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REVIEW ARTICLE

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Is opioid therapy for chronic non-cancer pain associated with a greater risk of all-cause mortality compared to non-opioid analgesics? A systematic review of propensity score matched observational studies

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Abstract

Background: The many risks associated with opioid therapy for chronic non-cancer pain (CNCP) have led to questions about use. This is particularly relevant for risk of increased mortality. However, underlying medical conditions of those using opioids may influence mortality findings due to confounding by indication. Similarly, non-opioid analgesics are also associated with an increased risk of mortality, too.

Methods: We have conducted a systematic review of propensity score matched observational studies comparing mortality associated with opioid use compared to non-opioid analgesics. Clinicaltrials.gov, Google Scholar, MEDLINE and Scopus were searched from inception to July 2020. Propensity score matched observational studies comparing opioids to non-opioid analgesics in real-world settings were analysed. Primary outcome was pooled adjusted hazard ratio (aHR) of all-cause death. Effects were summarized by a random effects model.

Results: Four studies with seven study arms and 120,186 patients were analysed. Pooled aHR for all-cause death was 1.69 (95% confidence interval [CI] 1.47, 1.95). When mortality risk was confined to out-of-hospital deaths, the pooled aHR was 2.12 (95% CI 1.46, 3.09). The most frequent cause of death was cardiovascular death. Before matching, patients with opioids were older and had more somatic diseases than patients with non-opioids. Despite extensive propensity score matchings and sensitivity analyses, all studies could not fully exclude confounding by indication.

Conclusions: Possibly, opioids are associated with an increased all-cause mortality risk compared to non-opioid analgesics. When considering treatment options for patients with CNCP, the possible risk of increased all-cause mortality with opioids should be discussed.

Significance: An increased all-cause mortality associated with opioid use compared to non-opioid analgesics for CNCP was identified by a systematic review of four propensity score matched cohort studies in real-world settings. The number needed to harm for an additional excess death per 10,000 person-years was 116. Despite extensive propensity score matchings and sensitivity analyses, all studies could not fully

exclude confounding by indication. The potential risk of increased all-cause mortality with opioids should be discussed with patients when considering opioid treatment.

1 | INTRODUCTION

A systematic review found that the average 1-month prevalence of moderate-to-severe non-cancer chronic (CNCP) pain was 19% in Europe (Reid et al., 2011). Analgesics such as opioids are frequently used to treat CNCP (Mathieson et al., 2020). There has been an increase in opioid prescriptions in first world countries in the last two decades. In North America, opioid prescription increase was associated with an increase in opioid abuse and dependence and opioid-related mortality, the so-called opioid crisis (DeWeerdt, 2019).

All-cause mortality associated with opioid therapy for CNCP compared to placebo in randomized controlled trials and long-term extension studies (sponsored by pharmaceutical companies) was very low (Bialas et al., 2020; Petzke et al., 2020; Sommer et al., 2020; Welsch et al., 2020). The mostly strict exclusion criteria and the close clinical surveillance during these studies do not reflect real-world clinical practice. Outside the study setting, patients may have multiple comorbidities and clinical care may be compromised due to limited ideal clinical follow-up. Studies conducted in real-word settings have found an increased all-cause mortality associated with opioid therapy compared to no opioid therapy (Macfarlane et al., 2020; Sjøgren et al., 2010).

Because the allocation of treatment in observational studies is not randomized and the indication for treatment may be related to the risk of future health outcomes, the resulting imbalance in the underlying risk profile between the treated and the comparison groups can generate biased results. Such bias by indication is frequently encountered in observational epidemiologic studies of medication effects (Signorello et al., 2002). Opioids are recognized as the most potent analgesics according to the ladder scheme of the WHO (Barnett, 2020). Treatment with opioids might be indicative of the severity of pain and/or the complexity of the underlying condition. Therefore, disease severity and not opioids per se might be the primary cause of increased mortality (Sjøgren et al., 2010).

In the clinical context of managing CNCP, potential benefits and risks of opioid therapy as well as the severe adverse effects that can be fatal of non-opioid medications must be taken into consideration. Some examples are cardiovascular and gastrointestinal events with non-steroidal anti-inflammatory drugs (NSAIDs), liver failure by antidepressants, heart failure by anticonvulsants and agranulocytosis by metamizole (Fuzier et al., 2013; McGettigan & Henry, 2011; Sarko, 2000; Stamer et al., 2017). Therefore, to give a balanced view on the risks of medications for CNCP, opioids need to be compared with non-opioid analgesics (and not placebo or no opioid therapy) in patients who are matched with regards to demographic and medical variables. Propensity score-based methods are increasingly used in observational research to exclude confounding by indication by including in the analyses only participants who have a similar propensity score and thus baseline characteristics (Freemantle et al., 2013).

To provide a balanced view on the risks of medication for CNCP, we conducted a systematic review of observational studies in real-world settings (real-world data which are derived from observational studies in heterogeneous patient populations with information obtained from electronic health records, claims and billing activities, product and disease registries), assessing the all-cause mortality of propensity score matched patients with CNCP of any age treated with opioids compared to non-opioid analgesics.

2 | METHODS

A completed 'Strengthening the Reporting of Observational Studies in Epidemiology statement–checklist' (Stroup et al., 2000) is presented in Supplementary Material 1.

2.1 | Protocol

2.1.1 | Criteria for considering studies for this review

Methods of analysis and inclusion criteria were specified in advance. To enable PROSPERO to focus on COVID-19 registrations during the 2020 pandemic, this registration record was automatically published exactly as submitted (Registration number CRD42020 190769). The PROSPERO team has not checked eligibility.

Types of participants and medications

We included men and women of all ages, race and ethnicity diagnosed with CNCP (pain duration >3 months) treated with any opioid by oral or transdermal route. Opioid-treated patients were matched to those treated with oral non-opioid analgesics (anticonvulsants and antidepressants used for pain management; dipyrone; muscle relaxants; non-steroidal agents [NSAIDs] and paracetamol).

Types of studies

We included fully published longitudinal observational studies (case–control studies, cohort studies) of any setting (primary,

secondary, tertiary care; health insurance databases; general population) which compared mortality of patients treated with opioids compared to matched patients treated with any non-opioid analgesics for any time period. We excluded randomized controlled trials of opioids for CNCP because the strict inclusion and exclusion criteria and the strict surveillance of patients in randomized controlled trials (RCTs) do not reflect the clinical practice.

Types of outcome measures

The primary variable of interest was the prevalence of all-cause mortality in the opioid and non-opioid group. Secondary outcomes were as follows: in-hospital and out-of hospital all-cause mortality and causes of death (cardiovascular events, gastrointestinal bleeding and infections) in the opioid and non-opioid group. In addition, we assessed whether the studies had reported duration of therapy and opioid dosage as a factor impacting opioid-associated deaths.

2.2 | Searches

2.2.1 | Electronic searches

The authors searched clinicaltrials.gov, Cochrane Library database, Google Scholar, PubMed and SCOPUS from inception to July 27, 2020, with these search terms: (Opioids AND chronic non-cancer pain AND mortality AND cohort study AND propensity score).

2.2.2 | Searching other resources

All authors searched bibliographies from retrieved relevant articles. Our search included all languages.

2.3 | Measures of treatment effect

For quantitative synthesis, we computed the pooled adjusted hazard ratio and corresponding 95% confidence interval (CI) of all-cause mortality by a fixed effects model. We considered a HR ≥1.57 to be clinically relevant, assuming an exponentially distributed survival time (Borate et al., 2015). In addition, we calculated the risk difference of excess death rates per 10,000 person-years for the opioid and non-opioid group.

2.3.1 | Assessment of heterogeneity

We extracted demographic and clinical characteristics of the patients and the study setting as potential sources of clinical heterogeneity. We used the I^2 statistic to describe the percentage variability of effect estimates that is due to heterogeneity. We combined results in a meta-analysis using a random-effects model. I^2 values above 75% indicate considerable heterogeneity, above 50% indicate substantial heterogeneity, between 25% and 50% moderate heterogeneity and below 25% low heterogeneity.

2.4 | Data collection and analysis

2.4.1 | Selection of studies

Two review authors (WH, TT) independently scrutinized all the titles and abstracts and selected studies based on inclusion and exclusion criteria. Any disagreements were resolved through discussion and if needed by the judgement of a third author (MAF).

2.4.2 | Data extraction and management

Using standardized forms, two authors (MAF, WH) independently extracted data on inclusion and exclusion criteria of studies, participant characteristics, clinical setting, interventions, country of study and type of opioid and non-opioid medications used. Any disagreements were resolved through discussion and if needed by the judgement of a third author (TT).

2.4.3 | Assessment of risk of bias in included studies

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess study quality. This scale consists of eight questions. The NOS evaluates three quality parameters (selection, comparability and outcome) divided across eight specific items, which slightly differ when scoring case control and longitudinal studies. Each item on the scale is scored for a maximum of 1 point, except for comparability, which can be adapted to the specific topic of interest to score a maximum of 2 points. Thus, the maximum points for a study is 9 (Wells et al., 2012). Thresholds for converting the Newcastle-Ottawa scales into Agency for Healthcare Research and Quality's (AHRQ) standards (good, fair and poor) are as follows (Viswanathan et al., 2012):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

2.5 | Subgroup analysis

Subgroup analyses were planned to study the reasons for existing statistical heterogeneity and to test the robustness of the overall estimate, respectively, if at least two studies were available: European versus US studies; studies with different settings; studies with low or high risk of bias. Data were analysed using the random-effects model and heterogeneity I^2 statistics to compare the subgroups.

2.6 | Sensitivity analysis

A sensitivity analysis was planned to identify potential outlying studies. For this analysis, an additional pooled effect estimate and 95% CI were generated after removing one study from the original full set of included studies (leave one-out meta-analysis). This demonstrates how each study affects the overall estimate of the rest of the studies. An individual study was considered an outlier if, upon removal, the effect estimate for the restricted set differed significantly from that of the full set of included studies.

2.7 | Metaregression analysis

To investigate whether the prevalence rates of opioid-associated mortality were changing over time, we intended to perform a random effects meta-regression with Tau^2 variance calculated by the method of maximum likelihood using the start of the study as a covariate.

2.8 | Publication bias

Potential publication bias was investigated using the Egger test, in which the standardized effect size (effect size calculated by standard error) is regressed on precision (inverse of standard error) (Egger et al., 1997). The intercept value is an estimate of asymmetry of the funnel plot. Positive values (>0) indicate higher levels of effect size in studies with smaller sample sizes. Moreover, Begg's rank correlation test was performed using $p < 0.05$ as the criterion for significance (Begg & Mazumdar, 1994).

2.9 | Software

RevMan Analysis (RevMan 5.3.1) software of the Cochrane Collaboration was used for statistical analyses (Review Manager, 2014).

3 | RESULTS

3.1 | Search

The search (last performed July 27, 2020) produced 760 records after duplicates were removed (see Figure 1). We excluded 754 records because they did not meet our inclusion criteria, namely longitudinal observational studies (case–control studies and cohort studies), which compared mortality of patients treated with opioids compared to matched patients treated with any non-opioid analgesics. We included four studies with seven study arms and 120,186 patients for the qualitative and quantitative analysis (Häuser, Schubert, et al., 2020; Ray et al., 2016; Solomon et al., 2010; Zeng et al., 2019). We contacted three study authors for details, but did not receive a response.

3.2 | Included studies

The main characteristics of the studies are summarized in Tables 1 and 2.

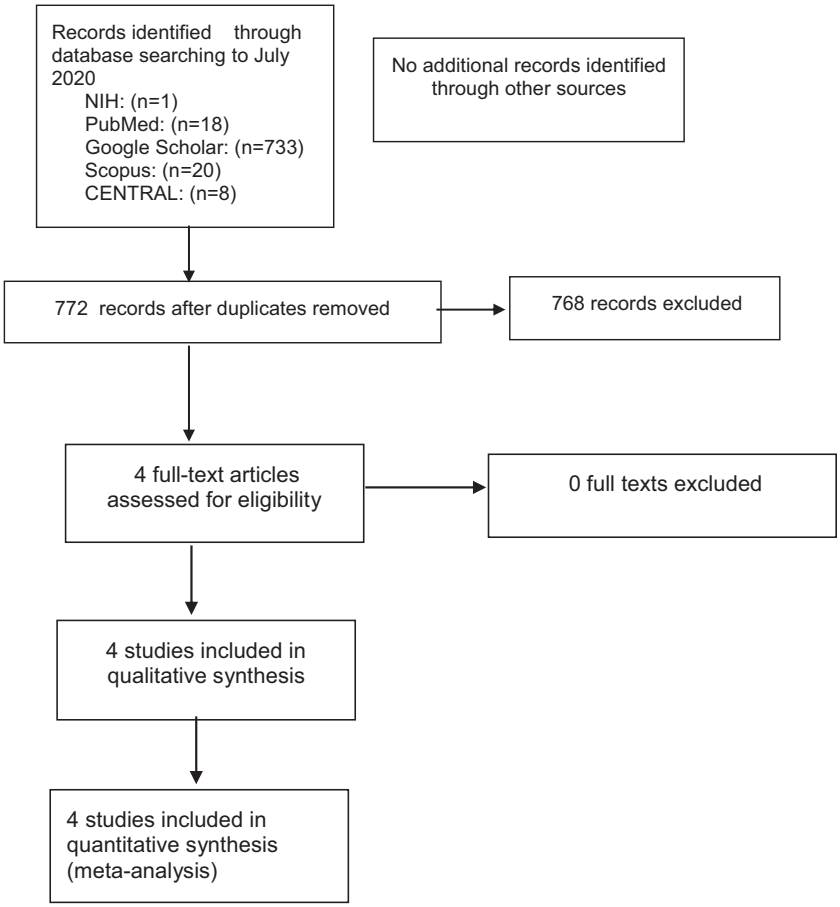
3.2.1 | Settings

Two studies each were conducted in the United States (Ray et al., 2016; Solomon et al., 2010) and in Europe (Germany and United Kingdom) (Häuser et al., 2020; Zeng et al., 2019). The two US studies included patients in federal and state programs that cover medical costs for some people with limited income and resources (Ray et al., 2016; Solomon et al., 2010). The UK study included patients from a general practitioner database (Zeng et al., 2019) and the German study included patients covered by 61 statutory health insurances (Häuser, Schubert et al., 2020).

3.2.2 | Participants

The German study included opioid prescriptions for diseases of the musculoskeletal system and connective tissue, headache syndromes, pain unspecified, somatoform pain disorder, other and unspecified polyneuropathies or diabetes mellitus with neurological complications defined by ICD-10 codes. The most frequent chronic pain syndromes in the opioid group were low back pain (22.6%), osteoarthritis (22.2%), pain not specified (9.7%), somatoform pain disorder (6.5%) and diabetic polyneuropathy (2.4%) (Häuse, Schubert et al., 2020). One US study included patients with osteoarthritis (ca 90%) and rheumatoid arthritis (ca 10%) (Solomon et al., 2010). The other US study included patients with chronic back, other musculoskeletal, abdominal and neurologic pain and headache (no ICD codes

FIGURE 1 PRISMA flow diagram



reported). The most common chronic pain diagnoses were back pain (75%), other musculoskeletal pain (63%) and abdominal pain (18%) (Ray et al., 2016). The British study included only patients with osteoarthritis (Zeng et al., 2019).

All studies excluded patients <18 years, as well as patients with cancer and those receiving end-of-life treatment. Ray excluded patients ≥75 years, nursing home residents and those on high-dose opioid- and anticonvulsants therapy (Ray et al., 2016). Zeng excluded patients <50 years (Zeng et al., 2019). The mean age in the studies was 66 years (Häuser, Schubert et al., 2020), 48 years (Ray et al., 2016), 80 years (Solomon et al., 2010) and 70 years (Zeng et al., 2019). Women prevailed in all study samples.

3.2.3 | Types of opioids and non-opioid analgesics

Häuser compared buprenorphine, fentanyl, morphine, oxycodone, oxycodone/naloxone, tapentadol, tilidine and tramadol with anticonvulsants and antidepressants indicated for chronic pain, dipyrone and NSAIDs (Häuser, Schubert et al., 2020). Ray compared long-acting opioids (morphine SR, oxycodone CR, transdermal fentanyl and methadone) with anticonvulsants indicated for chronic pain (gabapentin, pregabalin and carbamazepine), or low-dose cyclic antidepressants (Ray et al., 2016). Solomon compared codeine, hydrocodone, tramadol, oxycodone and prophoxypene with NSAIDs and coxibs (Solomon et al., 2010). These three studies pooled all non-opioid analgesics together for analysis. Zeng compared tramadol versus individual NSAIDs, namely naproxen, diclofenac, celecoxib and eterocoxib (Zeng et al., 2019).

Three studies required at least one opioid prescription for inclusion (Ray et al., 2016; Solomon et al., 2010; Zeng et al., 2019). One study required long-term opioid therapy defined by opioid prescription claims in at least three consecutive quarters (one quarter = 3 months) (Häuser, Schubert et al., 2020).

3.2.4 | Duration of opioid therapy

Twenty one per cent of the patients in the German study were on opioids for the whole study period (5 years) (Häuser, Schubert et al., 2020), whereas 51.5% of participants in the US study of Ray had opioid prescriptions for 31–180 days and 16.4% opioid prescriptions >180 days (Ray et al., 2016). Solomon did not report on the duration of opioid therapy (Solomon et al., 2010). The average duration of tramadol therapy in the UK general practice study was 22 (5–67) days (Zeng et al., 2019).

TABLE 1 Characteristics of includes studies

First author (alphabetical order) (Reference), Country	Study design data base	Study period Period of assessment of mortality
Häuser [10], Germany	Retrospective cohort study Anonymised insurance claims database including 4,711,668 insured persons who were covered by 61 German statutory health insurances	2013–2017 Exposure time was defined as a maximum of 60 months after the initial prescription
Ray [18], USA	Retrospective cohort study Tennessee Medicaid patients	1999–2012 Patients entered the cohort on the date of the filling of the first study drug prescription. They left the cohort on the earliest of: 1 year with no filled prescription, filling of a prescription for a drug in a different class (e.g., a study patient initiates a cyclic antidepressant, regardless of dose), death, failure to meet inclusion–exclusion criteria or end of the study
Solomon [25], USA	Retrospective cohort study Medicare beneficiaries from Pennsylvania and New Jersey who qualify for pharmaceutical assistance programmes for low-income older adults	1999–2005 1 year after initial prescription of an opioid
Zheng [32], UK	Retrospective cohort study Health Improvement Network database (records of general practitioners in the United Kingdom)	2000–2016 1 year after initial prescription of tramadol

Abbreviations: ICD, International Classification of Diseases; NSAIDs, Non-steroidal agents.

3.2.5 | Propensity matching

Before matching, patients treated with opioids were older and had more somatic and mental comorbidities in three studies. Solomon did not report the data before matching (Solomon et al., 2010). All studies matched for demographic factors, comorbidities and health care use. Only Zeng matched for lifestyle factors (BMI, smoking and alcohol) (Zeng et al., 2019). The number of covariates used for matching was as follows: Häuser 84 (Häuser, Schubert et al., 2020), Ray 122 (Ray

Participants **Exclusion criteria** **Number of persons analysed** **Mean age** **Females (%)** **Type of chronic non-cancer pain**	**Type of opioids** **Duration of opioid therapy**	**Comparator**
Age <18 years; cancer and palliative care diagnosis before index date; opioid addiction (ICD-10 Z51.83) within the study period. 3,232 persons in each group 66 years 55% women Diseases of the musculoskeletal system and connective tissue (ICD-10 M00*-M99*), headache syndromes (ICD-10 G43*-G44*, G50.0, G50.1, R10.1), pain unspecified (ICD-10 R52), somatoform pain disorder (ICD-10 F45.4*), other and unspecified polyneuropathies or diabetes mellitus with neurological complications (ICD_10 G62*, or E10.4*-E14•4 plus G63.3).	Oral or transdermal opioids: buprenorphine, fentanyl, morphine, oxycodone, oxycodone/naloxone, tapentadol, tilidine and tramadol Opioid prescription claims in at least three consecutive quarters (quarter = three months) with the same diagnosis of chronic pain 21% of the patients were on opioids for the whole study period (60 months)	Anticonvulsants and antidepressants indicated for chronic pain, dipyrone and NSAIDs.
Age <18 and >75 years; cyclic antidepressants >150 mg; long-acting opioids >180 mg morphine equivalents); anticonvulsants >1,800 mg gabapentin equivalents; cancer, other life-threatening diseases or evidence of hospice or other terminal care, and nursing home residents 22,912 in each group 48 years 60% Chronic non-cancer pain (back, other musculoskeletal, abdominal, headache, other neurologic) in the past 90 days (no ICD codes reported)	Long-acting opioids (morphine SR, oxycodone CR, transdermal fentanyl, methadone) At least one prescription 51.5% with opioid prescriptions 31–180 days 16.4% with opioid prescriptions >180 days	Anticonvulsants indicated for chronic pain (gabapentin, pregabalin, carbamazepine), or low-dose cyclic antidepressants
Age <18 years; diagnosis of a malignant neoplasm, use of hospice services in the preceding 365 days and dispensing of analgesics from two categories simultaneously, either as a combination product or two separate medications 4,280 in each of three group (opioids, NSAIDS, coxibs) 80 years 85% Osteoarthritis or rheumatoid arthritis recorded on two separate visits (ICD-9 codes)	Codeine, hydrocodone, tramadol, oxycodone, prophoxypene At least one prescription. Mean duration of therapy not reported	diclofenac, etodolac, flurbiprofen, ketorolac, ibuprofen, indomethacin, meloxicam, naproxen, piroxicam, sulindac, celecoxib, rofecoxib, valdecoxib
<50 years; history of cancer and opioid use disorder before study entry 88,902 70 years 61% Osteoarthritis of knee, hip or hand (according to Reed classification system)	Tramadol At least one prescription The mean treatment duration of a prescription for tramadol was 22 (5–67) days; naproxen 24 (5–0) days; diclofenac 24 (5–60) days; celecoxib, 31(5–60) days; etoricoxib 27 (5–0) days	naproxen or diclofenac, celecoxib, etoricoxib codeine (not used for analysis)

et al., 2016), Solomon 39 (Solomon et al., 2010) and Zeng 65 (Zeng et al., 2019). After matching, the characteristics between the matched cohorts were well balanced, with all standardized differences less than 0.10 in the studies of Ray (Ray et al., 2016) and Zeng (Zeng et al., 2019). In the study of Häuser, 10 covariates were more frequent (≥10% standardized difference) in the opioid group and three covariates were more frequent in the non-opioid group (Häuser, Schubert et al., 2020). Solomon did not report on standardized difference after matching (Solomon et al., 2010).

TABLE 2 Details of propensity score matching of the studies

First author (alphabetical order) (Reference) Country	Number of variables for propensity score matching	Number of variables with standardized difference ≥10% between the two groups before and after matching
Häuser [10], Germany	84 covariates: Demographic characteristics, diagnoses related to chronic pain, medical procedures including previous surgeries, medication use, diagnoses of mental and somatic diseases and medical care utilization	Before matching: 56 covariates were more frequent (≥10% standardized difference) in the opioid group After matching:10 covariates were more frequent (≥10% standardized difference) in the opioid and 3 covariates in the non-opioid group. C-score of the propensity score was 0.84. C-scores >0.8 indicate a good classification by the propensity score
Ray [18], USA	122 covariates: demographic characteristics, diagnoses related to chronic pain, use of short-acting opioids and other medications for pain, benzodiazepines and other psychotropic medications linked with risk of overdose death, psychiatric diagnoses, cardiovascular conditions, respiratory diseases, other illnesses and medical care utilization	Before matching: 14 of 25 selected variables exceeding 10% in the opioid group After matching: No standardized difference exceeding 3% and the majority less than 1%
Solomon [25], USA	39 covariates: prior cardiovascular diagnoses and medication use, osteoporosis and fracture diagnoses and medications associated with their risk, gastrointestinal tract diagnoses and treatments, and diagnoses associated with liver or renal disease	Before matching: Not reported After matching: 'The number of acute care hospital days was higher in the opioid users category than in the other exposure categories. A history of fracture and falls was more common among opioid users than the other exposures' (Standardized differences not reported)
Zheng [32], UK	58 sociodemographic factors age at index date, gender, Townsend Deprivation Index, body mass index, lifestyle factors (drinking habits and smoking status), osteoarthritis duration, comorbidities and prescriptions prior to the index date, and health care utilization during the 2 years before the index date	Before matching: 'participants in the tramadol cohort, in general, were older; had a higher BMI; had a longer duration of osteo-arthritis; and had a higher prevalence of comorbidities (e.g. peptic ulcer, chronic kidney disease, diabetes, hypertension, and cardiovascular diseases), other prescriptions (e.g. other NSAIDs, other opioids, aspirin, statin, antihypertensive medicine, and antidiabetic medicine), and health care utilization than participants in the NSAIDs cohorts before propensity score matching' 'After matching, the characteristics between the 5 matched cohorts were well balanced, with all standardized differences less than 0.10'

Abbreviations: CNCP, Chronic non-cancer pain; ICD, International Classification of Diseases; MEQ/d, Morphine equivalent/day; NSAIDs, Non-steroidal agents.

3.2.6 | Funding and conflicts of interest

The study of Häuser was financed by a pharmaceutical company producing opioids. Two authors reported a financial COI within and two authors outside the submitted work. Two authors reported no financial COI (Häuser, Schubert et al., 2020).

The study of Ray was supported by three grants: National Heart Lung and Blood Institute, National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Rheumatology Research Foundation. COIs were not reported in the publication (Ray et al., 2016).

The study of Solomon was supported by the Agency for Healthcare Research and Quality. One of the authors reported a financial conflict of interest outside the submitted work (Solomon et al., 2010).

The study of Zeng was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Natural Science Foundation of China. One of the authors reported a financial conflict of interest outside the submitted work (Zeng et al., 2019).

3.3 | Risk of bias in included studies

According to the predefined categories, all studies were assigned a good standard according to AHRQ- standards (see Supplementary Material 2).

Participants included/ screened	Model Statistics	Subgroup analyses Number of Sensitivity analysis
6,464/147,158 (4.4%)	Multivariate Cox proportional hazard models The model included age, gender, quarter of index treatment, estimated propensity score, Charlson Comorbidity Index, study opioid cohort and treatment duration as covariates	According to type of CNCP: Pain, not specified (ICD-10 R52*); persistent somatoform pain disorder (ICD-10 F45•4*); osteoarthritis (ICD-10M 15*M19*), low back pain (ICD-10 M54*) diabetic polyneuropathy (ICD-10 E10•4*-E14•4 plus G63•3 Morphine equivalent >100 mg and <100 mg/d) 1
45,824/155, 191 (29.5%)	Cox regression models To adjust for residual confounding, regression models were stratified according to deciles of the baseline propensity score. The primary models included age, calendar year and study medication as time-dependent covariates, estimated via a counting process formulation that accommodates non-proportional hazards	Methadone excluded Neurological pain diagnoses MEQ/d > and ≤60 mg/d 8
36,414/163,714 (22.2%)	Cox proportional hazards regression models Regression models contained only the analgesic exposures of interest, with nsNSAID as the reference exposure	None 5
88,902/11.1 Million (0.8%)	Cox-proportional hazard model adjusted for calendar year	None 6

3.4 | Quantitative and qualitative analyses

3.4.1 | All-cause mortality

Four studies with seven study arms and 102,660 participants were entered into the analysis of a pooled adjusted hazard ratio (aHR) of all-cause mortality. Pooled aHR was 1.69 (95% CI 1.47, 1.95) (I^2 = 0%) (see Figure 2). According to the predefined categories, the adjusted HR was clinically relevant.

Four studies with seven study arms were entered into an analysis of deaths per 10,000 person-years. There were 3,362 deaths per 80,000 (336 per 10,000) per person-years in the opioid group and 1999 deaths per 80,000 (250 per 10,000) person-years in the non-opioid groups resulting in an excess death rate of 86 (95% CI 84, 88) per 10,000 person-years (I^2 = 90%). The number needed to harm for an additional excess death per 10,000 person-years was 116 (95% CI 114, 119) (see Figure 3).

3.4.2 | In- and out-of-hospital all-cause mortality

Two studies (Häuser, Schubert et al., 2020; Ray et al., 2016) provided data for in- and out-of-hospital all-cause mortality. Out-of-hospital deaths constituted 52% of deaths in the German study (Häuser, Schubert et al., 2020) and 79% of deaths in the

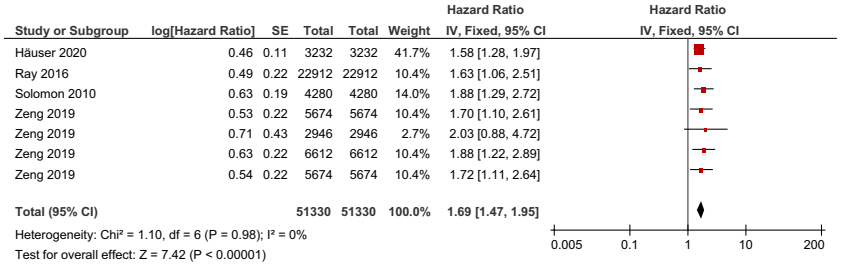


FIGURE 2 Pooled adjusted Hazard Ratio of all-cause mortality of patients with chronic noncancer pain treated with opioids compared to non-opioid analgesics in propensity-score matched cohort studies

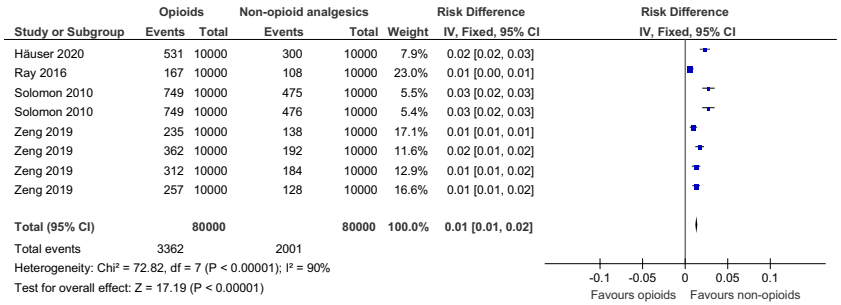


FIGURE 3 Risk difference of rate of death per 10,000 person years of patients with chronic noncacner pain treated with opioids compared to non-opioid analgesics in propensity score matched cohort studies

US study (Ray et al., 2016). The pooled adjusted HR was 2.12 (95% CI 1.46, 3.09) ($I^2 = 0\%$). According to the predefined categories, the adjusted HR was clinically relevant. The confidence interval for in-hospital deaths of both studies included zero .

3.4.3 | Causes of deaths

The HR of out-of-hospital cardiac death was 1.96 (95% CI 1.05, 3.67) in the study of Solomon (Solomon et al., 2010).

The most frequent category of non-overdose deaths was cardiovascular deaths with an HR of 1.65 (95% CI 1.10, 2.46) in the study of Ray (Ray et al., 2016).

The confidence interval of cardiovascular deaths and deaths due to gastrointestinal bleeding included zero for all four comparisons with NSAIDs/coxibs in the study of Zeng (Zeng et al., 2019). The confidence interval of deaths due to infections included zero for the comparison of tramadol with diclofenac and tramadol with etoricoxib. HR was 2.35 (95% CI 1.38, 3.98) for the comparison of tramadol with naproxen and 2.61 (95% CI 1.27, 5.38) for the comparison with celecoxib.

Due to German laws of data protection, causes of deaths as stated by death certificates were not available in the study of Häuser (Häuser, Schubert et al., 2020).

3.4.4 | Duration of therapy

In the study of Ray, the increased all-cause mortality for long-acting opioid-treated patients was limited to the first 180 days of prescribed therapy. During the first 30 days of therapy, the HR was 4.16 (95% CI 2.27, 7.63). For the remainder of the first 180 days, the HR was 1.56 (95% CI 1.05, 2.30). By contrast, once patients had more than 180 days of long-acting opioid therapy, the risk of death did not differ significantly from that of comparable control drug patients (HR 1.03 [95% CI 0.67,1.57] (Ray et al., 2016)).

In a multivariate analysis of predictors (gender, age, duration of therapy, comorbidity index and estimated propensity score) of all-cause mortality, the HR of duration of therapy was 0.996 (95% CI 0.995–0.996) in the German study (Häuser, Schubert et al., 2020).

The remaining two studies did not assess the impact of duration of therapy on all-cause mortality.

3.4.5 | Opioid dosages

The HR for all-cause death was 1.64 (95% CI 1.40, 1.89) for morphine equivalent (MEQ) <100 mg/d and 1.59 (95% CI 1.38, 1.82) for MEQ ≥ 100 mg/d in the study of Häuser (Häuser, Schubert et al., 2020).

In the study of Ray, the HR for low opioid doses (≤60 mg of morphine or its equivalent/day [MEQ/d]) was 1.54 (95% CI 1.01, 2.34) and for >60 mg MEQ/d was 1.94 (95% CI 1.40, 2.70) (Ray et al., 2016).

3.5 | Subgroup analysis

The adjusted HR of all-cause mortality for the European studies (Häuser, Schubert et al., 2020; Zeng et al., 2019) was 1.67 (95% CI 1.42–1.96) and 1.77 (95% CI 1.33–2.34) for the two US studies (Ray et al., 2016; Solomon et al., 2010).

The predefined subgroup analysis of studies with low or high risk of bias was not possible because all studies had a low

risk of bias. The predefined subgroup analysis of different settings was not possible for the following reason: both US studies were conducted with Medicaid/Medicare patients, and the databases of the United Kingdom (GP database) and German (statutory health insurance companies) were different.

3.6 | Sensitivity analysis

The predefined sensitivity analysis of our review was not necessary because there was no study with outlying results.

3.7 | Metaregression analysis

We did not perform the planned metaregression analysis because three of four studies were started in 1999 and 2000.

3.8 | Publication bias

Begg's and Egger's tests indicated a publication bias. Egger's intercept was 12.5 (p two tailed = 0.0003) and Begg's Kendall-tau without continuity correction was 0.89 (p two-tailed = 0.002).

4 | DISCUSSION

4.1 | Summary of main results

An increased all-cause mortality associated with opioid use compared to non-opioid analgesics for CNCP was identified by all four propensity score matched cohort studies analysed. The relative risk of increased all-cause mortality by opioids compared to non-opioid analgesics was clinically relevant. The absolute risk of increased all-cause mortality by opioids compared to non-opioid analgesics was small with 116 calculated as the number needed to harm for an additional excess death per 10,000 person-years.

All-cause mortality was confined to out-of-hospital deaths in two studies. Cardiovascular mortality was increased in two of three studies. Two studies found no impact of opioid dosage (cut-offs 60 and 100 mg MEQ/d) on all-cause mortality.

4.2 | Completeness and quality of evidence

4.2.1 | Publication bias

We found signals of publication bias. It is possible that observational studies demonstrating a comparable all-cause mortality between opioids and non-opioid analgesics may not have been published. The bias towards the selective publication of studies reporting adverse effects related to opioids can be seen as a consequence of the opioid epidemic in North America.

4.2.2 | Quality of evidence

All studies were assessed as having a good standard according to AHRQ standards.

Confounding by indication

Properly conducted randomization in clinical studies avoids bias by distributing both known and unknown patient characteristics between the experimental conditions on the basis of the play of chance. In contrast, propensity score-based analyses can only account for known and observed patient characteristics (Freemantle et al., 2013). Observational studies have the potential risk that treatment choice may be driven by patient characteristics. Confounding by indication refers to those situations where the disease per se, the disease prognosis or severity of the disease manifestations acts as a confounder (Salas et al., 1999). All studies in this analysis could not exclude confounding by severity. Patients were selected by diagnoses of health care utilization databases, e.g. ICD-10 codes, which do not capture the severity of chronic pain, e.g. in terms of intensity and/or disability. The German study (Häuser, Schubert et al., 2020) found differences in the prevalence of in- and outpatient treatments for the opioid and non-opioid groups during the study period: outpatient psychiatric or psychotherapeutic treatment 14.3% versus 10.1%, outpatient treatment by a pain physician 90.0% versus 17.4% and inpatient pain treatment (4.6% versus 0.7%) respectively (unpublished results). The increased health care utilization of the opioid group might be indicative of a greater severity of pain, or alternatively, opioid treatment might have been initiated as a treatment preference by pain physicians (Wilson et al., 2013) rather than prompted by the severity of pain.

Confounding by indication should not be confused with protopathic bias. The latter term is used if the first symptoms of the outcome of interest are the reasons for use of the treatment (Salas et al., 1999). The British study found a higher cancer-related mortality in the tramadol cohort than the NSAIDs cohorts. It is possible that some participants were experiencing pain from undetected early-stage cancer and therefore were given stronger pain medication to relieve the symptoms prior to cancer diagnosis (Zeng et al., 2019).

Other risks of bias

Risks of bias which are inherent in observational studies with administrative data must be kept in mind: All studies included in this analysis discussed that misclassification of exposures and end points could constitute other important

potential risks of bias. Due to the administrative nature of the databases used, the possibility of misclassification and miscoding of data exists. Once the drugs were dispensed there was no further clinical information about use. It is not known whether the dispensed drugs were used immediately, saved for later use, used according to prescribed directives or even diverted. There was no information on over-the-counter medication available. Death certificates to classify the cause of death may be incorrect.

4.3 | Comparison with other systematic reviews

We believe that this is the first systematic review on this topic. Therefore, we have looked to other recent systematic reviews of RCTs with opioids compared to placebo with CNCP for comparison with our current review. The mean duration of tramadol therapy in the study of Zeng was 3 weeks (Zeng et al., 2019) and thus lower than the usual 4–15 weeks of study duration of recent systematic reviews. Rate of deaths for opioids versus placebo was not different for systematic reviews of randomized placebo-controlled studies in low back pain (Petzke et al., 2020), osteoarthritis pain (Welsch et al., 2020) and neuropathic pain (Sommer et al., 2020). The rate of death in the opioid group as a study outcome for each of the aforementioned studies was none for the 1986 patients with low back pain (Petzke et al., 2020), one for the 211 patients with neuropathic pain (Sommer et al., 2020) and one for the 2,966 with osteoarthritis pain (Welsch et al., 2020). These studies covered a timeframe of 4–12 weeks. Most patients in the studies of Häuser (Häuser, Schubert et al., 2020) and Ray (Ray et al., 2016) were on long-term opioid therapy and were thus comparable with the study duration of the open label extension studies (26–156 weeks) of placebo-controlled RCTs analysed by Bialas (Bialas et al., 2020). Fourteen of 2,905 (0.5%) patients with different types of CNCP died during the study period (Bialas et al., 2020). Death rates of the propensity score matched cohort studies and death rates of the RCTs and their open label extension studies cannot be compared because different time measures of death were used. Nonetheless, the absolute death rate in all three types of studies is low.

4.4 | Types and causes of death

Häuser (Häuser, Schubert et al., 2020) and Ray (Ray et al., 2016) have hypothesized that the restriction of all-cause mortality to out-of-hospital death might be due to a closer surveillance of patients during in hospital care.

The greater risk of cardiovascular deaths found by two of three studies is surprising in view of the well-known cardiovascular risks of coxibs and NSAIDs (McGettigan & Henry, 2011). Ray hypothesized that increased risk of cardiovascular death could be related to adverse respiratory effects of long-acting opioids (Ray et al., 2016). Opioids can cause or exacerbate sleep-disordered breathing, including both obstructive and central sleep apnoea, and patients with sleep-disordered breathing have an increased incidence of nocturnal arrhythmias, myocardial ischemia or infarction, and sudden death (Schwarzer et al., 2015).

Death due to infections as found in two of four study arms in the UK study might contribute to the increased mortality risk of opioids compared to non-opioid analgesics, too (Zeng et al., 2019). High opioid doses and the initiation of opioid therapy for non-malignant pain have been correlated with a higher risk of infectious diseases such as pneumonia in epidemiological studies (Plein & Rittner, 2018), although confounding by indication may account for this association.

5 | CONCLUSIONS

Opioids as a treatment for CNCP are associated with an increased all-cause mortality risk compared to non-opioid analgesic treatments in observational studies in real-world settings. No adjustment method fully resolves confounding by indication in observational studies (Bosco et al., 2010): The four propensity score matched observational studies analysed could not exclude completely a risk of confounding and/or protopathic bias. On the other hand, the HR of all-cause mortality was very similar in all studies – despite the differences in control analgesics, patient characteristics, settings and different variables entered in the propensity score matching. In addition, there are plausible rationales available which can explain the risk of increased mortality with opioids (Macfarlane et al., 2020). However, the lack of correlation between opioid dose and mortality does not support the assumption that the increased mortality is specifically related to opioid dose.

Most clinical decisions are not based on high-quality evidence. When discussing treatment options for patients with CNCP, the potential risk of increased all-cause mortality associated with opioids should be included to the numerous known harms of this category of medication. Nevertheless, for some patients, the therapeutic benefits from opioids may outweigh the small absolute risk of increased mortality – especially, if the alternative treatments are not effective, poorly tolerated or contraindicated (Häuser, Bock, et al., 2020; Häuser et al., 2021).

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CONFLICTS OF INTEREST

MAF and WH have no financial conflicts of interest to declare. WH is the head of EFIC's task force of an updated position paper and of the German guidelines group on opioid therapy for chronic non-cancer pain. TT is member of EFIC's task force of an updated position paper and of the German guidelines group on opioid therapy for chronic non-cancer pain. TT has received honoraria for consultancies, travel grants and speaking fees for AOP Orphan, Almiral Hermal, Bionest Partners, Benkitt Renkiser, Grünenthal, Hexal, Indivior, Kaia Health, Lilly, Medscape, Mundipharma, MSD, Novartis, Pfizer, Recordati Pharma, Sanofi-Aventis and TAD Pharma.

AUTHORS' CONTRIBUTIONS

WH and TT performed the search of literature. All authors participated in analysing the data and writing the manuscript.

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