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English version of „Langzeittherapie mit Opioiden bei chronischem nicht- tumorbedingtem Schmerz”

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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**

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| --- |
| **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 non- cancer pain (CNCP) are increasing in western countries including Germany [47, 53]. Despite the several available ev- idence-based guidelines [37], the effica- cy of LtoT remains controversial for the following reasons: Firstly, although ran- domized 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 hither- to 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 medi- cine 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 opi- oid prescriptions, as well as of abuse of prescribed opioids and associated deaths in the US have been highlighted in edito- rials [40, 48]. There is thus no consistent good-quality evidence available for giv- ing 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 stud- ies of RCTs have been summarized by sys- tematic 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 system- atic review were as follows: to assess the long-term efficacy and harms of opioids in any type of CNCP in open-label exten- sion studies of RCTs with opioids. Specif- ically, we studied how many patients re- mained on opioid therapy, reported a sus- tained reduction of pain and disability or experienced serious harms (serious ad- verse events, SAE; death, aberrant drug behavior) in the long-term (≥6 months).

# Methods

The review was performed according to the Preferred Reporting Items for System- atic Reviews and Meta-Analyses (PRIS- MA) statement [32] and the recommen- dations of the Cochrane Collaboration [15].

Methods of analysis and inclusion cri- teria were specified in advance.

## Eligibility criteria

### Types of studies

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

The English full-text version of this article is free- ly available at SpringerLink (under“Supplemen- tary 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 se- ries studies, because these studies are as- sociated 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

F Efficacy: number of patients who

were on opioids at the end of open- label (related to the number of pa- tients randomized at baseline and to the number of patients included into open-label); changes in pain and dis- ability at the end of open-label com- pared to the end of randomized trial in patients on study medication at the end of the randomized period.

F 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 ab- errant drug behavior; death during open label

Outcome measures must have been vali- dated or used as a standard of care to be included in the analyses. In addition to these general inclusion criteria, we em- ployed two criteria for efficacy outcomes:

* 1. pain and disability outcomes must have been patient-reported; (2) outcome data must not have been collected retro- spectively (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 re- views [21, 41, 46, 52] for open-label ex- tension periods. These reviews updat- ed and expanded the literature search of the first version of the German guidelines on the long-term administration of opi- oids (LONTS), which searched the litera- ture up until October 2008 [43]. The up- dated and expanded search included the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Sco- pus from October 2008 to October 2013. Our search included all languages.

Two review authors (KB, WH) screened the references in recent system- atic reviews on long-term treatment of opioids in CNCP [20, 25, 36] for open-la- bel 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 “oyx- morphone” 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 da- ta from the full-text articles and entered the data independently into standard ex- traction forms (KB, WH). We extract- ed characteristics of patients and stud- ies, descriptions of the experimental and control groups, cointerventions, author affiliations and study sponsoring. Dis- agreements were resolved by consensus. If needed, a third review author was in- volved (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 stan- dard deviations (SDs) were not available for continuous data, we attempted to de- termine 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 fig- ures, these were extracted from figures.

## Risks of bias assessment

Two authors (KB, WH) independently as- sessed the risk of bias in each trial using eight domains recommended by the Co- chrane Collaboration: selection bias, per- formance bias, detection bias, attrition bi- as, reporting bias, selection bias, perfor- mance bias, detection bias and funding bi- as [15]. We slightly modified one item of the tool (selection bias) to adapt to the set- ting of an open-label extension trial (see supplementary table 1). The criteria were scored as “yes”, “no” or unclear”. Any dis- agreements were resolved by discussion. If needed, a third review author was in- volved (CM). We defined a high-quali- ty study as one that fulfilled six to eight, a moderate-quality study as one that ful- filled 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 us- ing means and SDs for each intervention. Examination of the combined results was performed using a random effects mod- el (inverse variance method), because this model is more conservative than the fixed effects model and incorporates both intra- study and interstudy variances. Pooled es- timates of event rates of categorical data (e.g. drop out due to SAE) were calculat- ed using a random effects model. Confi- dence intervals (95% CI) were calculated for all summary data. We used the I2 sta-

tistic to identify heterogeneity. Combined results with I2 >50% were considered sub- stantially heterogeneous [15].

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|  | **Abstract** |
|  | Schmerz 2014 · [jvn]:[afp]–[alp] DOI 10.1007/s00482-014-1428-0  © Deutsche Schmerzgesellschaft e.V. Published by Springer-Verlag Berlin Heidelberg - all rights reserved 2014  **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- 83.1%) of all patients primarily included in- term (≥6 months) opioid therapy (LtOT) in to the RCT. A total of 4.9% (95% CI 2.9–8.2%) chronic noncancer pain (CNCP) is under de- of patients dropped out due lack of effica- bate. A systematic review with meta-analysis cy; 16.8% (95% CI 11.0–24.8%) dropped out of the efficacy and harms of opioids in open- to due adverse events (AE) in the open-la- label extension studies of randomized con- bel period and 0.08% (95% CI 0.001–0.05%) trolled trials (RCTs) has not been conducted of patients died during the open-label peri- until now. od. Only one study systematically assessed **Methods.** We screened MEDLINE and clin- aberrant drug behavior of the patients: 5.7% icaltrials.gov (through to December 2013), (95% CI 3.4–9.6%) showed aberrant drug be- as well as reference sections of systemat- havior in the opinion of the investigators  ic reviews of long-term RCTs of opioids in and 2.6% (95% CI 1.2–5.8%) were judged to CNCP. We included open-label extension tri- show aberrant drug behavior by indepen- als with a study duration ≥26 weeks of RCTs dent expert assessment. There was no signif- of ≥2 weeks duration. Using a random effects icant change (p=0.50) in pain intensity be- model, pooled estimates of event rates for tween the end of the randomized period categorical data and standardized mean dif- and the end of open-label phase (SMD 0.19 ferences (SMD) for continuous variables were [−0.03, 0.41]; six studies with 1360 partici- calculated. pants).  **Results.** We included 11 open-label exten- **Conclusion.** Only a minority of patients se- sion studies with 2445 participants with no- lected for opioid therapy at randomization ciceptive (low back, osteoarthritis) and neu- finished the long-term open-label study. ropathic (radicular, polyneuropathy) pain. However, sustained effects of pain reduc- Median study duration was 26 (range 26– tion could be demonstrated in these patients.  108) weeks. Four studies tested oxycodone, LtOT can be considered in carefully select- two studies tramadol and buprenorphine; hy- ed and monitored CNCP patients who expe- dromorphone, morphine, oxymorphone and rience clinically meaningful pain reduction tapentadol were each tested in one study. Of with at least tolerable AE in short-term opi- the patients randomized at baseline, 28.5% oid therapy.  (95% confidence interval, CI, 17.9–39.2%) fin-  ished the open-label period; 53.5% (95% CI **Keywords**  38.1–68.2%) of patients entering the open-la- Chronic noncancer pain · Long-term therapy · bel period finished the open-label period. In Efficacy · Safety · Open-label extension  sum, the total loss was 71.5% (95% CI 60.9– studies |

We used the Grading of Recommenda- tions Assessment, Development and Eval- uation (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:

F Limitations of study design: >50% of

the participants from studies with a high-risk of bias.

F Inconsistency of results: I2 >50%.

F Indirectness: we assessed whether the

question being addressed in this sys- tematic review was different from the available evidence regarding the pop- ulation in routine clinical care, if ex- clusion of patients with clinically rel- evant somatic disease and/or ma-

jor mental disorders in the included studies resulted in >=50% of the to- tal patient collective of the systematic review coming from studies in which patients with relevant somatic disease and/or major mental disorders were excluded.

F Imprecision: there was only one tri-

al or when there was more than one trial, the total number of patients was <400 or when the pooled esti- mate of effect included no effect.

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

F High (++++): we are very confident

that the true effect lies close to that of the estimate of the effect.

F Moderate (+++): we are moderate-

ly 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 dif- ferent.

F Low (++): our confidence in the effect

estimate is limited; the true effect may be substantially different from the es- timate of the effect.

F Very low (+): we have very little con-

fidence in the effect estimate; the true effect is likely to be substantially dif- ferent from the estimate of effect; any estimate of effect is very uncertain.

## Additional analyses

### Subgroup analysis

Provided that at least two studies were available, subgroup analyses were pre- defined for type of opioid, type of chron- ic pain syndrome and study sponsoring. These subgroup analyses were also used to examine potential sources of clinical het- erogeneity.

### 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 sig- nificance 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** 8Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

**Included**

### Interventions

The duration of the open-label exten- sion period was 84 weeks in one study, 108 weeks in one other study, 52 weeks in two studies and 26 weeks in the remain-

Records identified through database searching

(n = 135)

Pubmed (n=30) [www.clinicaltrials.gov](http://www.clinicaltrials.gov/) (n= 105)

Additional records identified through other sources

(n = 18)

Records after duplicates removed (n = 90)

Records screened (n = 90)

Records excluded (n = 73)

Full-text articles assessed for eligibility

(n = 17)

Studies included in qualitative synthesis (n =11)

Full-text articles excluded, with reasons

(n = 6)

No details provided (n=5) Outcomes of interest not reported (n=1)

Studies included in quantitative synthesis (meta-analysis)

(n =11)

ing studies (see . **Tab. 1** for an overview

and supplementary table 2 for details). Four studies tested oxycodone, two stud- ies tramadol and buprenorphine, hydro- morphone, morphine, oxymorphone and tapentadol were each tested in one study. Most studies used an individually ti- trated flexible dosage of an extended- release formulation. The average dos- age 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 dos- age 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 av- erage 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**).

# Results

**Eligibility**

**Screening**

**Identification**

## 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 as- sessed for eligibility. Five studies (all stud- ies 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 supple- mentary 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 stud- ies. The range of the mean ages of partic- ipants 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 polyneu- ropathy pain. One study did not report in- clusion criteria. Patients with a history of substance abuse and/or major mental dis- order 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.

## Quality of evidence

Risk of bias could not be properly assessed in all studies due to poor method report- ing. 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 in- tensity at the end of open-label versus at the end of the double-blind period in pa- tients on study medication at the end of the randomized period. There was no significant change (p=0.50) in pain in-

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| **Tab. 1** Overview of open-label extension studies of randomized controlled trials included into the systematic review (grouped by type of opi- oid 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 re- lease); 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 trans- dermal  Mean daily dosage 14.3±5.7 μg/h | 26 weeks |
| *Hydromorphone* | | | | |
| Richarz et al. [68] 2013  USA | Low back pain, mus- culoskeletal pain, neuropathic pain | 504/112 (77.8%)/97 (13.4%)/total:  80.8% | Hydromorphone flexible 8–32 mg/d oral or Oxyco- done 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 eve- ning oral  42 (49%) remained on 30 mg/d morphine dose; 7 pa- tients increased to 120 mg/d | 26 weeks |
| *Oxycodone* | | | | |
| Cloutier et al. [62] | Low back pain | 83/50 (39.8%)/40 (20%)/total: | Oxycodone/Naloxone oral flexible 20/10 mg/d or | 26 weeks |
| 2013 |  | 51.8% | 30/15 mg/d or 40/20 mg/d |  |
| Canada |  |  | Mean daily dosage at the end of the open label: |  |
|  |  |  | 35.1/17.6 mg/d |  |
| 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 Ah- | Osteoarthritis pain | Not reported/153/61 (60.1%)/ | Oxymorphone oral flexible; mean values were | 52 weeks |
| dieh [66] |  | total: not calculable | 48 mg/d at week 1 and 62 mg/d at week 52 |  |
| 2005 |  |  |  |  |
| USA |  |  |  |  |
| *Tapentadol* | | | | |
| Johnson & Johnson | Non-malignant low | 1154/698 (39.5%)/not reported/ | Tapentadol oral flexible 200–500 mg/d | 52 weeks |
| [65] | back pain or osteo- | total: not calculable | The mean total daily dose of tapentadol was |  |
| US and Europe | arthritis knee or hip |  | 368.2 mg/d |  |
| 2010 | pain |  |  |  |
| *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] | Osteoarthritis | 100/53 (47%)/29 (45.3%)/total: | Tramadol oral flexible 100–400 mg/d | 26 weeks |
| 2008 |  | 71% | The mean daily final dose of tramadol was |  |
| Canada |  |  | 313.2±100.1 mg/d compared with 330.2±93.7 mg/d |  |
|  |  |  | duringthe last week of double-blind active treatment |  |
| *SD* standard deviation. | | | | |

tensity between these two study periods (SMD 0.19 [−0.03, 0.41], I2 =62; low-qual-

ity evidence; see supplementary figure 1 and . **Tab. 3**).

Two studies with 842 participants were entered into an analysis of mean physi-

cal function at the end of open-label ver- sus at the end of the double-blind peri- od 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 peri-

ods (SMD −0.10 [−0.23, 0.04], I2 =0; low-

quality evidence; see supplementary fig- ure 2 and . **Tab. 3**).

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

od: 53.5% [38.1–68.2%] (I2 =33.7%) of pa-

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

tients entering the open-label period fin- ished 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%] (I2 =0%) of patients randomized at base- line 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 pri- marily included into the RCT.

Six studies with 811 patients were en- tered into an analysis of dropping out due lack of efficacy: 4.9% [ 2.9–8.2%] (I2 =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%] (I2 =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%] (I2 =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 dur- ing the open label period: 0.08% [0.001– 0.05%] (I2 =85.8%) of patients died dur- ing the open-label period (low-quality ev-

idence; supplementary figure 8).

Only one study systematically assessed aberrant drug behavior of the patients. Based on the Research Abuse, Diversion and Addiction-Related Surveillance Sys- tem (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 inde- pendent experts (very low-quality evi- dence).

## Subgroup and sensitivity analyses

Due to the small number of studies we could not perform the predefined sub- group analyses. Removing one study for which we extracted outcomes from fig- ures did not change the results of the anal- ysis of pain intensity at the start and at the end of the open-label period of patients on study medication at the end of random- ized period.

## Heterogeneity

There was substantial heterogeneity in the outcomes pain intensity (I2 =62%) and death (I2 =58.8%).

## Publication bias

The Kendall tau of the Begg rank corre- lation test of the pooled estimate of pa- tients entering/finishing open-label peri- od was not significant (tau =0.16, p-val- ue two-tailed =0.13). The Egger intercept of the pooled estimate of patients enter- ing/finishing open-label period was not significant (intercept =0.12, p-value two- tailed =0.91)

Confounding bias

Funding bias

**Fig. 2** 8Risk of bias graph

Selection bias Allocation concealment (selection bias)

Blinding of participants and personnel (performance bias) Blinding of outcome assessment (detection bias) Incomplete outcome data (attrition bias) Selective reporting (reporting bias)

Confounding bias

Funding bias

0% 25%

50%

75% 100%

Low risk of bias Unclear risk of bias High risk of bias



Caldwell 2002 **? – – – ? – – –**

Cloutier 2013 **? – – – ? – – –**

Gordon 2010 **? – – – ? – ? –**

Harati 2000 **? – – – ? + ? –**

Johnson & Johnson 2010 **? – – – ? + – –**

McIlwain 2005 **? – – – ? – – –**

Portenoy 2007 **? – – – ? + ? –**

Richarz 2013 **? – – – ? + – –**

Roth 2000 **? – – – – – – –**

Sandner-Kiesling 2010 **? – – – ? + – –**

Thorne 2008 **? – – – – – – –**

Selection bias

Allocation concealment (selection bias)

Blinding of participants and personnel (performance bias)

Blinding of outcome assessment (detection bias)

Incomplete outcome data (attrition bias)

Selective reporting (reporting bias)

# 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].

**Fig. 3** 9Risk of bias summary

This statement is, however, valid for pla- cebo-controlled studies [41, 46, 52]. This review demonstrates—despite the limita- tions of open-label trials including only about one third of the primarily enrolled patients discussed later—a sustained effi-

cacy of LtOT in chronic nociceptive (low back and osteoarthritis) and neuropath- ic (radicular and polyneuropathy) pain in open-label extension studies of RCTs. The mean average reductions in pain and dis- ability were maintained from the end of the double-blind to the end of the open- label period up to 3 years later. Howev- er, average pain scores are unrepresenta- tive of patient experience and of very lim- ited utility [33, 34]. None of the open-la- bel extension studies reported the num- ber 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 (por- tion) of about 25% in CNCP. This remark- able result is in line with that of a short- term RCT with strict inclusion criteria such as failure of guideline-based pretreat- ment [24]. The findings from open-label extension studies also concur with the re- sults of long-term case series with select- ed patients of clinical centers. Of 121 pa- tients at a German pain center, 103 (85%) still took an opioid after an average treat- ment 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 im- provement in disability [57].

These case series [23, 24, 57] did not re- port a significant increase in opioid dos- age in the long-run. The findings are in line with the results of the open-label ex- tension studies: the average dosage of opi- oids 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 mor- phine equivalent) remains unknown.

Only 5% of the patients of the reviewed studies ended therapy due to a lack of ef- ficacy. 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.

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **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 I2 (%)** |
| 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. | | | | | |

The external validity of open-label ex- tension studies was comprised by a high- ly selected group of patients without ma- jor 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 effica- cy of opioids in routine clinical care [53]. This review found no increase in side effects in open-label extension studies, in- dicating safety of LtOT in chronic noci- ceptive (low back and osteoarthritis) and neuropathic (radicular and polyneurop- athy) pain. Again, these findings are bi- ased 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 sys- tematically 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 prescrip- tion opioid abuse was really rare in open- label extension studies or whether it was underestimated because of lack of assess- ment. 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 opi- oids were higher in studies with clinical and population-based samples. In a sys- tematic review of 67 studies, the rate of

opioid abuse and addiction varied be- tween 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 with- out these exclusion criteria, abuse rates tended to be higher [53]. In an US prima- ry care disease management program for opioid-treated patients with a high bur- den of comorbid mental disorders, sub- stance abuse was documented in 32% of the patients during the 3-month multi- disciplinary program [5]. However, differ- ences between countries in the availabil- ity of opioids and of nonpharmacologi- cal 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 ther- apies, the rates of aberrant drug behavior might be higher. A longitudinal popula- tion-based Danish study identified at least two of the six addictive behaviors in 22.6% of the long-term opioid users with chron- ic pain compared to 11.5% of the nonopi- oid users with chronic pain and 8.9% of the individuals without chronic pain [16]. An US study with one national, commer- cially insured population and one state- based, publicly insured population re- ported that among users of chronic opioid therapy, 3% of both samples had a claims- based opioid abuse/dependency diagno- sis. Mental health and substance use dis- orders were associated with an increased risk of opioid abuse/dependence [7, 8]. In contrast, in a cohort of new opioid us- ers in a nationwide Norwegian prescrip- tion database who started treatment with weak opioids, only 0.3 and 0.08% devel- oped prescription patterns indicating per- sistent opioid use and problematic opioid use, respectively, within 3 years [49]. Un- fortunately, data on opioid prescription abuse from larger cohorts of health insur-

ance companies in Germany are lacking. Case series of highly selected patients at a German tertiary care pain center dem- onstrated that problematic use, noncom- pliance, concealed use of other drugs and SAE were not major issues [19, 23]. How- ever, abuse of prescribed opioids was re- ported 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 low- er risk of GI bleeding [51]. Most of these alarming data came from the US, where prescription of mainly short-acting opi- oids is also the major cause of unintended deaths due to fatal overdose [53]. The un- derlying pathomechanisms of the report- ed 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]. Oth- er risks of opioids not reported by open- label extension studies are walking dis- turbances, increased risk of falls and in- creased risk of hip, leg and radial fractures [22, 51]. In contrast to previous findings that long-term treatment facilitates osteo- porosis, Li et al. [22] recently demonstrat- ed that the risk of fracture predominant- ly elevates only in the first period of opi- oid prescription, presumably due to titra- tion errors, and then declines—even after years of treatment. Nevertheless, neither the cardiovascular risks, nor sleep apnea or fracture were documented in the ma- jority 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 com- mon and potentially life-threatening.

The death rates during the open-la- bel extension phases were very low. These findings are in contrast to findings in the general US population. There were ap- proximately 15,000 prescription over- dose 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

than cocaine and heroin combined [26].

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 underes- timated the quality of studies because we did not ask the authors for missing details.

### Conclusion

**Infobox 1:** Excluded (for all stud- ies: no details provided)

1. Purdue Pharma. Safety of BTDS in Sub- jects With Osteoarthritic (OA) Pain of Hip or Knee: A 6-Month Open-label Extension Phase. NCT01141283. [http://clinicaltrials.](http://clinicaltrials/) gov/ct2/show/NCT01141283?term=NCT 01141283&rank=1. Accessed December 28,2013
2. Purdue Pharma. Safety of BTDS in Sub- jects With Low Back Pain: A 52-Week Ex- tension Phase of BUP3015. NCT01125917. <http://clinicaltrials.gov/ct2/show/NCT011> 25917?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

1. Purdue Pharma. Safety of Buprenorphine Transdermal Patch (BTDS) in Osteoar- thritis Pain: a 52-Week Extension Phase. NCT01135524. <http://clinicaltrials.gov/> ct2/show/NCT01135524?term=NCT0113 5524&rank=1
2. 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).

#### The evidence on long-term efficacy of opioids in CNCP is limited by the report- ing of average pain scores. Drug approv- al agencies should require pain respond- er analyses instead of reports of aver- age pain scores of open-label extension studies.

**The evidence on safety is limited by the lack of assessment of relevant AE in rou- tine clinical care. The majority of stud- ies did not systematically assess aberrant drug behavior. Internationally accept-**

**ed definitions of dependence and addic- tion are required for prescribed opioids [1]. The Analgesic, Anesthetic, and Addic- tion Clinical Trials, Translations, Innova- tions, Opportunities and Networks (ACT- TION) public–private partnership con- vened an expert panel to develop mu- tually exclusive and exhaustive consen- sus classifications and definitions to es- timate misuse, abuse and related events (MAREs) occurring in clinical trials of an-**

**tailed information about events of po- tential concern (e.g. unexpected urine drug testing results, loss of study medi- cation and dropping out of the trial) [39]. These instruments should be used in an- algesic clinical trials and postmarket-**

**ing AE surveillance and monitoring. Brief validated measures of patient-reported safety, efficacy and misuse must be de- veloped for primary care prescribers [2]. The long-term efficacy and safety of opi- oids in NCCP will most probably be more reliably assessed by cohort studies of health insurance companies and the clin- ical 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 thera- py. 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 opi- oid epidemic in the US highlights the need for psychosocial services in chronic pain management [17].**

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Death rates were associated with male

#### algesic medications to increase accura-

gender, poverty, doctor shopping and dos- ages >100 mg morphine equivalents per day [53]. Again, robust data from Europe- an 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 dimen- sions [42, 49, 58].

In summary, the harms (abuse of pre- scribed opioids, mortality) of LtOT in clinical practice are underestimated by long-term extension studies, probably be- cause patients with major medical diseas- es and mental disorders were excluded. In addition, the study context may not rep- licate clinical practice in terms of the in- tensity of monitoring, the experience of the prescribing physician and the willing- ness to respond to specific patient com- plaints [67].

The limitations of the review are as follows: we might have missed published

#### cy and consistency in characterizing their occurrence and prevalence in clinical tri- als [50]. The Initiative on Methods, Mea- surement, and Pain Assessment in Clini- cal Trials (IMMPACT) convened a consen- sus meeting to review the available evi- dence and discuss methods for improv- ing the assessment of the abuse liability (AL) for analgesics in clinical trials in pa- tients with pain. Recommendations for improved assessment included improv- ing assessment of AL in clinical trials (e.g. training study personnel in the principles of abuse and addiction behaviors, de- signing the trial to assess AL outcomes as primary or secondary outcome measures depending on the trial objectives), per- forming standardized assessment of out- comes, including targeted observations by study personnel and using structured AE query forms that ask all subjects spe- cifically for certain symptoms (such as euphoria and craving) and collecting de-

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# Compliance with ethical guidelines

**Conflict of interest.** W. Häuser received honorar-

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The accompanying manuscript does not include stud- ies on humans or animals.

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