good tolerability in both studies and even fared slightly, although non-significantly, better compared with weak opioids (*Figures* 3 and 4; Supporting Information, *Appendix* S5, *Table* 1). While side effects like drowsiness, restlessness, and sleep disturbances were more common under opioid therapy, flupirtine users were more likely to report gastrointestinal problems like stomach pain, heartburn, and nausea. Quality of evidence on aforementioned outcomes was moderate (Supporting Information, *Appendix* S5, *Table* 1).

Non-steroidal anti-inflammatory drugs

Monotherapy

Twenty-six studies comprising 2252 subjects with tumour pain tested various NSAIDs vs. placebo or other analgesics.

Diclofenac (p.o. and i.m.) was examined in eight studies[36–38,41,42,54,57,61] at dosages ranging from 50 to 100 mg (100–200 mg/day). All studies were able to show an analgesic effect compared with baseline. Complete statistical data on this outcome were only presented in half of these studies because the primary goal was the comparison with other analgesics.

Table 2 Characteristics of included studies

Study	Design	No.	Drugs compared	Result	Adverse events
			Opioid + acetaminophen		
Axelsson and Borup[20]	MD 7 days, X	42	Morphine + APAP (1000 mg) p.o. / Morphine + placebo	No difference (P = 0.22)	Ø
Chary et al.[24]	MD 4 days, P	24	Codeine (100/200/300 mg) p.o. / Codeine + APAP (60 + 600 mg) p.o.	Pain relief in all treatments; C 300 superior to C 100	More side effects under higher codeine dosage (P = 0.14)
Cubero and del Giglio[25]	MD 7 days, P	50	Methadone + APAP (750 mg) p.o. / Methadone + placebo	No difference (P = 0.57)	No difference
Israel et al.[30]	MD 5 days, X	31	'Strong' opioid + APAP (1000 mg) p.o. / 'Strong' opioid + placebo	No difference (P = 0.6)	No difference
Stambaugh[48]	SD, X	29	Butorphanol + APAP (4/650 mg) p.o. / APAP (650 mg) p.o. / Butorphanol (4 mg) p.o. / Placebo	Sig. pain relief only in B + APAP (P < 0.05); B + APAP superior to APAP (P < 0.05)	Fewer side effects (sedation) with APAP
Stockler et al.[53]	MD 2 days, X	34	'Strong' opioid + APAP (1000 mg) p.o. / 'Strong' opioid + placebo	Higher pain relief with APAP (in one pain scale); (VNS: P = 0.03)/(VAS: P = 0.09)	No difference
Tasmacioglu et al.[56]	MD 1 day, P	43	Morphine (PCA) + APAP (1000 mg) i.v. / Morphine (PCA) + placebo	No difference in pain (P > 0.05) or morphine consumption (P = 0.95)	No difference
Study	Design	No.	Drugs compared	Result	Adverse events
			Dipyrone		
Duarte Souza et al.[27]	MD 2 days, X	34	Morphine + dipyrone (500 mg) p.o. / Morphine + placebo	Higher pain relief with dipyrone (P < 0.001)	No difference
Rodriguez et al.[43]	MD 7 days, P	121	Dipyrone (1000 mg) p.o. / Dipyrone (2000 mg) p.o. / Morphine (10 mg) p.o.	Pain relief (all P < 0.001); higher pain relief with D2g and M than D1g; no difference between D2g and M	Lower rate of side effects with D (not significant)
Study	Design	No.	Drugs compared	Result	Adverse events
			Flupirtine		
Lüben et al.[35]	MD 4 weeks, P	71	Flupirtine (100 mg) p.o. / Tramadol (50 mg) p.o.	Pain relief in both treatments; no difference (P = 0.106)	Fewer side effects with flupirtine
Scheef and Wolf-Gruber[47]	MD 7 days, P	52	Flupirtine (100 mg) p.o. / Pentazocine (50 mg) p.o.	Pain relief in both treatments; flupirtine superior to pentazocine (P < 0.05)	More gastrointestinal side effects with flupirtine; more psychogenic side effects with pentazocine
Study	Design	No.	Drugs compared	Result	Adverse events
			Opioid III + NSAID		
Björkmann et al.[22]	MD 2 days, X	16	Morphine (PCA) + diclofenac (50 mg) supp / Morphine (PCA) + placebo	Decreased morphine consumption (P = 0.01)	None
Ferrer-Brechner and Ganz[29]	MD 1 day, X	30	Methadone (2.5 mg) + ibuprofen (600 mg) p.o. / Methadone (5 mg) + ibuprofen (600 mg) p.o.	Higher pain relief with ibuprofen (P < 0.05)	No difference

Table 2 (continued)

Opioid III + NSAID

Study	Design	No.	Drugs compared	Result	Adverse events
Johnson and Miller[32]	MD 1 day, 3-part-X	26	Methadone (2.5 mg) + placebo p.o. / Methadone (5 mg) + placebo p.o.	No difference (P = 0.29)	No difference
Lomen et al.[34]	MD 3 weeks, X	26	Opioid + CMT (1500 mg) p.o. / Opioid + placebo	No difference	Ø
Stambaugh and Drew[50]	MD 7 days, P	30	'Narcotics' + flurbiprofen (mg ? 'Ansaid') p.o. / 'Narcotics' + placebo	Higher pain relief with ibuprofen (P < 0.05); reduction of narcotis (P < 0.01)	No difference
Weingart et al.[62]	MD 3 days, 2-way-X	14	Oxycodene/APAP (5/325 mg) + ibuprofen (600 mg) p.o. / Oxycodene/APAP (5/325 mg) + placebo p.o. / Various opioids + ibuprofen (400 mg) p.o. / Various opioids + placebo	Higher pain relief ibuprofen	No difference

NSAIDs vs. opioid

Study	Design	No.	Drugs compared	Result	Adverse events
Dellemijn et al.[26]	MD 7 days, X	20	Naproxen (500 mg) p.o. / Slow-release morphine (30 mg) p.o.	Pain relief with both drugs; less rescue medication with naproxen (P < 0.01)	More under morphine (nausea/vomiting) (P < 0.05)
Estapé et al.[28]	MD 7 days, P	40	Ketorolac (10 mg) p.o. / Pentazocine (50 mg) p.o.	No difference between both treatments	More under pentazocine(WD: P < 0.005)nausea and/or vomiting
Jameel et al.[31]	MD max. 3 days, X	51	Ketorolac (30 mg) i.m. / Morphine (10 mg) i.m.	Pain relief in both treatments; no differences (P > 0.05)	More under morphine;nausea/vomiting (P = 0.0001)drowsiness (P = 0.05)WD (P = 0.0006)
Moertel et al.[39]	MD ? days, X	34	Aspirin (650 mg) p.o. / Codeine (60 mg) p.o. / Placebo	Pain relief in active treatments (ASA P < 0.05); no sig. differences	Ø
Staquet and Renaud[52]	SD, P	90	Piroxicam (40 mg) p.o. / Codeine (60 mg) p.o. / Piroxicam + codeine (20/30 mg) p.o.	Pain relief in all treatments; no difference	No difference
Sunshine and Olson[55]	SD, P	123	Ketoprofen (75 mg) p.o. / Ketoprofen (225 mg) p.o. / Morphine (5 mg) i.m. / Morphine (10 mg) i.m.	Pain relief in all treatments; K 225 to M 5 (P < 0.05); average effectiveness of both dosages K superior to M	No difference (nausea, dizziness, and vomiting)
Tonachella et al.[57]	MD 3 days, X	20	Diclofenac (75 mg) i.m. / Pentazocine (30 mg) i.m.	Pain relief in both treatments (P < 0.01); higher pain relief with D (P = 0.047)	Side effects only under pentazocine

Various NSAIDs

Study	Design	No.	Drugs compared	Result	Adverse events
Bergmann et al.[21]	SD, X	43	Naproxen (500 mg) p.o. / Placebo	Higher pain relief with naproxen (P = 0.001)	None
Levick et al.[33]	MD 3 days, P	143	Naproxen (550 mg) p.o. / Naproxen (275 mg) p.o. (initial all 550 mg)	Higher pain relief with 550 mg (for 'responders' P = 0.05)	No difference; mild, primarily gastrointestinal
Minotti et al.[37]	SD, P	180	Ketorolac (10 mg) i.m. / Ketorolac (30 mg) i.m.	Pain relief in all treatments; no difference	No difference (minor side effects)

Table 2 (continued)

Study	Design	No.	Various NSAIDs		
			Drugs compared	Result	Adverse events
Mohammadinejad et al.[41]	MD 6 weeks, P	56	Diclofenac (75 mg) i.m. Celecoxib 200 mg b.i.d. Diclofenac 50 mg b.i.d.	Pain relief in both treatments; no difference	Mainly abdominal symptoms/gastric discomfort
Pannuti et al.[42]	MD 7 days, X	138	Ketorolac (10 mg) p.o. Diclofenac (50 mg) p.o.	Pain relief; no difference	No difference; mostly gastric pain, nausea
Rodriguez et al.[44]	MD 7 days, P	115	Dexketoprofen (25 mg) p.o. Ketorolac (10 mg) p.o.	Pain relief in both treatments; no difference	Mostly gastrointestinal
Sacchetti et al.[45]	SD, iX	36	Ketoprofen (100 mg) i.v. Ketoprofen (400 mg) i.v. ASA (1000 mg) i.v.	Pain relief in all treatments; K400 superior to K100 and A ($P < 0.01$)	None
Saxena et al.[46]	MD 4 days, P	50	Piroxicam 20 mg p.o. ASA 500 mg p.o.	Pain relief in both treatments ($P < 0.05$); no difference	Piroxicam: dry mouth ($P = 0.051$); ASA: minor upper GI symptoms ($P < 0.05$)
Staquet[51]	SD, P	126	Ketorolac (10 mg) i.m. Ketorolac (30 mg) i.m. Ketorolac (90 mg) i.m. Placebo	Pain relief in active treatments ($P < 0.05$); no difference	No difference
Toscani et al.[58]	MD 2 weeks, P	68	Nimesulide (200 mg) p.o. Naproxen (500 mg) p.o.	Pain relief in both treatments ($P < 0.0001$); no difference ($P > 0.05$)	No difference (gastric pain, haemorrhage, and vomiting)
Turnbull and Hills[59]	MD 7 days, X	28	Naproxen (250 mg) p.o. ASA (600 mg) p.o.	Pain relief in both treatments ($P < 0.01$); no difference ($P > 0.05$)	None
Ventafridda et al.[60]	SD, 2 parallel X-groups	24	Indoprofen (p.o.) 200 mg ASA 600 mg (p.o.) Placebo vs. Indoprofen (p.o.) 100 mg ASA 1000 mg (p.o.) Placebo	Pain relief with I 100, I 200, and ASA 1000 ($P < 0.05$); dose relation for both drugs ($P < 0.05$)	No difference
Ventafridda et al.[61]	MD 7 days, iX	65	ASA (600 mg) p.o. APAP (500 mg) p.o. Diclofenac (100 mg) p.o. Ibuprofen (600 mg) p.o. Indomethacin (50 mg) p.o. Pirprofen (400 mg) p.o. Sulindac (300 mg) p.o. Naproxen (250 mg) p.o. Suprofen (200 mg) p.o.	Highest pain relief with naproxen, diclofenac, indomethacin, and ibuprofen Judged worst: APAP	Mainly gastric discomfort; diclofenac tolerated best

Various NSAIDs and combinations

Study	Design	No.	Drugs compared	Result	Adverse events
Carlson et al.[23]	SD, P	75	Ketorolac (10 mg) p.o. Codeine + APAP (60 + 600) mg p.o. Placebo	Pain relief with ketorolac and codeine + APAP (both $P \leq 0.04$); codeine + APAP superior to ketorolac	Mostly gastrointestinal in both treatments; more often headache under ketorolac
	MD 7 days, P		Ketorolac (10 mg) p.o. Codeine + APAP (60 + 600) mg p.o.		
Minotti et al.[36]	MD 10 days, P	99	Diclofenac (50 mg) p.o. Nefopam (60 mg) p.o. Codeine + ASA (40 + 640 mg) p.o.	Pain relief in all treatments ($P < 0.01$); no difference	Fewer side effects with diclofenac
Minotti et al.[38]	MD 7 days, P	184	Diclofenac + imipramine (50 + 10/25 mg) p.o. Diclofenac + codeine (50 + 40 mg) p.o. Diclofenac + placebo (50 mg) p.o.	Pain relief in all treatments; no difference	More adverse events with diclofenac + codeine
Moertel et al.[40]	SD, X	100	ASA (650 mg) p.o. ASA + caffeine (65 mg) p.o. ASA + pentobarbital (32 mg) p.o. ASA + promazine hydrochloride (25 mg) p.o. ASA + ethoheptazine citrate (75 mg) p.o. ASA + propoxyphene napsylate (100 mg) p.o. ASA + pentazocine hydrochloride (25 mg) p.o. ASA + oxycodone (9.76 mg) p.o. ASA + codeine (65 mg) p.o. Placebo	Pain relief in active treatment (ASA to placebo $P < 0.05$); higher pain relief in combination with codeine, oxycodone, and pentazocine ($P < 0.05$)	Increase in sedative effects in combination
Stambaugh and Drew[49]	SD, P	160	Ketoprofen (100 mg) p.o. Ketoprofen (300 mg) p.o. ASA + codeine (650/60 mg) p.o. Placebo	Pain relief in active treatments ($P < 0.05$); no difference	No difference (somnolence, nausea/vomiting/dyspepsia)
Strobel[54]	MD 7 days, P	184	Diclofenac + codeine (50 + 50 mg) p.o. Diclofenac (50 mg) p.o.	Pain relief in both treatments; higher pain relief with codeine + diclofenac ($P < 0.05$)	No difference (mainly nausea/vomiting, gastric pain, and dizziness)

APAP, acetaminophen; ASA, aspirin; CMT, choline magnesium trisalicylate; i.M, intramuscular; i.V, intravenous; MD, multi-dosage; P, parallel; SD, single dosage; supp, suppository; WD, withdrawals; X, crossover.
(Duration stated for each drug/study arm in crossover comparisons).

Figure 2 Analysis 1.1. Non-opioids vs. opioids: withdrawals due to inadequate pain relief. CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs.
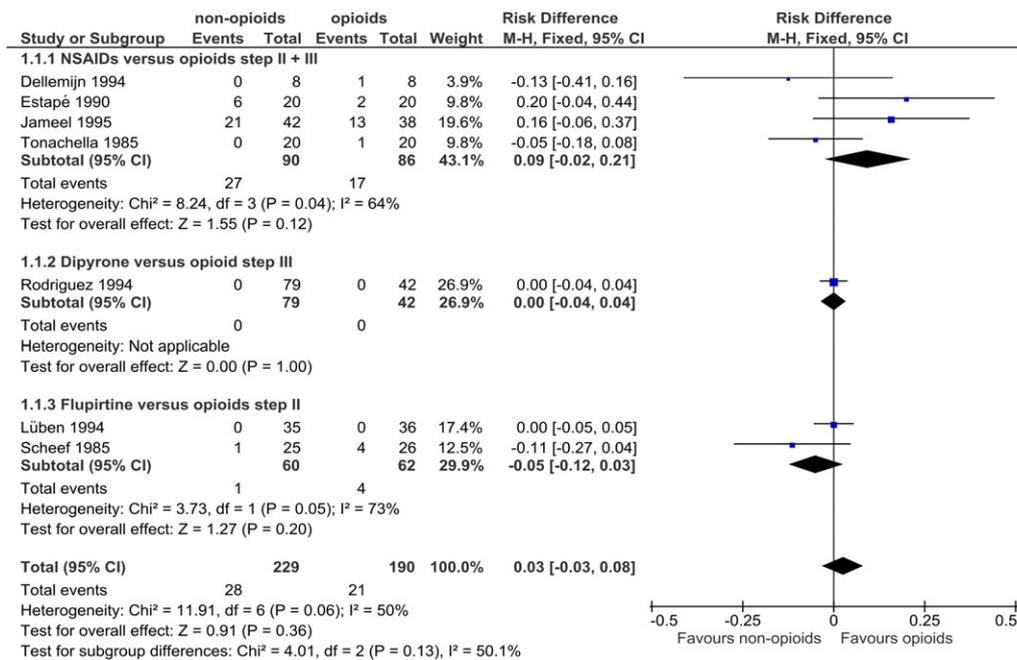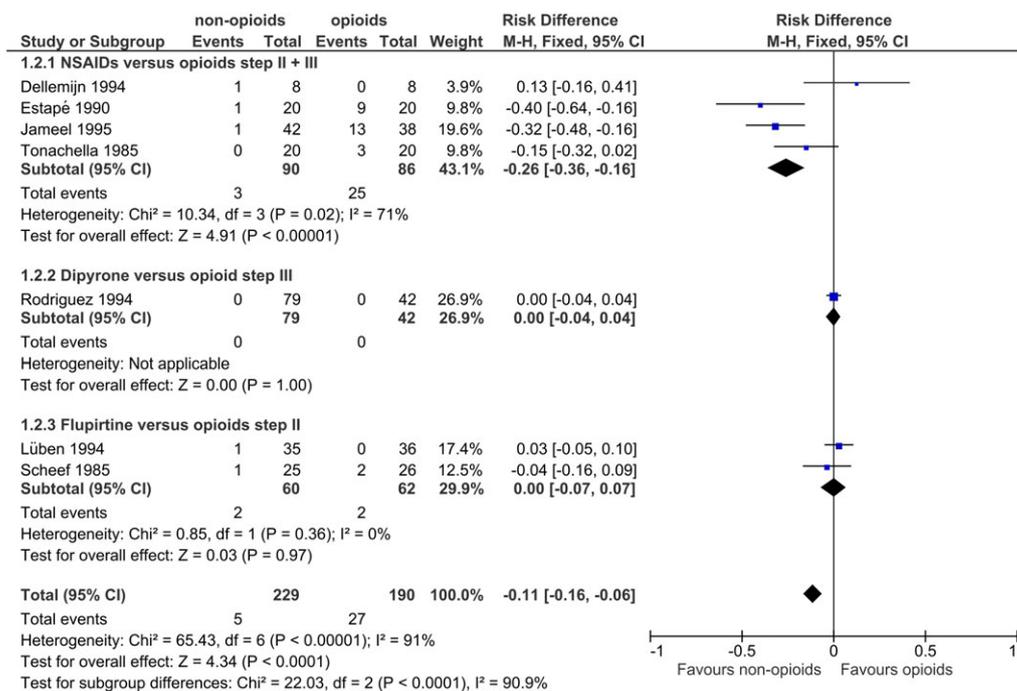

Figure 3 Analysis 1.2. Non-opioids vs. opioids: withdrawals due to adverse events. CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs.

The efficacy of naproxen was researched in six studies.[21,26,33,58,59,61] In a single-dose study,[21] 500 mg of naproxen showed significant analgesic properties (*P* = 0.001) in 43 patients when compared with a placebo. Four papers focused on a dose range from 250 to 500 mg comparing it with another analgesic and with the baseline, finding a significant

Figure 4 Analysis 1.3. Non-opioids vs. opioids: number of patients with adverse events. CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs.
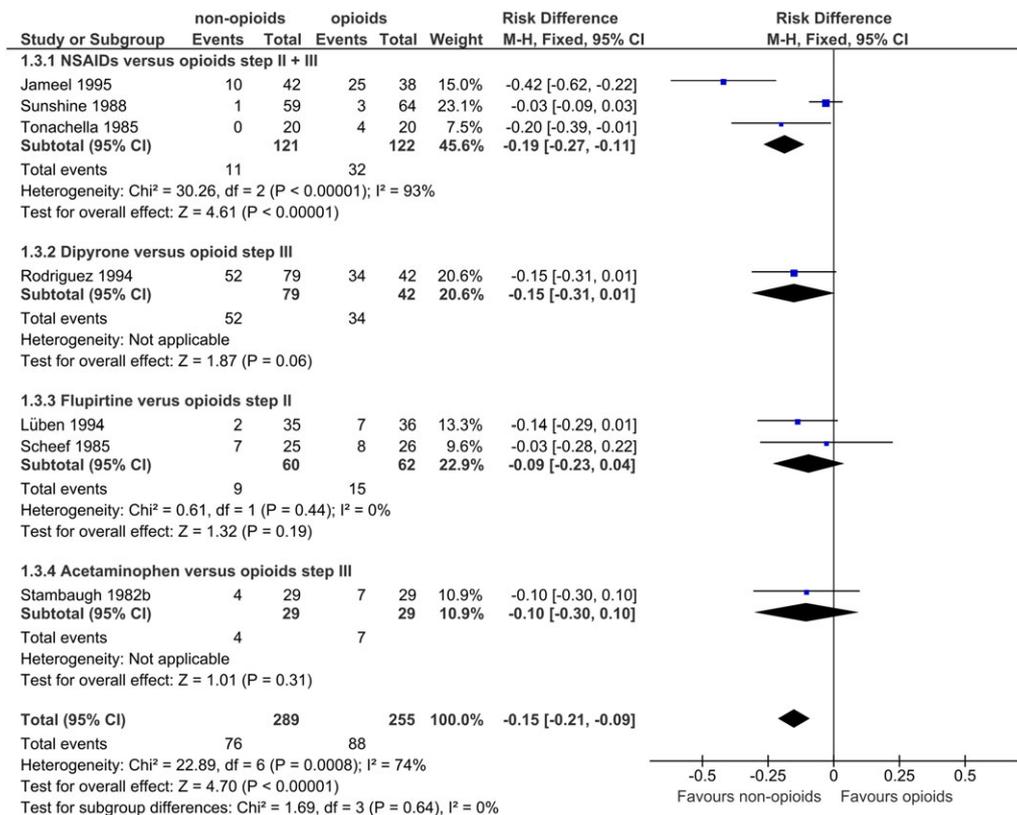
analgesic effect: Dellemijn et al.[26] ($P < 0.05$, $d = 4.05$ [1.628 to 6.467]), Toscani et al.[58] ($P < 0.0001$), Turnbull and Hills[59] ($P < 0.01$), and Ventafridda et al.[61] ($d = 2.14$ [0.401 to 3.877]). The comparison between 275 and 550 mg naproxen sodium administered three times a day showed an improved effect for the higher dosage but became only significant after subjects were categorized into naproxen responders and non-responders.[33] The recommended maximum dosage of 1100 mg/day for healthy individuals was exceeded in the higher dosage group.

Ketorolac was tested (10 mg p.o.[23] and 10–90 mg i.m.[51]) against placebo and showed a significant analgesic effect. Compared with opioids, it displayed analgesic properties via oral (10 mg) and intramuscular (30 mg) routes of administration without significant differences to pentazocine (50 mg)[28] or morphine (10 mg).[31] The oral administration of 10 mg of ketorolac over the course of 1 week in comparison with the combination of codeine + acetaminophen showed slight but significant disadvantages on two of seven study days.[23] Analgesic properties were also obvious in the direct comparison with another NSAID (diclofenac and dexketoprofen) (i.m. 10 and 30 mg[37] and p.o. 10 mg[42,44]) when compared with baseline. Two single-dose i.m. studies were not able to prove a significant increase in analgesic potency by raising the dose

from 10 to 30 mg,[37] or even 90 mg,[51] although the frequency of side effects remained comparable.

Oral piroxicam displayed a sufficient analgesic effect compared with baseline in two comparison studies with a patient pool of 140. In one study, 20 mg of piroxicam was compared with aspirin[46] while in the other, 40 mg of piroxicam was compared with a weak opioid.[52]

Ketoprofen showed a sufficient analgesic effect when compared with the baseline or placebo. The effect of a 1 week long oral 25 mg (100 mg/day) dexketoprofen therapy showed no significant difference when compared with ketorolac[44] but did compared with the baseline. When taken orally, there were no statistically significant analgesic differences between 100 and 300 mg[49] as well as 75 and 225 mg.[55] This was different when comparing 100 with 400 mg i.v.,[45] where a significant difference was found ($P < 0.01$). However, the higher dosage exceeded the recommended maximum dosage of 300 mg per day in these single-dose trials. Reported side effects were mostly of gastrointestinal nature.

An acetylsalicylic acid monotherapy was tested in seven studies,[39,40,45,46,59–61] with a combined number of 337 patients. The dose range was between 500 and 1000 mg for the oral administration and 1000 mg for intravenous use. A significant difference was found when compared with

placebo ($P < 0.05$).[39,40,60] In comparison with other analgesics,[39,45,46,59,61] no significant differences were found.

The COX-2 inhibitors, celecoxib[41] and nimesulide,[58] were also tested. Celecoxib showed analgesic properties over the course of 6 weeks, but compared with diclofenac had no significant difference in analgesic effect. Nimesulide was tested against naproxen and showed a significant reduction in pain compared with baseline, albeit no significant difference between the two drugs concerning pain reduction and side effects could be established. The main side effects included gastrointestinal problems with abdominal pain, nausea, and vomiting leading to a 15% dropout rate in the nimesulide/naproxen study.

A significant superiority of a specific NSAID within the recommended dosage range was not found in any study.[45,61]

In four trials,[21,23,38,42] at least 50% of patients suffered from bone metastases, but a significant advantage of NSAIDs in the treatment of pain caused by bone metastases was not described.

Regarding side effects, we specifically analysed the impact of NSAIDs on renal function. In 13 of 32 studies analysing NSAIDs, severe or clinically significant renal impairment had been defined as exclusion criterion; in these trials, the majority of studies showed a study length of at least 3 days (10 studies), three studies were single-dose trials, the latter giving little insight into the development of renal impairment. In two of these studies, the impact of NSAIDs on renal function was specifically addressed: in both studies, diclofenac had no negative impact on renal function over a period of 7[38] and 10 days,[36] respectively.

In the other 19 studies, renal impairment had not been defined as an exclusion criterion. Seven studies were single-dose studies, four studies showed a study length of 1–2 days, and eight trials showed a study length of at least 3 days. In these studies, only Stambaugh and Drew[50] reported a case of haematuria after application of a combination of oxycodone/acetaminophen and ibuprofen over 7 days.

Dosage increase meta-analysis

Non-steroidal anti-inflammatory drugs were weighed as a group and not individually in the meta-analysis (*Figures* 5 and 6; Supporting Information, *Appendix* S5, *Table* 2).

The number of 'withdrawals due to inadequate pain relief' was slightly higher in four low-dosage studies with a patient pool of 359. Nonetheless, no significant differences were seen ($P = 0.58$; RD -0.02 [-0.11, 0.06]). The quality of evidence was graded as moderate.

The number of 'patients with adverse events' was somewhat higher in the high-dosage groups within the seven relevant studies comprising 566 participants; however, these differences did not reach statistical significance ($P = 0.23$; RD 0.03 [-0.02, 0.09]). The quality of evidence was graded as high.

Figure 5 Non-steroidal anti-inflammatory drugs high dosage vs. low dosage: withdrawals due to inadequate pain relief. CI, confidence interval.
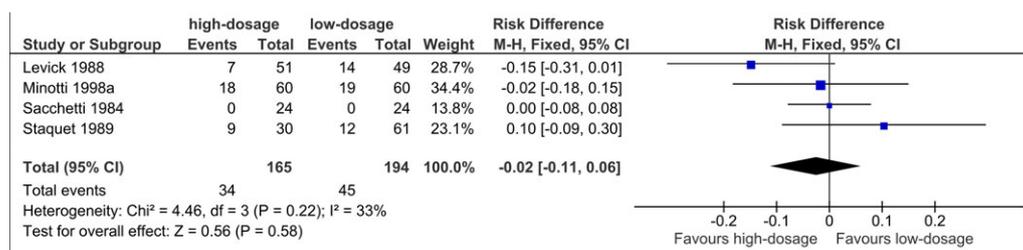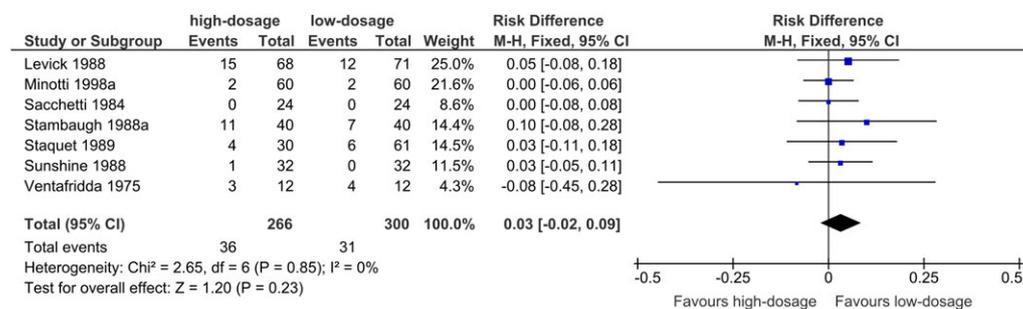

Figure 6 Non-steroidal anti-inflammatory drugs high dosage vs. low dosage: number of patients with adverse events. CI, confidence interval.

Non-steroidal anti-inflammatory drugs compared with opioids

Non-steroidal anti-inflammatory drugs were compared with morphine (5–10 mg) in three studies.[26,31,55] Intramuscular injections of 30 mg of ketorolac showed no significant difference in pain reduction to 10 mg of morphine.[31] There was, however, a significantly higher number of dropouts because of inadequate pain relief in the NSAID group (P = 0.007), but overall there were more withdrawals because of side effects under morphine therapy (P = 0.0006). A total dropout rate of 64% limits the validity of this study.

Sunshine and Olson[55] reported 'unpublished data', which claimed to show that oral ketoprofen in doses of 225 mg had a better effect than intramuscular application of 5 mg of morphine. The efficacy of 10 mg of morphine i.m. was comparable.

Dellemijn et al.[26] showed that not only had an oral dose of 500 mg of naproxen stronger analgesic effects than 30 mg of oral morphine in regard to neuropathic pain but also that the use of a rescue medication significantly diminished under the NSAID (P < 0.01 in the first week). The validity of this crossover study is limited because of its low number of participants and high dropout rate (11 out of 20 participants dropped out).

Diclofenac (75 mg i.m.) showed a significantly greater pain reduction (P = 0.047) compared with 30 mg of pentazocine.[57] Twenty patients participated in this study with a dropout rate of 20%. No significant difference in regard to analgesia was found when comparing ketorolac (10 mg p.o.) with pentazocine (50 mg p.o.).[28] Both studies exhibited an increased number of side effects under the opioid, especially frequent were nausea and vomiting, leading to high dropout rates in the pentazocine group.

A slight, albeit not significant, advantage was shown for aspirin (650 mg) over codeine (60 mg).[39]

Similarly, no significant difference was found when comparing 40 mg of piroxicam (double the daily recommended dose of 20 mg) with 60 mg of codeine.[52]

Non-steroidal anti-inflammatory drugs showed a lower rate of side effects. Symptoms like drowsiness, nausea, and vomiting were more commonly reported in the opioid groups (Figure 4; P < 0.00001; RD −0.19, 95% CI −0.27 to −0.11). The NSAID groups also experienced a lower dropout rate

because of adverse events (Figure 3; P < 0.00001; RD −0.26, 95% CI −0.36 to −0.16) (Supporting Information, Appendix S5, Table 3).

Non-steroidal anti-inflammatory drugs in addition to step III opioids

Six studies[22,29,32,34,50,62] explored the efficacy of a variety of NSAIDs in combination with a step III opiate in comparison with opiate therapy + placebo.

Diclofenac 50 mg suppositories were combined with a patient-controlled analgesia morphine therapy in 16 patients to yield a result that showed a decrease in the amount of morphine use[22] (P = 0.01, d = −0.263 [−1.279 to 0.754]) and a statistical trend towards a greater pain reduction (P = 0.09, d = 2.55 [1.142 to 3.965]). Oral ibuprofen was combined with a strong opiate at doses of 400 mg ibuprofen[62] as well as 600 mg[29,50] leading to an improved analgesic effect. Weingart et al.[62] described the addition of ibuprofen to various opioids in 14 patients and showed a significant difference in pain reduction. A 30-patient strong study[29] was able to produce a significantly higher pain reduction, using the combination of ibuprofen (600 mg) with methadone (2.5 and 5.0 mg). When 600 mg of ibuprofen was added to the fixed combination of oxycodone/acetaminophen (5/325 mg), a significant advantage was found for pain intensity/pain relief (P < 0.05) and reduction of narcotics use (P < 0.01).[50]

Both NSAIDs, choline magnesium trisalicylate[32] and flurbiprofen,[34] showed an insignificantly more effective pain reduction when combined with an opiate.

No dropouts were reported because of inadequate pain relief. However, all patients were undergoing an opiate therapy. Significant differences in side effects were not observed (Supporting Information, Appendix S5, Table 7; Figures 7–9).

Non-steroidal anti-inflammatory drugs + step II opioid vs. non-steroidal anti-inflammatory drugs

Two studies[38,54] comprising 368 patients showed that diclofenac (50 mg) was able to achieve a sufficient reduction

Figure 7 Opioids step III + NSAID vs. opioids step III + placebo: withdrawals due to inadequate pain relief. CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs.
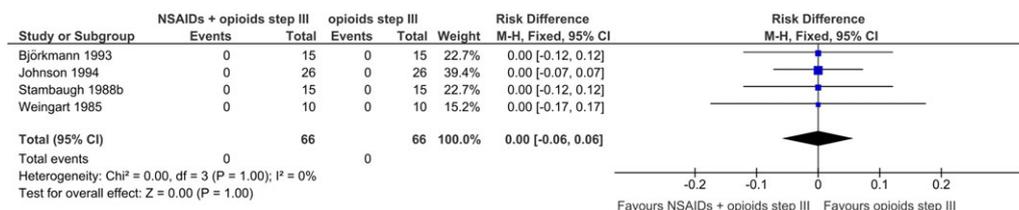

Study or Subgroup	NSAIDs + opioids step III Events	Total	opioids step III Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Björkmann 1993	0	15	0	15	22.7%	0.00 [-0.12, 0.12]
Johnson 1994	0	26	0	26	39.4%	0.00 [-0.07, 0.07]
Stambaugh 1988b	0	15	0	15	22.7%	0.00 [-0.12, 0.12]
Weingart 1985	0	10	0	10	15.2%	0.00 [-0.17, 0.17]
Total (95% CI)		**66**		**66**	**100.0%**	**0.00 [-0.06, 0.06]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 3 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

Favours NSAIDs + opioids step III   Favours opioids step III

Figure 8 Opioids step III + NSAID vs. opioids step III + placebo: withdrawals due to adverse events. CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs.
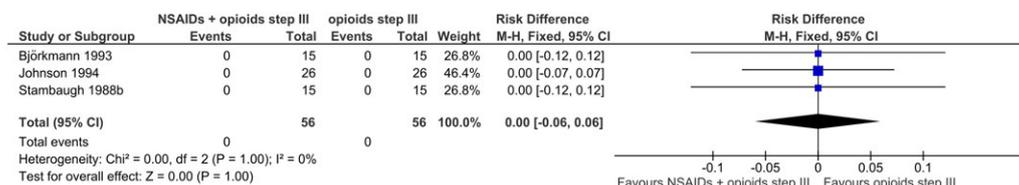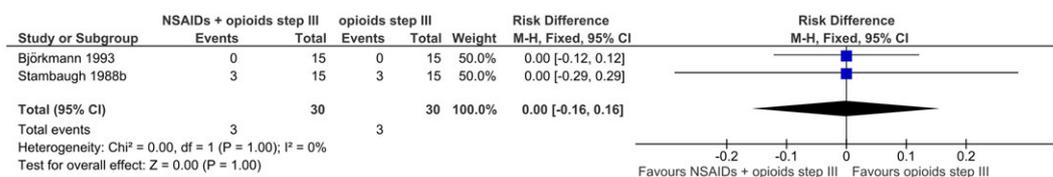

Figure 9 Opioids step III + NSAID vs. opioids step III + placebo: number of persons with adverse event. CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs.

in pain compared with baseline when combined with codeine. The addition of 40 mg of codeine[38] did not lead to a significantly higher difference compared with a diclofenac monotherapy, while the addition of 50 mg of codeine[54] did lead to a significant difference ($P < 0.05$). Only one study[38] exhibited a higher rate of side effects under the combination of diclofenac and codeine (Supporting Information, *Appendix* S5, *Table* 4; Supporting Information, *Appendix* S6).

Aspirin combined with codeine or pentazocine[40] had a significantly better analgesic effect than a monotherapy of aspirin ($P < 0.05$) but a higher number (not significant) of reported side effects (sedation). The external validity of this low-quality study is limited.

Staquet and Renaud[52] investigated the individual analgesic properties of piroxicam (40 mg) and codeine (60 mg), as well as their combination (20 mg piroxicam + 30 mg codeine), and discovered a comparable significant efficacy in all three treatments. It is possible to speculate an even higher analgesic effect, because only half the monotherapeutic dosage was used for each medication in the combined treatment. The recommended daily dose of piroxicam is 20 mg.

Pharmaceutical form

In the analysed studies, NSAIDs were administered in various pharmaceutical forms. Regarding diclofenac, the oral[36,41,42,61] as well as the intramuscular application[37,57] showed significant pain relief. The rectal administration[22] in combination with intravenous morphine led a significant reduction in morphine use.

Ketorolac proved to be effective in oral[23,28,42,44] as well as intramuscular form.[31,37,51]

Ketoprofen led to significant pain relief when administered orally[44,49,55] as well as intravenously.[45]

There were no studies comparing the efficacy of different pharmaceutical forms of the same drug.

Quality of life

The combination of acetaminophen and strong opioids compared with placebo showed no significant difference in the quality of life index in two studies.[20,56] Merely, in one study,[53] a slight advantage in overall well-being was recorded ($P = 0.05$, 95% CI 0.0 to 1.4).

For the various NSAIDs, an increase in restful sleep time has been described in monotherapy. Thus, for acetylsalicylic acid and piroxicam, a significant increase in sleep duration was reported ($P < 0.05$ each).[46] Moreover, in the study by Ventafridda *et al.*,[61] ibuprofen, diclofenac, and pirprofen lengthened sleep duration by 13.3%, 11.4%, and 10.5%, respectively. However, no statistics on significance levels were presented in the latter study.

No significant differences were found comparing dexketoprofen trometamol and ketorolac[44] in regard to quality of life utilizing Karnofsky scores. Furthermore, comparison of ketorolac and diclofenac showed no significant difference in the quality of life score.[42]

Analgesia with flurbiprofen in combination with other opiates[34] compared with placebo was associated with a significantly higher Karnofsky score ($P = 0.05$). However, the Karnofsky scores differed widely between the two investigators in this study with a very small sample size, so that this result has limited meaningfulness.

Discussion

This study is the first to systematically review the use of non-opioids across the whole spectrum of palliative care. Despite the prevalence of patients with cardiovascular diseases (38.5%), respiratory diseases (10.3%), HIV (5.7%), and diabetes (4.5%) in need of palliative care according to the WHO Global Atlas of Palliative Care,[1] our comprehensive search strategy identified no relevant studies on the aforementioned diseases. All identified studies dealt with cancer pain, which accounts only for one-third of patients in need of palliative care. This can be explained by the fact that until recently, it was widely believed that pain does not play an important role in patients dying of non-malignant diseases.[67] However, there is growing evidence that patients dying from cardiac failure, chronic obstructive pulmonary disease, and other palliative diseases suffer from similar,[68,69] sometimes even greater,[70] levels of pain than cancer patients. Despite this lack of evidence in the WHO list of essential medicines for pain and palliative care,[71] the non-opioids acetylsalicylic acid, ibuprofen, and acetaminophen are still listed. In our search strategy, we desired to be as inclusive as possible covering all relevant trials for the field of palliative medicine. We therefore included all studies of sufficient methodological quality (randomized-controlled double-blinded studies) without defining a specific study size, length, or dosage range. This search strategy takes into account the specific clinical situation in palliative care with smaller sample sizes and potentially shorter duration of therapy compared with other clinical specialities. On the basis of this search strategy, we were able to include 43 studies in our review.

The systematic review provides substantial evidence regarding the efficacy of NSAIDs compared with placebo for palliative care cancer pain, overall quality of evidence on withdrawals due to inadequate pain relief, and adverse events ranged from moderate to high. In all seven[21,23,39,40,49,51,60] analysed studies on this subject, a superior efficacy for cancer pain relief was confirmed. However, only in one study of moderate quality investigating the intramuscular application of 10–90 mg of ketorolac,[51] effect sizes could be calculated, which ranged between 3.5 and 4.5. For diclofenac, ketorolac, and ketoprofen, the efficacy of various pharmaceutical forms could be proven. However, because of a lack of studies, comparisons of different routes of administration of the same drug were not possible. Further analyses provided evidence that there is no higher rate of adverse events in NSAIDs compared with placebo (Supporting Information, *Appendix* S7; Supporting Information, *Appendix* S5, *Table* 5), which corresponded to a satisfactory adherence. However, all analysed trials were single-dose studies, and none of the studies investigated adverse events over a longer study period of several weeks. Therefore, the clinical meaningfulness is limited. There is no convincing evidence concerning the superiority of one specific NSAID within the recommended dosage range. The only study reporting relevant differences showed severe methodological weaknesses.[61] A possible clinical benefit via a dosage increase was investigated in ketorolac, ketoprofen, and naproxen. Overall quality of evidence for withdrawals due to inadequate pain relief was moderate. Only for ketoprofen did a quadrupling of the intravenous dose from 100 to 400 mg lead to a relevant increase in pain reduction. However, this dosage was above the recommended maximum dosage,[45] thus putting its clinical relevance in doubt. Surprisingly, we were only able to include two studies on cancer pain that compared the effectiveness of NSAIDs with COX-2 inhibitors. Neither celecoxib[41] nor nimesulide[58] was significantly superior for pain relief or drug compatibility when compared with diclofenac and naproxen, respectively. The most important adverse events for both substances were gastrointestinal side effects such as nausea and abdominal pain.

The aetiology of pain in cancer is multifaceted; it can be tumour related, treatment related, or unrelated to the underlying cancer condition.[15] The adequate assessment of the diverse types and causes of cancer pain remains a demanding task for the treating physician and a necessary prerequisite for satisfactory pain management.[4,72] The pharmacotherapeutic treatment of cancer pain is based on the analgesic ladder approach introduced 30 years ago by the WHO.[71] Ever since, the opioid-based pharmacotherapy has been viewed as the most important treatment option for moderate to severe cancer pain.[16] The WHO pain ladder implies an analgesic superiority of opioids over NSAIDs, therefore is the comparison of these pharmacological agents of particular interest. The overall quality of evidence comparing NSAIDs with opioids on withdrawals due to inadequate pain relief was moderate. Our analyses did not support a superior analgesic efficacy of opioids over NSAIDs for doses up to 15 mg of morphine or opioids with equianalgesic potency. Thus, oral intake of 10 mg of ketorolac had a similar analgesic effect as that of 50 mg of pentazocine.[28] Aspirin dosed at 650 mg showed no significant difference in analgesic potency to 60 mg of codeine[39]; the same applied to 40 mg of piroxicam and 60 mg of codeine.[52] In comparison with 10 mg of morphine (i.m.), an intramuscular application of ketorolac 30 mg[31] or an oral intake of 75 mg ketoprofen[55] displayed equal pain relief. Two studies even described a significant superiority of NSAIDs over opioids.[26,57] In one of these studies of moderate quality, intramuscular diclofenac (75 mg) led to higher pain reduction than oral intake of 30 mg of pentazocine.[57] The second study showed a superiority of naproxen (500 mg) to 30 mg of morphine; however, the high dropout rate of over 50% casts some doubt over the findings of the study.[26] Meta-analyses (*Figures* 3 and 4; Supporting Information, *Appendix* S5, *Table* 3) of adverse events displayed a significantly better drug tolerability of NSAIDs compared with opioids. However, all analysed studies mainly investigated the short-term analgesic efficacy over

several hours or up to 1 week, thus limiting the clinical meaningfulness of the findings.

We further analysed the question of whether the combination of an NSAID with an opioid would allow for a reduction in the needed opioid dose as well as opioid-related side effects. Analysing the evidence from six studies, our systematic review provides moderate support for a beneficial analgesic effect of NSAIDs in addition to step III opioids. The analysed studies mainly investigated patients suffering from pain due to skeletal metastases. A 50 mg diclofenac suppository[22] led to a significant reduction of morphine intake via patient-controlled analgesia. Oral intake of 400 to 600 mg of ibuprofen in addition to a step III opioid led to an increase in pain relief[29,50,62] or a dose reduction of opioid analgesics.[50] However, studies on choline magnesium trisalicylate[32] and flurbiprofen[34] in addition to step III opioids could not prove an increase in analgesic potency. The addition of NSAIDs to step III opioids did not lead to an increase in adverse events compared with opioid monotherapy. Most of the studies evaluated the short-term analgesic efficacy over a period of up to 1 week.

Two out of the four studies[38,40,52,54] analysing the efficacy of NSAIDs plus weak opioids against NSAIDs displayed a higher pain reduction in the combination group.[40,54] However, in the other two studies, there were no differences in efficacy to be found.[38,52] There was no significant difference regarding tolerability. Three studies compared a combination of codeine and aspirin[36,49] or acetaminophen[23] with another NSAID. The analgesic effect of codeine + acetaminophen was superior to ketorolac.[23] The comparison of codeine + aspirin with diclofenac[36] and ketoprofen[49] showed no difference.

In our systematic review, we included the whole spectrum of non-opioids relevant in clinical practice. One study comparing acetaminophen with placebo did not show a significant relief from cancer pain[48]; another study comparing it with various NSAIDs showed the smallest effect size of all tested NSAIDs.[61] In both trials, drug compatibility was good. The addition of 650 to 1000 mg of acetaminophen to step III opioids showed no significant benefit in four of six analysed studies,[20,25,30,56] while only two studies provided some support for an analgesic benefit.[48,53] Moreover, two[20,56] out of three studies measuring quality of life did not find a significant increase compared with placebo. In summary, our systematic review did not find convincing evidence for the analgesic efficacy of acetaminophen in cancer pain, which is in agreement with other reviews.[8,73,74]

On the contrary, we found evidence for the efficacy of dipyrone alone[43] in doses between 1 and 2 g, which provided substantial pain relief with large effect sizes for cancer pain. In doses of 2 g, the analgesic effect was not significantly different from 10 mg of morphine. In combination with morphine,[27] it also showed significant pain relief in patients with metastatic diseases, with effect sizes ranging from 4.96 to 3.27. Drug compatibility was satisfactory in both studies.

A recent review[75] on dipyrone in cancer pain was based on altogether four studies including two additional studies (one cohort study and one non-blind RCT study) compared with our review due to different inclusion criteria. Nonetheless, the review also came to the conclusion that dipyrone can be recommended for pain treatment as an alternative to other non-opioids either alone or in combination with opioids. Oral application of flupirtine (100 mg) was analysed in two studies. In patients suffering from severe pain mainly due to metastatic disease, it showed an analgesic efficacy similar to 50 mg of tramadol over the course of 4 weeks.[35] In a second study[47] in patients with severe pain, flupirtine was superior to 50 mg of pentazocine in terms of pain intensity and fewer dropouts over the course of 1 week due to insufficient pain relief. Our meta-analyses (*Figures* 3 and 4; Supporting Information, *Appendix* S5, *Table* 1) showed no significant differences regarding adverse side effects between flupirtine and opioids. The most common side effects suffered by affected patients were mainly gastrointestinal symptoms.

Even though improvement of quality of life is the ultimate goal of palliative care as defined by the WHO,[76] only very few studies included quality of life measures in their study design. There was convincing evidence for an increase in restful sleep time for acetylsalicylic acid and piroxicam compared with placebo.[46] Another study[61] reporting a lengthened sleep duration for ibuprofen, diclofenac, and pirprofen compared with placebo failed to report essential statistics. The comparison of different NSAIDs on quality of life did not show significant differences.

Although two-thirds of studies [29] showed at least moderate study quality and 14 trials were of low quality, there were relevant obstacles to drawing clear conclusions. There was a great heterogeneity in terms of agents, dosages, pharmaceutical forms, types of cancer, types of pain, pain severity, and outcome measures. This heterogeneity limits the informative value of our meta-analyses. Another talking point is the fact that in the vast majority of studies, the investigation period only lasted up to 1 week with 25% of studies being single-dose trials. Consequently, there is a lack of data regarding long-term effects of NSAIDs. Regarding renal impairment, our analysis showed except for one case no negative impact of NSAIDs on renal function. This is in line with previous meta-analyses, which found no evidence for a relationship between heavy protracted NSAID use and the incidence of chronic renal impairment in patients without chronic kidney disease.[77,78] Renal side effects seem mainly to be relevant, if NSAIDs are prescribed in patients with chronic kidney diseases.[79,80] These findings may be of specific importance for clinicians, which might think that prescribing NSAIDs and skipping over acetaminophen mean increasing the overall risk of renal injury.

Analgesia in cancer pain is still practiced in accordance with the recommendations of the WHO ladder for cancer

pain relief. On the basis of our systematic review, the recommendation of non-opioids for mild pain in palliative care cancer pain as the first step has to be modified insofar as we found evidence for clinically relevant pain relief for NSAIDs, dipyrone, and flupirtine, however no convincing evidence for a beneficial effect of acetaminophen. Consequently, acetaminophen should only be used on a case-by-case basis. For the treatment of mild to moderate pain, the second step of the pain ladder recommends the addition of a weak opioid. In all analysed trials, patients showed at least mild to moderate pain at baseline; in many trials, patients perceived severe pain. Our systematic review did not provide substantial evidence for a clear superiority of the combined treatment of an NSAID and weak opioid to an NSAID monotherapy. Nonsteroidal anti-inflammatory drugs were superior in terms of drug compatibility. Therefore, the WHO step 2 recommendations of the pain ladder, suggesting the combination of a weak opioid and a non-opioid, are not supported by our findings. Thus, to maximize pain relief and minimize adverse events in palliative care cancer pain, an increased dosage of NSAIDs, dipyrone, or flupirtine should be considered first before adding an opioid.

Our methodological approach differed from recent systematic reviews focusing on NSAID and cancer pain[7,8] insofar, as we included RCTs regardless of study size, dosage regimen, and pharmaceutical form, thereby reflecting the specific situation in palliative medicine. Thus, compared with the systematic review on NSAIDs (not including acetaminophen) in cancer pain, we included a total of 36 studies[21–23,26–29,31–47,49–52,54,55,57–62] compared with 11 studies.[23,36,41–44,58,59,81–83] Three studies included in the systematic review by Derry were excluded because of methodological weaknesses such as blinding/double blinding.[81–83] Derry and colleagues defined a sample size of <25 participants per study arm and <5 days study length as exclusion criteria. As we decided to reflect the specific situation in palliative medicine, we also included single-dose studies with fewer participants, which led to the inclusion of 28 additional studies.[21,22,26–29,31–35,37–40,45–47,49–52,54,55,57,60–62] Derry and colleagues came to the conclusion that there is no high-quality evidence supporting the use of NSAIDs in cancer pain as part of the WHO ladder and no additional pain-relieving effects when combined with strong opioids. Based on our findings, we found substantial evidence of moderate quality for a satisfactory pain relief in cancer due to NSAIDs, flupirtine, and dipyrone compared with placebo. There was no evidence for a superiority of one specific non-opioid, and an increase in dosage showed no further benefit. Furthermore, we found moderate quality of evidence for a similar pain reduction by NSAIDs in the usual dosage range compared with up to 15 mg of morphine or opioids of equianalgesic potency. There were no statistically significant differences in tolerability or safety. With regard to step 2 of the WHO pain ladder, we found no high-quality support for the superiority of a combination of a weak opioid and an NSAID compared with an NSAID alone; in contrast, there was a beneficial effect of the combination of an NSAID and a step III opioid, with tolerability and safety staying comparable.

Compared with the recent systematic review on the use of acetaminophen in cancer pain,[8] we included six additional studies in our review, analysing nine[20,23–25,30,48,53,56,61] compared with three[20,25,30] studies. However, both reviews come to the conclusion that for lack of efficacy the use of acetaminophen as an analgesic in monotherapy or in combination with opioids cannot be recommended.

Our systematic review highlights the urgent need for studies on the use of non-opioids across the whole spectrum of end-stage diseases to optimize the quality of pain treatment in palliative care. Current guidelines[84] on the use of non-opioids in palliative medicine are mainly based on studies dealing with cancer pain due to a complete lack of evidence regarding other disease entities. Additionally, empirical evidence on the efficacy of non-opioids is not adequately mirrored in clinical guidelines claiming international validity, for example, dipyrone not being listed as essential medicine in palliative care,[84,85] as well as clinical practice, for example, acetaminophen being the most prescribed analgesic in palliative patients in the USA.[86] With regard to cancer pain particularly, the efficacy of non-opioids in cancer-related pain of different aetiologies remains unanswered. Furthermore, the long-term safety, efficacy of chronic non-opioid use, and the impact on quality of life in palliative patients with cancer need to be established. To shed further light on the impact of non-opioid treatment on patients' well-being, future studies should regularly include measures on quality of life.

Acknowledgements

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1: Example search strategy (CENTRAL)
Appendix S2: Risk of bias graph
Appendix S3: Risk of bias summary
Appendix S4: Exclude studies with reason
Appendix S5: Summary of findings table 1–7
Appendix S6: Analysis NSAIDs + step II opioid versus NSAIDs
Appendix S7: Analysis NSAIDs versus placebo

Conflict of interest

The authors declare that there is no conflict of interest.

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