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Long-term opioid therapy in chronic noncancer pain

A systematic review and meta-analysis of efficacy, tolerability and safety in open-label extension trials with study duration of at least 26 weeks

Supplementary material online

This article contains supplementary evidence reports and tables. These are available at: dx.doi.org/10.1007/s00482-014-1452-0

Wherever you look, you will only see what you are looking for.

Introduction

The rates of long-term (>6 months) [4] opioid therapy (LtOT) in chronic noncancer pain (CNCP) are increasing in western countries including Germany [47, 53]. Despite the several available evidence-based guidelines [37], the efficacy of LtoT remains controversial for the following reasons: Firstly, although randomized controlled trials (RCTs) of up to 12 weeks demonstrated the superiority of opioids over placebo in neuropathic [28], low back [4] and osteoarthritis pain [38], the number of published trials is hitherto limited [25]. One critical research gap concerning the use of opioids is the lack of effectiveness studies on the long-term benefits and harms of opioids [6]. Most placebo-controlled RCTs in pain medicine had a study duration of 12 weeks, as required by drug agencies if the drug is submitted for approval [34]. In our recent systematic search of the literature relating to RCTs with opioids in CNCP, we did not find any placebo-controlled study with a study duration >26 weeks [21, 41, 46, 52]. Secondly, the safety of opioid treatment in terms of risk of addiction and death from overdose has not been properly assessed, due to the complexity of these outcomes in RCTs [20]. The increasing rates of opioid prescriptions, as well as of abuse of prescribed opioids and associated deaths in the US have been highlighted in editorials [40, 48]. There is thus no consistent good-quality evidence available for giving a strong clinical recommendation for the long-term administration of opioids in CNCP in the form of guidelines [20].

Clinical guidelines should reflect all knowledge—not only (meta-analyses of) placebo-controlled RCTs [59]. Case series, open-label and open-label extension studies of RCTs have been summarized by systematic qualitative reviews [20, 25, 36] in order to address the question of long-term efficacy and safety of opioids in CNCP. No systematic search of databases for open-label extension safety studies of RCTs has been conducted until now. To the best of our knowledge, no quantitative synthesis of study results on benefits and harms of long-term observational studies of opioids in CNCP has been performed until now.

Therefore, the aims of this systematic review were as follows: to assess the long-term efficacy and harms of opioids in any type of CNCP in open-label extension studies of RCTs with opioids. Specifically, we studied how many patients remained on opioid therapy, reported a sustained reduction of pain and disability or experienced serious harms (serious adverse events, SAE; death, aberrant drug behavior) in the long-term (≥6 months).

Methods

The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [32] and the recommendations of the Cochrane Collaboration [15].

Methods of analysis and inclusion criteria were specified in advance.

Eligibility criteria

Types of studies

We included open-label extension studies of RCTs. Study duration of the RCTs

The English full-text version of this article is freely available at SpringerLink (under "Supplementary Material").

should have been at least 2 weeks and of the open-label extension phase at least 6 months. We excluded registered open-label studies without a prior double-blind randomized period and pre–post case series studies, because these studies are associated with a higher risk of bias than open-label extension studies of RCTs [34]. Studies should include at least 20 patients. Studies should have reported at least one of the outcomes defined below.

Types of participants

Participants of interest were patients of any age with pain due to any cause other than cancer lasting for at least 3 months prior to trial enrolment.

Types of interventions

Any opioid taken by oral or transdermal route in any dose compared to placebo, another opioid or a nonopioid analgesic.

Types of outcome measures

- Efficacy: number of patients who were on opioids at the end of open-label (related to the number of patients randomized at baseline and to the number of patients included into open-label); changes in pain and disability at the end of open-label compared to the end of randomized trial in patients on study medication at the end of the randomized period.
- Harms: number of patients who dropped out due to lack of efficacy; number of patients who dropped out due to adverse events (AE); number of SAE; number of patients with aberrant drug behavior; death during open label

Outcome measures must have been validated or used as a standard of care to be included in the analyses. In addition to these general inclusion criteria, we employed two criteria for efficacy outcomes: (1) pain and disability outcomes must have been patient-reported; (2) outcome data must not have been collected retrospectively (e.g. posttreatment surveys/questionnaires).

Data sources, searches and selection of studies

Two review authors (KB, WH) screened the abstracts of all RCTs with opioids compared to placebo and other opioids which were included into systematic reviews [21, 41, 46, 52] for open-label extension periods. These reviews updated and expanded the literature search of the first version of the German guidelines on the long-term administration of opioids (LONTS), which searched the literature up until October 2008 [43]. The updated and expanded search included the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Scopus from October 2008 to October 2013. Our search included all languages.

Two review authors (KB, WH) screened the references in recent systematic reviews on long-term treatment of opioids in CNCP [20, 25, 36] for open-label extension studies.

We searched clinicaltrials.gov with the search terms "open-label extension study" AND "buprenorphnie" OR "codeine" OR "fentanyl" OR "hydromorphone" OR "moprhine" OR "oxycodone" OR "oyxmorphone" OR "tapentadol" OR "tilidine" or "tramadol" through December 2013.

We searched MEDLINE with the search terms "open-label extension study AND (buprenorphine OR codeine OR fentanyl OR morphine OR oxycodone OR oxymorphone OR analgesics, opioid OR tapentadol OR tilidine OR tramadol)" through to December 2013.

Disagreements on study selection were resolved by consensus. If needed, a third review author was involved (CM).

Data extraction and management

Two review authors extracted the data from the full-text articles and entered the data independently into standard extraction forms (KB, WH). We extracted characteristics of patients and studies, descriptions of the experimental and control groups, cointerventions, author affiliations and study sponsoring. Disagreements were resolved by consensus. If needed, a third review author was involved (CM).

Dealing with missing data

If data were not available in a format that was appropriate for data extraction, we did not contact the authors of the trial for further clarification. If means and standard deviations (SDs) were not available for continuous data, we attempted to determine an estimate of treatment effect from reported statistics (e.g., t-values, F-values, p-values). If means and SDs were not reported in the text, but rather in figures, these were extracted from figures.

Risks of bias assessment

Two authors (KB, WH) independently assessed the risk of bias in each trial using eight domains recommended by the Cochrane Collaboration: selection bias, performance bias, detection bias, attrition bias, reporting bias, selection bias, performance bias, detection bias and funding bias [15]. We slightly modified one item of the tool (selection bias) to adapt to the setting of an open-label extension trial (see supplementary table 1). The criteria were scored as "yes", "no" or unclear". Any disagreements were resolved by discussion. If needed, a third review author was involved (CM). We defined a high-quality study as one that fulfilled six to eight, a moderate-quality study as one that fulfilled three to five and a low-quality study as one that fulfilled zero to two of the eight validity criteria.

Data synthesis and analysis

Data entry (WH) was checked by another author (KB). Discrepancies were resolved by consensus.

Standardized mean differences (SMD) of continuous variables were calculated using means and SDs for each intervention. Examination of the combined results was performed using a random effects model (inverse variance method), because this model is more conservative than the fixed effects model and incorporates both intrastudy and interstudy variances. Pooled estimates of event rates of categorical data (e.g. drop out due to SAE) were calculated using a random effects model. Confidence intervals (95% CI) were calculated for all summary data. We used the I^2 sta-

tistic to identify heterogeneity. Combined results with I^2 >50% were considered substantially heterogeneous [15].

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [14] approach to assess the overall quality of evidence. The quality of evidence was downgraded by one level for each of the following factors that were encountered:

- Limitations of study design: >50% of the participants from studies with a high-risk of bias.
- Inconsistency of results: I^2 >50%.
- Indirectness: we assessed whether the question being addressed in this systematic review was different from the available evidence regarding the population in routine clinical care, if exclusion of patients with clinically relevant somatic disease and/or major mental disorders in the included studies resulted in >=50% of the total patient collective of the systematic review coming from studies in which patients with relevant somatic disease and/or major mental disorders were excluded.
- Imprecision: there was only one trial or when there was more than one trial, the total number of patients was <400 or when the pooled estimate of effect included no effect.

We categorized the quality of evidence as follows [12]:

- High (++++): we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate (+++): we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low (++): our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low (+): we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect; any estimate of effect is very uncertain.

Abstract

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W. Häuser · K. Bernardy · C. Maier

Long-term opioid therapy in chronic noncancer pain. A systematic review and meta-analysis of efficacy, tolerability and safety in open-label extension trials with study duration of at least 26 weeks

Abstract

Background. The efficacy and safety of long-term (≥6 months) opioid therapy (LtOT) in chronic noncancer pain (CNCP) is under debate. A systematic review with meta-analysis of the efficacy and harms of opioids in open-label extension studies of randomized controlled trials (RCTs) has not been conducted until now.

Methods. We screened MEDLINE and clinicaltrials.gov (through to December 2013), as well as reference sections of systematic reviews of long-term RCTs of opioids in CNCP. We included open-label extension trials with a study duration ≥26 weeks of RCTs of ≥2 weeks duration. Using a random effects model, pooled estimates of event rates for categorical data and standardized mean differences (SMD) for continuous variables were calculated.

Results. We included 11 open-label extension studies with 2445 participants with nociceptive (low back, osteoarthritis) and neuropathic (radicular, polyneuropathy) pain. Median study duration was 26 (range 26–108) weeks. Four studies tested oxycodone, two studies tramadol and buprenorphine; hydromorphone, morphine, oxymorphone and tapentadol were each tested in one study. Of the patients randomized at baseline, 28.5% (95% confidence interval, CI, 17.9–39.2%) finished the open-label period; 53.5% (95% CI 38.1–68.2%) of patients entering the open-label period finished the open-label period. In sum, the total loss was 71.5% (95% CI 60.9–83.1%) of all patients primarily included into the RCT. A total of 4.9% (95% CI 2.9–8.2%) of patients dropped out due lack of efficacy; 16.8% (95% CI 11.0–24.8%) dropped out to due adverse events (AE) in the open-label period and 0.08% (95% CI 0.001–0.05%) of patients died during the open-label period. Only one study systematically assessed aberrant drug behavior of the patients: 5.7% (95% CI 3.4–9.6%) showed aberrant drug behavior in the opinion of the investigators and 2.6% (95% CI 1.2–5.8%) were judged to show aberrant drug behavior by independent expert assessment. There was no significant change (p=0.50) in pain intensity between the end of the randomized period and the end of open-label phase (SMD 0.19 [−0.03, 0.41]; six studies with 1360 participants).

Conclusion. Only a minority of patients selected for opioid therapy at randomization finished the long-term open-label study. However, sustained effects of pain reduction could be demonstrated in these patients. LtOT can be considered in carefully selected and monitored CNCP patients who experience clinically meaningful pain reduction with at least tolerable AE in short-term opioid therapy.

Keywords

Chronic noncancer pain · Long-term therapy · Efficacy · Safety · Open-label extension studies

Additional analyses

Subgroup analysis

Provided that at least two studies were available, subgroup analyses were predefined for type of opioid, type of chronic pain syndrome and study sponsoring. These subgroup analyses were also used to examine potential sources of clinical heterogeneity.

Sensitivity analyses

Sensitivity analyses were predefined by excluding studies with imputed means and SDs.

Assessment of publication bias

For analyses with at least 10 studies, we used the Egger intercept test [9] and the Begg rank correlation test [3] at the significance level p<0.05.

Software used for assessment

Comprehensive meta-analysis (Biostat, Englewood, NJ, USA) and the RevMan Analysis software (RevMan 5.2 [44]) of the Cochrane Collaboration were used for statistical analyses.

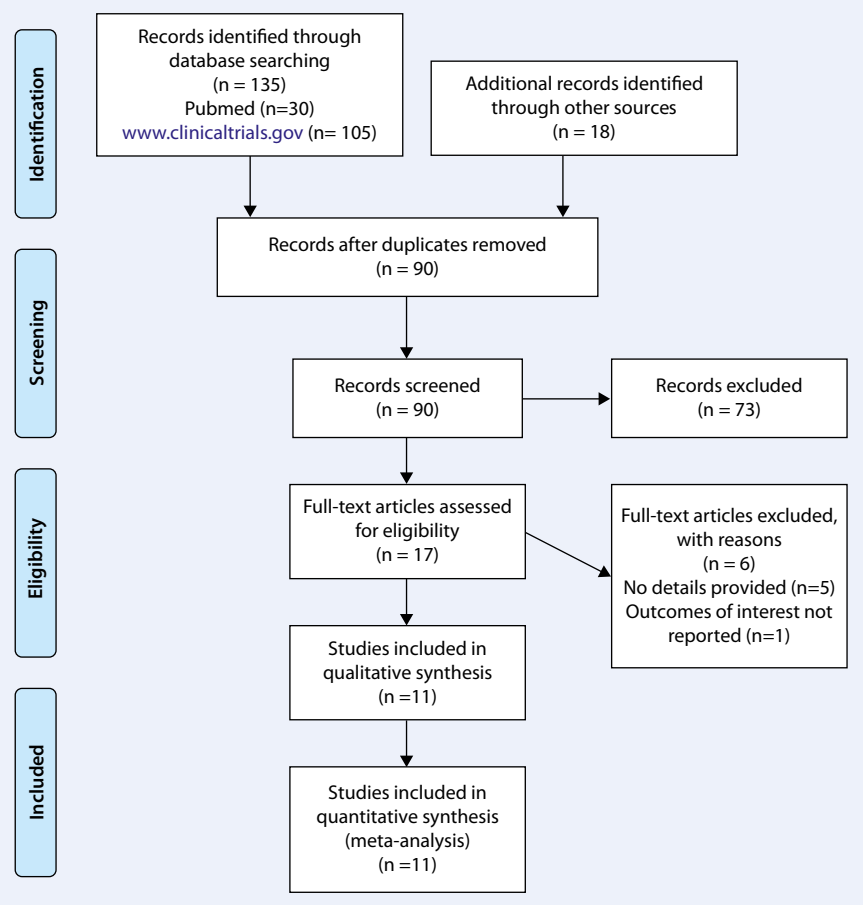

Fig. 1 ▲ Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

Results

Search

After removing duplicates, the literature search produced 90 unique citations. Of these, 74 records were excluded through screening and 16 full-text articles were assessed for eligibility. Five studies (all studies conducted with buprenorphine by Purdue Pharma) did not provide study outcomes in clinicaltrials.gov and one study did not report predefined outcomes. Eleven studies were included in the meta-analysis (see **Fig. 1**).

Study characteristics

See **Tab. 1** for a summary and supplementary table 2 for details.

Settings

All studies were multicenter studies of which eight were conducted in North America, two in Europe and one in more than one continent.

Participants

The meta-analysis included 2445 patients. Only adults were included into the studies. The range of the mean ages of participants in the studies was 32–57 years. The participants were predominantly white. Inclusion criteria were osteoarthritis in four studies, low back pain in two studies, low back pain and osteoarthritis in three studies, and diabetic polyneuropathy pain in one study. One study included patients with low back, osteoarthritis and polyneuropathy pain. One study did not report inclusion criteria. Patients with a history of substance abuse and/or major mental disorder were excluded in all studies but one. One study did not detail whether patients with a history of substance abuse and/or major mental disorder were excluded. All studies excluded patients with critical medical illnesses such as liver and kidney diseases.

Interventions

The duration of the open-label extension period was 84 weeks in one study, 108 weeks in one other study, 52 weeks in two studies and 26 weeks in the remaining studies (see **Tab. 1** for an overview and supplementary table 2 for details). Four studies tested oxycodone, two studies tramadol and buprenorphine, hydromorphone, morphine, oxymorphone and tapentadol were each tested in one study.

Most studies used an individually titrated flexible dosage of an extended-release formulation. The average dosage did not exceed 120 mg/d morphine equivalents, which is considered to be a mostly sufficient and safe dosage [8, 27]: Mean oxycodone dosage was ≤60 mg/day, mean buprenorphine transdermal dosage was <20 µg/h, morphine dosage was ≤120 mg/d, mean tramadol dosage was ≤400 mg/d and mean tapendatol dosage was ≤500 mg/d. Three studies used dosages higher than 120 mg/d morphine equivalents: oxycodone up to 140 mg/d [67], oxycodone up to 80 or 140 mg/d [68, 69]. Four studies reported a slight average increase and three studies reported a slight decrease in opioid dosage from the end of the randomized to the end of open-label phase (see **Tab. 2**).

Quality of evidence

Risk of bias could not be properly assessed in all studies due to poor method reporting. In general, the risk of bias was high for selection, performance and detection bias in all included studies, due to study design. All studies were funded by the manufacturers of the drug (see **Fig. 2** and **Fig. 3** for risk of bias summary and graph). Detailed information regarding risk of bias assessments of every study are given in supplementary table 3.

Synthesis of results

Results are reported with 95% CIs.

Six studies with 1360 participants were entered into an analysis of mean pain intensity at the end of open-label versus at the end of the double-blind period in patients on study medication at the end of the randomized period. There was no significant change (p=0.50) in pain in-

Tab. 1 Overview of open-label extension studies of randomized controlled trials included into the systematic review (grouped by type of opioid in alphabetical order)

Reference; year; countries of study centers	Indication	Number of patients randomized at study entry/included into open-label (%)/finished open-label (% of withdrawal)/total: % of total loss since study entry)	Study medication (all drugs were extended release); mean dosage (mean ± SD)	Duration of open-label trial
Buprenorphine				
Gordon et al. [63] 2010 USA, Canada	Low back pain	79/42 (46.8%)/26 (38.1%)/total: 67.1%	7-day buprenorphine flexible 5 or 10 or 20 µg/h transdermal Mean daily dosage 14.3±5.7 µg/h	26 weeks
Hydromorphone				
Richarz et al. [68] 2013 USA	Low back pain, musculoskeletal pain, neuropathic pain	504/112 (77.8%)/97 (13.4%)/total: 80.8%	Hydromorphone flexible 8–32 mg/d oral or Oxycodone flexible 20–80 mg/d oral Mean daily dosage not reported	28 weeks
Morphine				
Caldwell et al. [61] 2002 USA	Osteoarthritis pain	295/181 (38.6%)/86 (52.5%)/total: 70.8%	Morphine 30 mg/d once daily in the morning or evening oral 42 (49%) remained on 30 mg/d morphine dose; 7 patients increased to 120 mg/d	26 weeks
Oxycodone				
Cloutier et al. [62] 2013 Canada	Low back pain	83/50 (39.8%)/40 (20%)/total: 51.8%	Oxycodone/Naloxone oral flexible 20/10 mg/d or 30/15 mg/d or 40/20 mg/d Mean daily dosage at the end of the open label: 35.1/17.6 mg/d	26 weeks
Portenoy et al. [67] 2007 USA	Osteoarthritis and low back pain	227/39 (82.8%)/not reported/total: not calculable	Oxycodone flexible 20–140 mg/d Overall mean (± SD) daily dose 52.5 (±38.5) mg. range: 10.0–293.5 mg/d	108 weeks
Roth et al. [69] 2000 USA	Osteoarthritis pain	133/106 (20.3%)/15 (85.8%)/total: 88.7%	Oxycodone oral flexible 20–80 mg/d The dose became constant at approximately 40 mg/d by week 16	26 weeks
Sandner-Kiesling 2008 Europe	Osteoarthritis and low back pain	463/258 (44.3%)/243 (5.8%)/total: 47.5%	Oxycodone oral fixed 20 or 40 mg/d 35.6±16.53 mg/d after 2 weeks to 43.7±22.53 mg/d at the end of the extension phase	52 weeks
Oxymorphone				
McIlwain und Ahdieh [66] 2005 USA	Osteoarthritis pain	Not reported/153/61 (60.1%)/total: not calculable	Oxymorphone oral flexible; mean values were 48 mg/d at week 1 and 62 mg/d at week 52	52 weeks
Tapentadol				
Johnson & Johnson [65] US and Europe 2010	Non-malignant low back pain or osteoarthritis knee or hip pain	1154/698 (39.5%)/not reported/total: not calculable	Tapentadol oral flexible 200–500 mg/d The mean total daily dose of tapentadol was 368.2 mg/d	52 weeks
Tramadol				
Harati et al. [64] 2000 USA	Painful Diabetic polyneuropathy	1317/117 (91.1%)/58 (50.4%)/total: 95.6%	Tramadol oral Flexible 100–400 mg/d Mean daily dosage not reported	26 weeks
Thorne et al. [71] 2008 Canada	Osteoarthritis	100/53 (47%)/29 (45.3%)/total: 71%	Tramadol oral flexible 100–400 mg/d The mean daily final dose of tramadol was 313.2±100.1 mg/d compared with 330.2±93.7 mg/d duringthe last week of double-blind active treatment	26 weeks

SD standard deviation.

tensity between these two study periods (SMD 0.19 [−0.03, 0.41], I^2 =62; low-quality evidence; see supplementary figure 1 and **Tab. 3**).

Two studies with 842 participants were entered into an analysis of mean physical function at the end of open-label versus at the end of the double-blind period of patients on study medication at the end of randomized period. There was no significant change (p=0.16) in physical function between these two study periods (SMD −0.10 [−0.23, 0.04], I^2 =0; low-quality evidence; see supplementary figure 2 and **Tab. 3**).

Eleven studies with 2453 participants were entered into an analysis of patients entering/finishing the open-label peri-

Tab. 2 Overview of mean pain scores (baseline, end of double-blind, end of open-label phase) of the opioid groups of open-label extension studies of randomized controlled trials included into the systematic review (grouped by author in alphabetical order)

Reference; year; drug	Pain intensity score baseline mean (SD); (scale)	Pain intensity score at the end of double-blind mean (SD); (scale)	Pain intensity score at the end of double-blind mean (SD); (scale)	Comments
Caldwell et al. [61] 2002 Morphine	313 (107)* (0–500)	Ca 270*,** (0–500)	Ca 260*,** (0–500)	*Group once daily in the morning **Data extracted from figures; mean change reported
Cloutier et al. [62] 2013 Oxycodone	2.5 (0.6) (0–4)	2.1 (0.8) (0–4)	1.8 (0.7) (0–4)	
Gordon et al. [63] 2010 Buprenorphine	62.1 (15.5) (0–100)*	38.5 (7.9) (0–100)**	32.9 (28.1) (0–100)**	*Total group **Buprenorphine group
Harati et al. [64] 2000 Tramadol	2.5 (0.63) (0–4)	1.4 (0.93) (0–4)	1.4 (0.95) (0–4)	
Johnson & Johnson [65] 2010 Tapentadol	Not reported	Not reported	Not reported	Pooled analysis of four studies; no analyses possible
McIlwain und Ahdieh [66] 2005 Oxymorphone	Not reported	Not reported	Not reported	Only data of placebo group switched to oxymorphone available
Portenoy et al. [67] 2007 Oxycodone	Not reported	Not reported	Not reported	Pooled analysis of four studies; no mean pain scores reported; no analyses possible
Richarz et al. [68] 2013 Hydromoprhone Oxycodone	Hydromorphone: 6.8 Oxycodone: 7.0 (0–10)	Hydromorphone: 3.8 Oxycodone: 3.6 (0–10)	Hydromorphone: 3.9 Oxycodone: 4.2 (0–10)	
Roth et al. [69] 2000 Oxycodone	2.5 (0.6) (0–4)	2.0 (0.7)* (0–4)	1.9 (0.8) (0–4)	*Data extracted from figures
Sandner-Kiesling et al. [70] 2010 Oxycodone	No baseline scores reported	3.8 (1.48)	3.8 (1.48)	
Thorne et al. [71] 2008 Tramadol	50.8 (17.3) (0–100)	35.4 (22.7) (0–100)	26.3 (17.9) (0–100)	

SD standard deviation.

od: 53.5% [38.1–68.2%] (I^2 =33.7%) of patients entering the open-label period finished the open-label period (low-quality evidence; see supplementary figure 3).

Eight studies with 1982 participants were entered into an analysis of patients randomized at baseline who finished the open-label period: 28.5% [17.9–39.2%] (I^2 =0%) of patients randomized at baseline finished the open label period (very low-quality evidence; see supplementary figure 4). In sum, the total loss was 71.5% (95% CI 60.9–83.1%) of all patients primarily included into the RCT.

Six studies with 811 patients were entered into an analysis of dropping out due lack of efficacy: 4.9% [2.9–8.2%] (I^2 =9.8%) of patients dropped out due lack of efficacy (low-quality evidence; supplemental figure 5).

Nine studies with 2320 participants were entered into an analysis of patients dropping out due to AE: 16.8% [11.0–24.8%] (I^2 =0) of patients dropped out to due AE in the open-label period (low-quality evidence; supplementary figure 6).

Seven studies with 2148 participants were entered into an analysis of SAE: 9.9% [6.3–15.3%] (I^2 =7.6%) of SAE were reported in the open-label period (low-quality evidence; supplementary figure 7).

Three studies with 1493 patients were entered into an analysis of death during the open label period: 0.08% [0.001–0.05%] (I^2 =85.8%) of patients died during the open-label period (low-quality evidence; supplementary figure 8).

Only one study systematically assessed aberrant drug behavior of the patients. Based on the Research Abuse, Diversion and Addiction-Related Surveillance System (RADAR) [67], 5.7% [3.4–9.6%] of patients showed aberrant drug behavior in the opinion of the investigators and 2.6% [1.2–5.8%] were judged to show aberrant drug behavior upon assessment by independent experts (very low-quality evidence).

Subgroup and sensitivity analyses

Due to the small number of studies we could not perform the predefined subgroup analyses. Removing one study for which we extracted outcomes from figures did not change the results of the analysis of pain intensity at the start and at the end of the open-label period of patients on study medication at the end of randomized period.

Heterogeneity

There was substantial heterogeneity in the outcomes pain intensity (I^2 =62%) and death (I^2 =58.8%).

Publication bias

The Kendall tau of the Begg rank correlation test of the pooled estimate of patients entering/finishing open-label period was not significant (tau =0.16, p-value two-tailed =0.13). The Egger intercept of the pooled estimate of patients entering/finishing open-label period was not significant (intercept =0.12, p-value two-tailed =0.91)

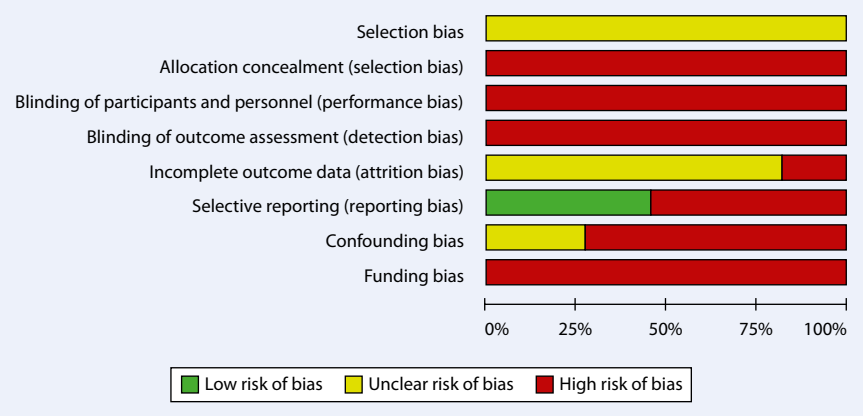

Fig. 2 ▲ Risk of bias graph

Fig. 3 ◀ Risk of bias summary

Discussion

Our review challenges the conclusion of recent systematic reviews on LtOT (>6 months) in CNCP that there is a lack of literature on LtOT in CNCP [20, 25]. This statement is, however, valid for placebo-controlled studies [41, 46, 52]. This review demonstrates—despite the limitations of open-label trials including only about one third of the primarily enrolled patients discussed later—a sustained efficacy of LtOT in chronic nociceptive (low back and osteoarthritis) and neuropathic (radicular and polyneuropathy) pain in open-label extension studies of RCTs. The mean average reductions in pain and disability were maintained from the end of the double-blind to the end of the open-label period up to 3 years later. However, average pain scores are unrepresentative of patient experience and of very limited utility [33, 34]. None of the open-label extension studies reported the number of patients with a clinically significant (30 or 50%) pain reduction (responders). However, we assume that only patients with any benefit were treated after the RCT. Considering the high loss of patients (about 75%) for various reasons, there would be a long-term response rate (portion) of about 25% in CNCP. This remarkable result is in line with that of a short-term RCT with strict inclusion criteria such as failure of guideline-based pretreatment [24]. The findings from open-label extension studies also concur with the results of long-term case series with selected patients of clinical centers. Of 121 patients at a German pain center, 103 (85%) still took an opioid after an average treatment time of 66 months (37–105 months; 87% more than 5 years) [23]. At a US pain center, 84 patients were followed-up every 3 months for a median of 11 years. Most patients in the total sample reported 50% or greater pain relief and a moderate improvement in disability [57].

These case series [23, 24, 57] did not report a significant increase in opioid dosage in the long-run. The findings are in line with the results of the open-label extension studies: the average dosage of opioids did not substantially increase in most studies. However, these outcomes were not reported by two studies. Only one study reported the range of dosages; the other studies reported only mean values. Therefore the percentage of patients with a high-dosage therapy (>120 mg morphine equivalent) remains unknown.

Only 5% of the patients of the reviewed studies ended therapy due to a lack of efficacy. This finding does not support the position of Sullivan [53] that most patients in open-label extension studies stopped opioids due to a lack of efficacy.

Tab. 3 Effect sizes of opioids (end of double-blind vs. end of open-label extension period) on selected outcome variables

Outcome title	Number of studies	Number of patients	SMD [95% CI]	Test for overall effect p-value	Heterogeneity I^2 (%)
Pain	6	1376	0.18 [−0.03, 0.40]	0.10	63
Disability	2	842	−0.10 [−0.23, 0.04]	0.16	0

SMD standardized mean difference, *CI* confidence interval.

Most notably, the positive effects of opioids in long-term open-label studies cannot be disentangled from those of cotherapies not controlled for, from unspecific (placebo) effects because of the lack of a placebo group [14] or from spontaneous recovery [18] because of the lack of a no treatment group.

The external validity of open-label extension studies was comprised by a highly selected group of patients without major medical diseases or mental disorders. The self-selected group of patients who were willing to participate in the open-label extension studies does not permit a clear conclusion on the long-term efficacy of opioids in routine clinical care [53].

This review found no increase in side effects in open-label extension studies, indicating safety of LtOT in chronic nociceptive (low back and osteoarthritis) and neuropathic (radicular and polyneuropathy) pain. Again, these findings are biased by low-quality evidence: the rates of SAEs were not reported in three studies and death rates were not reported in eight studies. Aberrant drug behavior was systematically assessed in only one study. The safety assessments in the four studies with tapentadol [65] included the Subjective Opiate Withdrawal Scale (SOWS) [13], which assesses opioid withdrawal by rapid opioid detoxication but not signs of abuse or addiction. We do not know if prescription opioid abuse was really rare in open-label extension studies or whether it was underestimated because of lack of assessment. In addition, there is uncertainty as to whether assessments of aberrant drug behavior were deliberately not conducted in order to conceal this SAE or because of a lack of standardized instruments.

The rates of abuse of prescribed opioids were higher in studies with clinical and population-based samples. In a systematic review of 67 studies, the rate of opioid abuse and addiction varied between 0.2 and 3.3%. The overall rates of aberrant drug behavior were between 15 and 20% [10]. In most of the studies reviewed, patients with mental disorders were excluded. In cohort studies without these exclusion criteria, abuse rates tended to be higher [53]. In an US primary care disease management program for opioid-treated patients with a high burden of comorbid mental disorders, substance abuse was documented in 32% of the patients during the 3-month multidisciplinary program [5]. However, differences between countries in the availability of opioids and of nonpharmacological interventions for chronic pain must be kept in mind. In countries where it is comparatively easy to prescribe opioids as compared to other chronic pain therapies, the rates of aberrant drug behavior might be higher. A longitudinal population-based Danish study identified at least two of the six addictive behaviors in 22.6% of the long-term opioid users with chronic pain compared to 11.5% of the nonopioid users with chronic pain and 8.9% of the individuals without chronic pain [16]. An US study with one national, commercially insured population and one state-based, publicly insured population reported that among users of chronic opioid therapy, 3% of both samples had a claims-based opioid abuse/dependency diagnosis. Mental health and substance use disorders were associated with an increased risk of opioid abuse/dependence [7, 8]. In contrast, in a cohort of new opioid users in a nationwide Norwegian prescription database who started treatment with weak opioids, only 0.3 and 0.08% developed prescription patterns indicating persistent opioid use and problematic opioid use, respectively, within 3 years [49]. Unfortunately, data on opioid prescription abuse from larger cohorts of health insurance companies in Germany are lacking. Case series of highly selected patients at a German tertiary care pain center demonstrated that problematic use, noncompliance, concealed use of other drugs and SAE were not major issues [19, 23]. However, abuse of prescribed opioids was reported in 4% of patients at a German pain center [56].

During recent years, a growing body of data has indicated that in elder patients with osteoarthritis, the overall mortality is higher among opioid-treated than among nonsteroidal anti-inflammatory drug (NSAID)-treated patients, despite a lower risk of GI bleeding [51]. Most of these alarming data came from the US, where prescription of mainly short-acting opioids is also the major cause of unintended deaths due to fatal overdose [53]. The underlying pathomechanisms of the reported increased risk of cardiovascular events is still unclear. However, there are some case series on the association between opioid treatment and sleep apnea, which is a well-known risk factor for stroke and myocardial infarction [11, 31, 55, 60]. Other risks of opioids not reported by open-label extension studies are walking disturbances, increased risk of falls and increased risk of hip, leg and radial fractures [22, 51]. In contrast to previous findings that long-term treatment facilitates osteoporosis, Li et al. [22] recently demonstrated that the risk of fracture predominantly elevates only in the first period of opioid prescription, presumably due to titration errors, and then declines—even after years of treatment. Nevertheless, neither the cardiovascular risks, nor sleep apnea or fracture were documented in the majority of the long-term open-label studies, highlighting the limitations of this type of study for detecting (unexpected) to side effects, even if these are obviously common and potentially life-threatening.

The death rates during the open-label extension phases were very low. These findings are in contrast to findings in the general US population. There were approximately 15,000 prescription overdose deaths in the USA in 2008, which is 3-times higher than in 1999 [53]. In the US, opioid analgesics are now responsible for more deaths than suicide and motor vehicle crashes, as well as for more deaths

Infobox 1: Excluded (for all studies: no details provided)

1. Purdue Pharma. Safety of BTDS in Subjects With Osteoarthritic (OA) Pain of Hip or Knee: A 6-Month Open-label Extension Phase. NCT01141283. http://clinicaltrials.gov/ct2/show/NCT01141283?term=NCT01141283&rank=1. Accessed December 28,2013
2. Purdue Pharma. Safety of BTDS in Subjects With Low Back Pain: A 52-Week Extension Phase of BUP3015. NCT01125917. http://clinicaltrials.gov/ct2/show/NCT01125917?term=NCT01125917&rank=1
3. Purdue Pharma. Safety of Buprenorphine Transdermal Systems in Subjects With Chronic Nonmalignant Pain—a 28-week Extension Study. NCT01151098. http://clinicaltrials.gov/ct2/show/NCT01151098?term=NCT01151098&rank=1
4. Purdue Pharma. Safety of Buprenorphine Transdermal Patch (BTDS) in Osteoarthritis Pain: a 52-Week Extension Phase. NCT01135524. http://clinicaltrials.gov/ct2/show/NCT01135524?term=NCT01135524&rank=1
5. Miller K, Yarlas A, Wen W, Dain B, Lynch SY, Brennan MJ, Ripa SR. Buprenorphine transdermal system and quality of life in opioid-experienced patients with chronic low back pain [30] (no placebo, but active control double-blind; safety data of open-label period not reported).

than cocaine and heroin combined [26]. Death rates were associated with male gender, poverty, doctor shopping and dosages >100 mg morphine equivalents per day [53]. Again, robust data from European countries on opioid therapy-associated deaths are lacking. Preliminary data from the UK and Germany suggest that both countries do not currently face an "opioid epidemic" of US and Norwegian dimensions [42, 49, 58].

In summary, the harms (abuse of prescribed opioids, mortality) of LtOT in clinical practice are underestimated by long-term extension studies, probably because patients with major medical diseases and mental disorders were excluded. In addition, the study context may not replicate clinical practice in terms of the intensity of monitoring, the experience of the prescribing physician and the willingness to respond to specific patient complaints [67].

The limitations of the review are as follows: we might have missed published open-label extension studies by our search strategy. The results of some published open-label extension studies have not yet been published. We might have underestimated the quality of studies because we did not ask the authors for missing details.

Conclusion

The evidence on long-term efficacy of opioids in CNCP is limited by the reporting of average pain scores. Drug approval agencies should require pain responder analyses instead of reports of average pain scores of open-label extension studies.

The evidence on safety is limited by the lack of assessment of relevant AE in routine clinical care. The majority of studies did not systematically assess aberrant drug behavior. Internationally accepted definitions of dependence and addiction are required for prescribed opioids [1]. The Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities and Networks (ACTTION) public–private partnership convened an expert panel to develop mutually exclusive and exhaustive consensus classifications and definitions to estimate misuse, abuse and related events (MAREs) occurring in clinical trials of analgesic medications to increase accuracy and consistency in characterizing their occurrence and prevalence in clinical trials [50]. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) convened a consensus meeting to review the available evidence and discuss methods for improving the assessment of the abuse liability (AL) for analgesics in clinical trials in patients with pain. Recommendations for improved assessment included improving assessment of AL in clinical trials (e.g. training study personnel in the principles of abuse and addiction behaviors, designing the trial to assess AL outcomes as primary or secondary outcome measures depending on the trial objectives), performing standardized assessment of outcomes, including targeted observations by study personnel and using structured AE query forms that ask all subjects specifically for certain symptoms (such as euphoria and craving) and collecting detailed information about events of potential concern (e.g. unexpected urine drug testing results, loss of study medication and dropping out of the trial) [39]. These instruments should be used in analgesic clinical trials and postmarketing AE surveillance and monitoring. Brief validated measures of patient-reported safety, efficacy and misuse must be developed for primary care prescribers [2].

The long-term efficacy and safety of opioids in NCCP will most probably be more reliably assessed by cohort studies of health insurance companies and the clinical registers of pain centers than it will be by open-label studies sponsored by the manufacturer of the drug.

In summary, LtOT can be considered in carefully selected and monitored CNCP patients who experience a clinically meaningful pain reduction with at least tolerable AE in short-term opioid therapy. Careful monitoring of these patients and the prescription of mean dosages of opioid equivalents less than 120 mg/d [8, 27] have been recommended to decrease the risk of harms caused by LtOT. The opioid epidemic in the US highlights the need for psychosocial services in chronic pain management [17].

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Compliance with ethical guidelines

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The accompanying manuscript does not include studies on humans or animals.

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