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Reduction in Mortality Risk with Opioid Agonist Therapy: A Systematic Review and Meta-Analysis

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- Data used in this analysis will be provided freely through the Open Science Framework upon completion of the study.

ABSTRACT

Introduction

Opioid agonist therapies are effective medications that can greatly improve the quality of life of individuals with opioid use disorder. However, there is significant uncertainty about the risks of cause-specific mortality in- and out-of-treatment.

Objective

This systematic review and meta-analysis explored the association between methadone or buprenorphine with cause-specific mortality among opioid-dependent persons.

Methods

We searched six online databases to identify relevant cohort studies, calculating all-cause and overdose-specific mortality rates during periods in- and out-of-treatment. We pooled mortality estimates using multivariate random effects meta-analysis of the crude mortality rate per 1000 person-years of follow-up as well as relative risks comparing mortality in-versus-out of treatment.

Results

32 cohort studies (representing 150,235 participants, 805,423.6 person-years, and 9112 deaths met eligibility criteria. Crude mortality rates were substantially higher among methadone cohorts than buprenorphine cohorts. Relative risk reduction was substantially higher with methadone relative to buprenorphine when time in-treatment was compared to time out-of-treatment. Furthermore, the greatest mortality reduction was conferred during the first four weeks of treatment. Mortality estimates were substantially heterogeneous, and varied significantly by country, region, and by the nature of the treatment provider.

Conclusion

Precautions are necessary for the safer implementation of opioid agonist therapy, including baseline assessments of opioid tolerance, ongoing monitoring during the induction period, education of patients about the risk of overdose, and coordination within healthcare services.

INTRODUCTION

Opioid use disorder (OUD) is a substantial contributor to the global burden of disease and mortality (1). In 2010, there were 15.5 million opioid dependent persons globally, accounting for 9.2 disability adjusted life years (DALYs) – a 73% increase from 1990 (1). In addition to premature mortality and disability, OUD not only has a profound impact on the quality of life of affected individuals, but also their families and society as a whole (1). In recent years, the opioid overdose crisis has become a major global public health concern, which shows no signs of slowing down (2).

Given growing concerns about opioid dependence and opioid overdose mortality, there has been increasing demand for effective, evidence-based treatments for OUD and for the prevention of opioid overdose mortality (2–4). Many countries have responded to the opioid crisis by increasing the availability of the rapid-acting opioid antagonist naloxone, which can quickly reverse the effects of an opioid overdose (5). National and international medical bodies are also collaborating to develop opioid prescribing standards and guidelines with the intent of improving opioid stewardship (6,7). The success of these efforts, however, are dependent on the identification of at-risk patients and improved access to harm reduction interventions (2).

A disproportionate amount of opioid overdose fatalities occur among individuals who are opioid dependent. Therefore, finding effective treatments for OUD is expected to be a major component of the solution to the opioid overdose epidemic. Opioid agonist therapies (OATs) are a safe and effective class of medications that can greatly improve the quality of life of opioid dependent persons (2,3). OATs, including methadone and buprenorphine, suppress opioid cravings and withdrawal (3), reduce illicit opioid use (8), decrease criminality (9,10), and lower the risk of drug-related HIV transmission (11–13). These therapies are particularly effective when they are combined with one or more evidence-based psychosocial interventions, such as motivational interviewing (14) or contingency management (15).

There is a wealth of evidence supporting the use of the long-acting synthetic opioid agonist methadone for the treatment of opioid withdrawal and the management of opioid dependence. Methadone is the best-researched and first widely-used opioid agonist for the treatment of opioid dependence (12). The partial opioid receptor agonist buprenorphine has become increasingly popular in the last decade for its superior safety profile while retaining efficacy for the dual treatment of opioid withdrawal and dependence (13,16). Opioid agonist therapies are also effective for the management of opioid dependence in pregnancy, and can reduce the risk of neonatal abstinence syndrome (17).

Growing evidence, however, suggests that mortality during and after OAT is time-dependent and agent-specific (3,18–20). For example, methadone is associated with higher rates of mortality during the induction phase of OAT if initial doses are too high, owing to its full-agonist properties at the μ -opioid receptor (21). Conversely, the partial agonist buprenorphine self-titrates activity at the μ -opioid receptor, causing a ceiling effect (13). Due to this effect, methadone is superior at retaining patients in OAT treatment relative to buprenorphine (13). This has been cited as a major limitation in buprenorphine therapy because mortality risk is thought to increase abruptly after discontinuation of OAT (19,20).

Despite the global prevalence of opioid use, there have been few studies looking specifically at the burden of opioid overdose mortality in general, let alone among those with opioid use disorder. Effect estimates from available individual studies have not been conclusive due to limited statistical power from small sample sizes, number of events, and low exposure prevalence. As individual cohort studies have been underpowered to detect nuances in mortality risks, and randomized controlled trials are unlikely to be feasible for this purpose. An alternative approach is necessary.

A systematic review and meta-analysis would allow for the appraisal of available evidence regarding opioid overdose mortality rates, provide a more precise estimate of the exposure effect of opioid agonist therapy on mortality, and help explain heterogeneity in the findings of individual studies. As a synthesis of research findings, a meta-analysis would provide a summary of effect measures, as well as determine necessity and questions for future research. Systematic reviews and meta-analyses are particularly valuable in distilling the differential risks of mortality associated with different times and types of opioid agonist therapy by pooling together the results of several cohort studies.

While Sordo and colleagues carried out a meta-analysis on this topic in 2017 (18), it was limited by having only three studies of buprenorphine, and only half of the papers (10 in total) explored overdose specific mortality. The study was only able to identify a total of three buprenorphine cohorts, severely limiting their ability to make grounded conclusions about its impact on overdose mortality. Furthermore, the majority of articles captured by their meta-analysis focused on all-cause mortality, with only half (ten of nineteen cohorts) exploring opioid overdose specific mortality. This is particularly relevant in the wake of the current global opioid epidemic. As several additional studies have been published on this topic since 2017, we considered that an updated synthesis was warranted.

Therefore, our objective was to estimate the association between exposure to opioid agonist therapy and all-cause and overdose-specific mortality among individuals with opioid use disorder.

METHODS

Registration

This review was registered with the Open Science Framework on June 14, 2019 (<https://osf.io/nhs7y/>). Although an a priori protocol was used, it was not published online in advance of the review.

Data Sources

We searched seven online databases (Medline, Embase, PsycINFO, CINAHL, Cochrane CENTRAL Library, Allied and Complementary Medicine, ProQuest, and Web of Science) by using different combinations of free text and data-base specific index terms related to the topics of opioid dependence, opioid agonist treatment, mortality, and cohort studies. Details of the full search strategy are provided in Appendix 1. The search was conducted in January 2019 and updated in June 2019. As a complement to this search, we also reviewed the reference lists of relevant original papers and reviews. We followed both the PRISMA and MOOSE guidelines (Appendix 2) for reporting systematic reviews and meta-analyses throughout (22,23).

Eligibility criteria

We included cohort studies comparing mortality among people with opioid dependence. To be eligible, studies had to include follow-up data during and after opioid agonist treatment with methadone or buprenorphine. The following eligibility criteria were applied:

1. Study designs
 - a. Included: cohort studies
 - b. Excluded: clinical trials, case-control studies, cross sectional surveys, case reports, case series, qualitative research, editorials, methods, reviews, research letters, protocols

2. Population
 - a. Included: adults with opioid dependence
 - b. Excluded: non-human studies (e.g., preclinical studies, animal studies)
3. Exposure
 - a. Included: any opioid agonist therapy (including methadone or buprenorphine maintenance)
 - b. Excluded: studies with unknown treatment
4. Outcome
 - a. Included: studies providing aggregate or raw data on all-cause and overdose-specific causes of death over a defined follow-up period (e.g., number of deaths and person years broken down by follow-up period in and out of treatment)
 - b. Excluded: studies where insufficient data was provided to enable computation of mortality rates during periods in and out of treatment
5. Other
 - a. For cohorts spanning several reports, we used data from the primary cohort and excluded overlapping follow-up periods from each report.

Study selection and data extraction

Two reviewers independently completed all aspects of the systematic review process (screening records by title and abstract, reviewing full-text articles, data extraction, and quality assessment rating) using Cochrane's Covidence, a systematic review manager. Disagreements were resolved by consensus with an additional reviewer.

For each eligible study, we retrieved information on baseline population characteristics, including study location, sex and age distribution, primary opioid of misuse, and prevalence of opioid injection, non-opioid drug use, HIV infection, and psychiatric and medical comorbidity; number of cohort participants entering opioid agonist treatment during the study period (untreated participants and those under other types of treatment were excluded); treatment features, including drug type (methadone or buprenorphine), average daily dose, induction method (inpatient or ambulatory), and provider (addiction medicine specialist or general practitioner); and main follow-up characteristics, including calendar period, average length of follow-up from the start of maintenance treatment (excluding any previous detoxification period), loss to follow-up, and mortality outcomes.

We also registered detailed information on the number of deaths, person years at risk, and mortality rates from all causes and overdose during follow-up periods in and out of treatment and, whenever possible, during specific time intervals since treatment initiation and cessation.

Quality assessment

We used a 9-item quality assessment framework for non-randomized observational studies, which we adapted from a previous meta-analysis exploring opioid-related mortality in order to capture ratings for times in-and-out of opioid agonist therapy (20). This included a general appraisal of case ascertainment, measurement, diagnosis, statistical measures, completeness, representativeness, and age/sex estimates. Total quality scores ranged from 0 to 19, with higher scores indicating higher study quality. Details of the quality assessment tool and a per-study rating of quality are described in Appendix 3.

Publication bias assessment

Publication bias was assessed qualitatively—by examining funnel plots for gross symmetry—and quantitatively, using the Egger and trim-and-fill methods (24–26). These are described further in Appendices 4 and 5.

Statistical analysis

For each selected cohort, we calculated crude all-cause and overdose-specific mortality rates during periods in and out of treatment by dividing the number of deaths registered in each period by the person years contributed. This approach allowed us to estimate pooled mortality rates, pooled rate differences and rate ratios comparing periods in and out of treatment. Therefore, the specific effect sizes used in this meta-analysis were rate ratios for mortality during periods in versus out of treatment.

When not explicitly reported, we obtained the number of person years by treatment period from the available summary statistics. All-cause and overdose-specific mortality rates in and out of treatment were jointly combined across all methadone or buprenorphine cohorts by using a bivariate random effects meta-analysis on log transformed mortality rates in both treatment periods (27,28).

For treatment cohorts that reported mortality data by time interval in and out of treatment, we combined cause-specific mortality rates before and after four weeks of treatment using a multivariate random effects meta-analysis with log-transformed mortality rates during these treatment intervals.

To evaluate whether mortality rates differed by baseline population characteristics, treatment delivery, and follow-up features of treatment cohorts, we extracted the following moderator variables:

- Publication year
- Proportion HIV+ (%)
- Proportion with psychiatric comorbidity (%)
- Proportion male (%)
- Average dose of buprenorphine or methadone (mg)
- Nature of opioid agonist therapy provider (general practitioner, specialist, mixed)
- Proportion who injected opioids (%)
- Country of study
- Quality score
- Mean age (years)

Due to insufficient reporting of all variables, we performed bivariate meta-regression analysis to assess the combined impact of each moderator variables separately on the mortality risk reduction associated with opioid agonist therapy. We fit all models using restricted maximum likelihood methods with unstructured between-cohort covariance matrices in the R package metafor (29). We also conducted subgroup analyses to stratify cohorts by type of opioid agonist (e.g., buprenorphine vs. methadone).

Assessment and management of heterogeneity

We examined the overall heterogeneity across studies visually by way of Forest plots, but also quantitatively by examining the Cochran χ^2 test and the I^2 statistic, which described the proportion of total variation in study specific mortality rates because of heterogeneity. Consistent with previous literature (18,30,31), we categorized I^2 values using <25%, 25-50%, and >50% as representative of low, moderate, and high heterogeneity, respectively. We

anticipated a very high level of statistical heterogeneity between studies. After reviewing the Cochrane guidelines (32), we applied the following seven strategies to address heterogeneity.

1. First, we confirmed that the data were correctly extracted and entered into our statistical program.
2. Second, we considered the possibility of not doing a meta-analysis but opted against this as we wanted to measure the intervention effect of opioid agonist therapy.
3. Third, given the large number of studies identified, we explored causes of heterogeneity by conducting subgroup analyses investigating characteristics of studies that were pre-specified in our review protocol.
4. Fourth, we conducted sensitivity analyses by conducting a fixed-effects meta-analyses, which ignores heterogeneity; the pooled effect estimate from a fixed-effect meta-analysis is normally interpreted as being the best estimate of the intervention effect.
5. Fifth, we performed a random-effects meta-analysis, which may be used to incorporate heterogeneity among studies. Although this is not a substitute for a thorough investigation of heterogeneity, it can be helpful to quantify heterogeneity that cannot be explained.
6. Sixth, we assessed the impact of using an alternative effect measure, as heterogeneity may be an artificial consequence of an inappropriate choice of effect measure. For example, the choice of effect measure for dichotomous outcomes (odds ratio, relative risk, or risk difference) may affect the degree of heterogeneity among results.
7. Seventh, we explored the impact of excluding studies, as some heterogeneity may be due to the presence of one or more outlying studies with results that conflict with the rest of the studies. Although it is generally unwise to exclude studies from a meta-analysis on the basis of their results as this may introduce bias, it is advisable to perform analyses both with and without outlying studies as part of a sensitivity analysis. The influence of each study on pooled estimates was evaluated via sensitivity analysis with leave-out-one meta-analysis, allowing the removal of each individual study from the analysis.

RESULTS

Systematic review findings

Of the 2506 distinct records identified by our search strategy, we selected 32 distinct cohorts from 28 articles (33–50,50–55,19,56–59) for inclusion in the meta-analysis (Figure 1).

Study characteristics

Tables 1 and 2 show the main characteristics of selected cohorts. The studies were published between 1974 and 2018 and were all carried out in high income countries: eighteen in Europe, five in North America, five in Australia, and two in Asia. There were mixed baseline prevalences of opioid injection and HIV infection, except six cohorts (38,39,42,53,54,56) that enrolled only opioid injectors, two of them further restricted to patients positive for HIV (39,57). There was limited information on psychiatric and medical comorbidities. More than 70% of participants were men, and the mean age at baseline ranged from 23.4 to 39.6 (Table 1).

All 32 studies reported all-cause mortality during follow-up periods in and out of treatment, of which 21 also reported opioid overdose-specific mortality. Methadone was prescribed in 27 cohorts including 129,248 participants over the period 1965–2015. Buprenorphine was prescribed in five cohorts including 20,987 participants over 1990–2010 (Table 2). Average daily doses of methadone ranged from 47 mg to 116 mg, while average doses of buprenorphine ranged from 10 mg to 12 mg. Treatment was initiated on an

ambulatory basis in 14 cohorts, primarily recent ones, and provided by addiction medicine specialists in 13 cohorts and general practitioners or mixed staff in ten cohorts. The average duration of follow-up varied from 0.5 to 13.9 years for methadone and 1.0 to 4.5 years for buprenorphine.

Overall all-cause and overdose-specific mortality rates among opioid agonist therapy users

The all-cause mortality rates varied widely ($I^2 = 98.62\%$, $p < 0.001$, Figure 2). The overall all-cause crude mortality rate (CMR) was 16 deaths per 1000 person-years (PY) of follow-up (95% confidence interval [CI], 14-17 deaths per 1000 PY). Mortality rates were substantially higher among methadone users (CMR = 17 deaths per 1000 PY, 95% CI, 15-20) than buprenorphine users (CMR = 7 deaths per 1000 PY, 95% CI, 6-8).

Similarly, the overdose-specific varied widely ($I^2 = 97.52\%$, $p < 0.001$, Figure 3). The overall overdose-specific CMR was 6 overdose deaths per 1000 PY of follow-up (95% CI, 5-7 deaths per 1000 PY). Again, mortality rates were substantially higher among methadone users (CMR = 6 overdose deaths per 1000 PY, 95% CI, 5-7) than buprenorphine users (CMR = 3 overdose deaths per 1000 PY, 95% CI, 3-4).

Overall all-cause and overdose-specific mortality rate reduction among opioid agonist therapy users in-versus-out-of-treatment

The overall all-cause mortality rate was significantly lower during periods in opioid agonist therapy treatment compared to periods out of treatment (risk ratio (RR) = 0.372, 95% CI, 0.322-0.430, Figure 4). The mortality risk reduction was significantly greater with methadone (RR = 0.350, 95% CI, 0.300-0.408), however, the overall mortality reduction was not statistically significant among buprenorphine users (RR = 0.630, 95% CI, 0.364-1.092).

Similarly, the overdose-specific mortality rate reductions were 0.266 overall (95% CI, 0.204-0.348, Figure 5) 0.258 with methadone (95% CI, 0.194-0.342), and 0.556 with buprenorphine (95% CI, 0.083, 3.74). Again, the buprenorphine sample did not lead to a statistically significant reduction in overdose-specific mortality rates.

All-cause and overdose-specific mortality rate reduction in-vs-out of treatment during the first four weeks and after four weeks of treatment with opioid agonist therapy

The relative risk of mortality during the first four weeks of opioid agonist treatment was 0.279 (95% CI, 0.130-0.599, Figure 6) for those in treatment compared to those not in treatment. Similarly, the relative risks were 0.304 (0.123-0.753) and 0.234 (0.120-0.458) for methadone and buprenorphine, respectively.

Similarly, the relative risk of overdose mortality during the first four weeks of treatment was 0.445 (0.372-0.531, Figure 7) for those in treatment compare to those who were not. The relative risks were 0.429 (0.350-0.526) and 0.546 (0.325-0.919) for methadone and buprenorphine, respectively.

After four weeks of treatment, the relative risk of all-cause mortality with opioid agonist therapy was not statistically significantly for those in versus out of treatment (RR = 0.412, 95% CI, 0.128-1.328, $I^2 = 82.06\%$, Figure 8). However, the relative risk of overdose-specific mortality with opioid agonist treatment was significantly lower (RR = 0.455, 95% CI, 0.315-0.656, $I^2 = 73.03\%$, Figure 9).

Analysis of potential moderating variables

We conducted bivariate meta-regression analysis to separately explore the impact of all pre-specified variables on all-cause and overdose-specific mortality rate reductions in-versus-out-of-treatment with opioid agonist therapy—these are outlined in Table 3.

For all-cause mortality rate reduction, the type of opioid agonist therapy, prescriber, and geographic region were significant moderators: mortality rate reduction was greater with methadone (relative to buprenorphine), with addiction specialist providers (relative to others), and in North America and Asia (relative to Europe and Australia).

For overdose-specific mortality rate reduction, the proportion who injected opioids and publication year of the study were also significant moderators, with greater mortality rate reduction as the proportion of injection drug use and publication year increased. Similar to all-cause mortality, region and type of provider were statistically significant; however, the type of opioid agonist therapy was not statistically associated with overdose mortality risk.

Assessment of publication bias for all-cause and overdose-specific mortality rates are provided in Appendices 4 and 5, respectively. Using both qualitative (funnel plot) and quantitative methods (Egger's test, Trim & Fill), we found little evidence suggestive of publication bias. For overdose-specific mortality, trim-and-fill suggested there was one missing study; however, augmentation with this one study did not significantly impact our mortality estimates ($p=0.5588$).

Sensitivity analyses

We explored the influence of each study on pooled estimates via sensitivity analysis with leave-out-one meta-analysis, allowing the removal of each individual study from the analysis (Appendices 6 and 7 for all-cause and overdose-specific mortality rate reduction estimates).

Additional analyses of crude all-cause and overdose-specific mortality rates

We conducted additional analyses to further explore the absolute and relative differences in all-cause mortality rates (Appendices 8 and 9, respectively) and overdose-specific mortality rates (Appendices 10 and 11, respectively).

DISCUSSION

In our review, we identified 32 cohort studies, summing 150,235 participants, 805,423.6 person-years, and 9112 deaths, including 3801 overdoses. Our findings suggest that enrollment in opioid agonist therapy with methadone and buprenorphine reduces all-cause and overdose-specific mortality—particularly during the first four weeks of treatment.

Although methadone and buprenorphine showed similar trends in mortality over time, buprenorphine was associated with lower all-cause and overdose-specific mortality rates than methadone, which is consistent with its established superior safety profile. We tended to observe larger relative effect sizes, as measured by the rate ratio, for overdose than all-cause deaths with methadone but not buprenorphine, which is also consistent with previous literature emphasizing differential safety profiles of the two opioid agonist therapies. Our findings that the first four weeks after the onset and cessation of methadone treatment are the highest risk periods suggest these are key periods during which to focus efforts for prevention of drug-related deaths. These findings are important because some patients cycle in and out of OAT and are therefore exposed to repeated periods of high risk for mortality (20). Such changes primarily reflect changes in the risk of fatal overdose – and this has been more accurately assessed in the present meta-analysis as we were able to identify a larger number of cohorts specifically reporting overdose deaths.

The increased mortality risk during the first few weeks of treatment could be explained by the bioaccumulation of methadone, which often exceeds opioid tolerance in the early stages of treatments (60). Psychological factors and concomitant use of other respiratory depressant drugs or cocaine could also synergistically increase mortality risk (18). We also observed large increases in mortality in the first four weeks after cessation compared, which could be explained by the loss of tolerance to opioids—assuming that many patients may resume illicit opioid use (18). This parallels the observed trends in drug-related

mortality in other scenarios where opioid tolerance is probably diminished, for example, after prison release (53) or hospital discharge (60). Lifestyle factors and comorbid conditions may also increase all-cause mortality, as deaths from suicide and injury are also more common during this high-risk period (61).

Data from five cohorts (three from Australia) suggest that opioid agonist therapy with buprenorphine can reduce all-cause mortality. However, the disparity in mortality rates in periods in and out of treatment did not reach statistical significance for either all-cause or overdose-specific mortality. Other sources of data have suggested that buprenorphine could be more effective than methadone in reducing mortality, especially from overdose (45,62,63). Unlike methadone, there is a ceiling for respiratory depressant effects of buprenorphine as dose increases, and the probability of triggering arrhythmias is lower (64–66).

When we compared mortality between periods in and out of treatment, we found a greater reduction in mortality with methadone than with buprenorphine (measured as the rate difference or rate ratio between periods). When we compared mortality between them—first within the treatment period and then in the period off treatment—we found a significantly lower mortality with buprenorphine than methadone in both periods.

This meta-analysis synthesized all available evidence from 32 cohort studies published until 2018 on the risk of mortality in people who are dependent on opioids during and after opioid agonist treatment, separately for buprenorphine and methadone. We have updated previous time-dependent mortality patterns reported for both methadone and buprenorphine with the most recently available data (18).

Heterogeneity

Despite the strengths of this study, the high level of statistical heterogeneity represents a key limitation to the interpretation of its findings. The existence of heterogeneity suggests that there may not be a single intervention effect but rather, a distribution of intervention effects. This suggests that the receipt of opioid agonist therapy on its own does not necessarily impact mortality risk, but rather, the combination of opioid agonist therapy and other variables may account for the observed findings.

While random-effects meta-analysis is the most commonly used meta-analysis model when heterogeneity is encountered (28), authors often compare estimates obtained from random-effects modelling to those from a fixed-effect model—which in contrast, assumes there is no heterogeneity between studies (67–71). However, the use of fixed-effects models is controversial as such estimates may not be realistic, particularly when studying real-world phenomenon that are highly heterogeneous. In any case, we compared fixed- and random-effects estimates as a form of sensitivity analysis. For example, for the comparison of all-cause mortality comparing in-versus-out-of-treatment periods, the relative risk for mortality was 0.37 (95% CI, 0.32–0.43, $I^2=84\%$) using random-effects modeling, and 0.41 (95% CI, 0.39–0.43, $I^2=84\%$) with a fixed-effects model. These differences indicate that there is substantial residual heterogeneity in our sample that cannot be fully explained using measured covariates.

In consultation with the Cochrane guidelines (72), we followed additional strategies to address heterogeneity. We confirmed that the data were correctly extracted and entered into our statistical program by reviewing and resolving discrepancies between reviewers. Although meta-analyses are often abandoned in the face of substantial between-study heterogeneity, we opted to pursue meta-analysis alongside a rigorous attempt to explain the observed heterogeneity. We explored causes of heterogeneity by conducting subgroup analyses investigating characteristics of studies that were pre-specified in our review.

protocol, such as the type of opioid agonist, in-versus-out of treatment, and the duration of treatment (up to 4 weeks and after 4 weeks): each of these reduced the total heterogeneity slightly, but not substantially.

Ultimately, we presented random-effects meta-analysis to incorporate heterogeneity among studies. We also assessed the impact of using an alternative effect measure—such as the odds ratio and risk difference—but this did not lead to substantial changes in heterogeneity.

Limitations

Several additional limitations of this study must also be taken into consideration. First, as the same patients enrolled in treatment are followed over time, they may enter and re-enter treatment at multiple timepoints—often in a non-random way—hence creating potential for confounding in the comparisons of all-cause and overdose-specific mortality risks in and out of treatment.

Second, although some studies provided diverse demographic and clinical data on the baseline characteristics of study participants, adjustment for these potential confounders often produced similar or even increased out-to-in mortality rate ratios, merely reflecting that the above conditions tended to be less prevalent at baseline among patients who later left or were discharged from treatment than those who remained in treatment. As these baseline characteristics were not measured at each point of contact, we are unable to obtain unbiased estimates of the preventive effect of OAT on all-cause and overdose-specific mortality. Individual cohort studies are prone to confounding and selection bias because of differential loss to follow-up, however, this is difficult to assess without the available information on the magnitude and direction of bias projected onto the pooled mortality estimates.

Third, as there were almost no studies representative of low- and middle-income countries, this limits the generalizability of our mortality estimates to these countries.

Fourth, as follow up was often spread over many decades, with highly variable average lengths of follow-up. The bulk of our data reflect mortality among males. As some studies suggest overdose and all-cause mortality experiences among opioid users is different between males and females, this is a significant limitation of our study.

Fifth, as very few studies reported sex-specific mortality figures, we were not able to conduct sex-stratified sub-analyses to address this potentially interesting analysis. This would have been valuable and is a potential area for future research to focus on more in-depth.

Sixth, delayed records of treatment cessation may have led to the misclassification of out-of-treatment deaths as occurring in-treatment, which would make our estimates on the impact of OAT on mortality more conservative. Similarly, misclassification between overdose and non-overdose death due to inconsistent definitions and coding of causes of death would tend towards underestimating deaths due to overdose.

Seventh, our study is limited to studies using controlled opioid agonist therapies. As such, we have not captured mortality estimates from OAT initiated in the illicit drug market.

Eight, differences in mortality might also reflect confounding through differences in characteristics of patients, such as age, severity of opioid dependence, injection drug use, other drug use, comorbidities, prison history, overdose history, patient's preference); characteristics of treatment (such as previous treatment, specialization of the doctor who controls the treatment, dose, provision characteristics, cointerventions, retention, or drop outs), or the sociopolitical context in which studies have been conducted. For example, the initial prognosis might be better in those given buprenorphine than those given methadone (that is, fewer comorbidities, milder opioid dependence) (19,49,50,73), although this was not clearly found in a recent US study (74). The role of such confounding factors has received almost no empirical examination. As very few details on patient or treatment characteristics

were reported in the component articles in this meta-analysis (Tables 1 and 2), this precluded a more detailed examination of this potential issue and the possibility of an assessment for confounding. A previous sensitivity simulation analysis, however, has suggested that the comparatively lower mortality associated with buprenorphine related to methadone in the first four weeks of treatment was unlikely to be due to unmeasured confounding (19).

Ninth, the quality assessment framework used was an adaptation of a previously used 11-item instrument; as such, it has not been specifically validated for the purposes addressed in this review and may not be optimal for use in meta-analysis. Tenth, despite multiple attempts to explain and account for heterogeneity—such as with subgroup analyses—there remained substantial residual heterogeneity in our meta-analysis estimates; as a result, it may be invalid to pool the results and generate a single summary estimate.

Significance of Findings

Globally, the number and proportion of deaths attributable to opioid use is substantial. Overdoses remain preventable causes of death, which warrant wider implementation of harm-reduction and preventive interventions. Our review provides evidence that OAT reduces mortality among opioid-dependent persons, but in order to establish causality, further research utilizing study designs that can assess for a wide range of confounding variables are needed. Future studies, such as multicentered cohort studies directly comparing opioid agonists in a head-to-head manner, would be helpful in determining the comparative effectiveness of methadone and buprenorphine for mortality reduction, controlling for relevant confounders. Further studies should be conducted in low-and middle- income countries to address gaps in knowledge.

Conclusions

Although methadone and buprenorphine are listed as essential medicines, coverage remains low in many countries worldwide (75). Collaboration between policy makers, clinicians and researchers is needed to improve access to these treatments. Our findings suggest that precautions are necessary for the safer implementation of opioid agonist therapy, including baseline assessments of opioid tolerance, ongoing monitoring during the induction period, education of patients about the risk of overdose during treatment, and coordination of patients within healthcare services. Efforts to improve retention in treatment remain important as a strategy to reduce mortality. Although our review identified a lower risk of mortality associated with buprenorphine, making wide-sweeping generalizations about the relative offering of treatments is beyond the scope of this review.

Figure 1. PRISMA Flow Diagram

Figure 2. Forest plot of pooled, random-effects meta-analysis comparing all-cause crude mortality rates among individuals receiving methadone, buprenorphine, and overall.

Figure 3. Forest plot of pooled, random-effects meta-analysis comparing overdose-specific crude mortality rates among individuals receiving methadone, buprenorphine, and overall.

Figure 4. Forest plot of pooled, random-effects meta-analysis comparing all-cause crude mortality rate reduction (RR) among individuals in-versus-out of treatment with methadone, buprenorphine, and overall.

Figure 5. Forest plot of pooled, random-effects meta-analysis comparing overdose-specific crude mortality rate reduction (RR) among individuals in-versus-out of treatment with methadone, buprenorphine, and overall

Figure 6. Forest plot of pooled, random-effects meta-analysis comparing all-cause crude mortality rate reduction (RR) among individuals in-versus-out of treatment with methadone, buprenorphine, and overall within the first four weeks of treatment.

Figure 7. Forest plot of pooled, random-effects meta-analysis comparing overdose-specific crude mortality rate reduction (RR) among individuals in-versus-out of treatment with methadone, buprenorphine, and overall within the first four weeks of treatment.

Figure 8. Forest plot of pooled, random-effects meta-analysis comparing overdose-specific crude mortality rate reduction (RR) among individuals in-versus-out of treatment with methadone, buprenorphine, and overall after four weeks of treatment.

Figure 9. Forest plot of pooled, random-effects meta-analysis comparing overdose-specific crude mortality rate reduction (RR) among individuals in-versus-out of treatment with methadone, buprenorphine, and overall after four weeks of treatment.

Table 1. Baseline population characteristics of cohort studies on mortality risk in people with opioid dependence during and after opioid agonist therapy with methadone or buprenorphine

Study	Opioid Agonist	Country	PWID (%)	HIV+ (%)	Psychiatric Comorbidity (%)	Male (%)	Baseline Age (Years)
Gearing et al. 1974 (33)	Methadone	United States	NA	0	0	79	30.0
Cushman 1977 (34)	Methadone	United States	NA	0	2.9	73	38.5
Grönbladh et al. 1990 (35)	Methadone	Sweden	NA	0	Unknown	78.3	27.5
Caplehorn et al. 1994 (36)	Methadone	Australia	NA	0	Unknown	72	23.4
Caplehorn et al. 1996 (37)	Methadone	Australia	NA	0	Unknown	100	31.8
Fugelstad et al. 1995 (38)	Methadone	Sweden	100	0	38.6	50	29.3
Fugelstad et al. 1998 (39)	Methadone	Sweden	100	100	Unknown	71.5	28.0
Risser et al. 2001 (40)	Methadone	Austria	NA	67.9	Unknown	77	32.6
Buster et al. 2002 (41)	Methadone	Netherlands	34.7	NA	70	78	32.0
Scherbaum et al. 2002 (42)	Methadone	Germany	100	NA	Unknown	79	30.0
Esteban et al. 2003 (43)	Methadone	Spain	90	NA	Unknown	76.5	29.3
Brugal et al. 2005 (44)	Methadone	Spain	59	66	65.9	68.4	34.8
Soyka et al. 2006 (76)	Methadone	Germany	NA	51	13	80	31.5
Davoli et al. 2007 (46)	Methadone	Italy	72	5.9	Unknown	100	38.2
Fugelstad et al. 2007 (47)	Methadone	Sweden	NA	8	Unknown	67.6	39.6
Clausen et al. 2008 (48)	Methadone	Norway	92.5	27.5	Unknown	64.8	29.6
Degenhardt et al. 2009 (49)	Methadone	Australia	NA	3.5	Unknown	69.3	30.1
Cornish et al. 2010 (50)	Methadone	United Kingdom	NA	NA	41.6	73.6	37.6
Peles et al. 2010 (51)	Methadone	Israel	NA	NA	32.9	64.8	30.0
Cousins et al. 2011 (52)	Methadone	Scotland	NA	8.4	Unknown	88.0	37.0
Huang et al. 2011 (53)	Methadone	Taiwan	100	NA	10.7	85.1	35.8
Huang et al. 2013 (54)	Methadone	Taiwan	100	9	23.1	64.2	35.3
Evans et al. 2015 (55)	Methadone	United States	55.2	18.3	Unknown	65.8	33.4
Kimber et al. 2015 (19)	Methadone	Australia	NA	NA	22.8	68.7	30.5
Nosyk et al. 2015 (56)	Methadone	Canada	100	NA	34.3	71.4	34.5
Cousins et al. 2016 (57)	Methadone	Scotland	NA	100	Unknown	67.6	34.8
Russolillo et al. 2018 (58)	Methadone	Canada	NA	NA	Unknown	64.8	29.6
Soyka et al. 2006 (76)	Buprenorphine	Germany	92.5	3.5	Unknown	69.3	30.1
Degenhardt et al. 2009 (49)	Buprenorphine	Australia	NA	3.5	Unknown	73	30.5
Cornish et al. 2010 (50)	Buprenorphine	United Kingdom	NA	3.5	Unknown	70.7	32.5
Reece 2010 (59)	Buprenorphine	Australia	NA	NA	0	79	30.0
Kimber et al. 2015 (19)	Buprenorphine	Australia	NA	NA	2.9	73	38.5

PWID = people who inject drugs (the proportion of the cohort that was actively injecting); HIV+ = proportion of the cohort that were HIV positive; NA=not available

Table 2. Treatment delivery and follow-up features of cohort studies on mortality risk in people with opioid dependence during and after opioid agonist therapy with methadone or buprenorphine

Study	No of cohort participants [†]	Average OAT dose (mg/day)	Inpatient induction (%)	OAT Provider	Follow-up period	Average follow-up (years) [‡]	Loss to follow-up (%) [§]	Mortality outcome	Quality Score [¶]
Gearing et al. 1974 (33)	3000	100	17.6	Specialist	1965-1972	6.2	4	All, OD	9
Cushman 1977 (34)	547	100	NA	Specialist	1966-1975	3.6	23.2	All, OD	6
Grönbladh et al. 1990 (35)	166	75	100.0	Specialist	1967-1987	11	0	All, OD	4
Caplehorn et al. 1994 (36)	305	116	32.3	Specialist	1970-1990	13.9	14.4	OD	6
Caplehorn et al. 1996 (37)	305	116	32.3	Specialist	1970-1990	13.9	14.4	All, OD	6
Fugelstad et al. 1995 (38)	135	NA	100.0	Specialist	1986-1990	2.1	0	All	6
Fugelstad et al. 1998 (39)	56	80	100.0	Specialist	1986-1993	4.2	0	All	6
Risser et al. 2001 (40)	1729	NA	NA	NA	1995-1997	3.0	0	All, OD	11
Buster et al. 2002 (41)	5200	48	0.0	Mixed	1986-1998	5.7	0	All, OD	8
Scherbaum et al. 2002 (42)	244	47	0.0	Specialist	1988-1996	5.3	15.6	All, OD	7
Esteban et al. 2003 (43)	1487	NA	NA	NA	1990-1997	3.0	9.2	All, OD	11
Brugal et al. 2005 (44)	5049	71	NA	NA	1992-1997	4.6	0	All, OD	9
Soyka et al. 2006 (76)	2013	NA	NA	NA	1993-1994	1.0	39.6	All, OD	11
Davoli et al. 2007 (46)	5276	NA	0.0	Specialist	1998-2001	1.3	3.7	OD	11
Fugelstad et al. 2007 (47)	679	NA	100.0	Specialist	1988-2000	6.9	6.2	All	3
Clausen et al. 2008 (48)	3229	112	0.0	Mixed	1997-2003	2.4	0	All, OD	7
Degenhardt et al. 2009 (49)	31846	70	0.0	Mixed	1985-2000	6.8	0	All	17
Cornish et al. 2010 (50)	4894	50	0.0	GP	1990-2005	1.9	17.5	All	9
Peles et al. 2010 (51)	613	113	0.0	Specialist	1993-2008	7.7	0.8	All, OD	9
Cousins et al. 2011 (52)	3162	60	NA	NA	1993-2004	3.6	0	OD	11
Huang et al. 2011 (53)	1982	NA	NA	NA	2007-2008	1.0	0	All	14
Huang et al. 2013 (54)	1616	48.3	100.0	Specialist	2006-2008	0.5	38.9	All	13
Evans et al. 2015 (55)	32322	NA	0.0	Specialist	2006-2010	2.3	5	All	12
Kimber et al. 2015 (19)	26064	70	0.0	Mixed	2001-2010	5.3	0	All, OD	13
Nosyk et al. 2015 (56)	1326	NA	0.0	GP	1996-2010	4.2	7.9	All	13
Cousins et al. 2016 (57)	6983	72	0.0	GP	2004-2010	4.1	2	All, OD	11
Russolillo et al. 2018 (58)	14530	NA	NA	NA	1998-2015	6.9	0	All, OD	18
Soyka et al. 2006 (76)	662	NA	NA	NA	1993-1994	1.0	39.6	All, OD	11
Degenhardt et al. 2009 (49)	4494	NA	0.0	Mixed	2001-2006	6.8	0	All	17
Cornish et al. 2010 (50)	1373	10	0.0	GP	1990-2005	1.1	10.3	All	9
Reece 2010 (59)	2518	NA	0.0	GP	2000-2007	3.2	1.2	All	13
Kimber et al. 2015 (19)	11940	12	0.0	Mixed	2001-2010	4.5	0	All, OD	13

NA=not available; OAT=opioid agonist treatment; [†]Participants receiving opioid agonist treatment at least once during study period. [‡]Average follow-up from start of opioid agonist treatment combining subsequent periods in and out of treatment. [§]Percentage loss to follow-up before end of study period or death. If not otherwise specified, complete case ascertainment assumed for studies based on population mortality registries. [¶]Quality assessment score ranging from 0 (lowest quality) to 19 (highest quality).

Table 3. Bivariate meta-regression analysis of moderators for all-cause crude mortality rate reduction in-versus-out-of-treatment with opioid agonist therapy

Moderator	Coefficient	Standard Error	<i>p</i>-value
All-cause			
Pub. Year	0.003	0.009	0.746
HIV+ (%)	0.001	0.004	0.741
Psych (%)	-0.003	0.006	0.626
Men (%)	-0.007	0.010	0.472
Avg. OAT dose	-0.006	0.003	0.053
OAT Provider	-0.933	0.155	<0.001
PWID (%)	-0.011	0.008	0.156
Region	-0.979	0.116	<0.001
Country	-0.552	0.176	0.002
Quality Score	0.015	0.024	0.515
Mean Age	-0.020	0.023	0.391
Opioid Agonist	0.581	0.269	0.031
Overdose-specific			
Pub. Year	0.028	0.14	0.045
HIV+ (%)	0.003	0.012	0.791
Psych (%)	0.000	0.012	0.989
Men (%)	-0.049	0.032	0.123
Avg. OAT dose	-0.011	0.007	0.105
OAT Provider	-1.135	0.260	<0.001
PWID (%)	-0.038	0.010	<0.001
Region	-1.383	0.227	<0.001
Country	-1.175	0.376	0.002
Quality Score	0.064	0.048	0.187
Mean Age	-0.016	0.048	0.740
Opioid Agonist	0.575	0.695	0.408

Appendix 1. Search Strategy

MEDLINE: inception to June 11, 2019

Order	Search Term	Results
1.	exp Methadone/	11975
2.	buprenorphine.mp. or exp Buprenorphine, Naloxone Drug Combination/ or exp Buprenorphine/	6980
3.	exp Opiate Substitution Treatment/ or opioid agonist therapy.mp.	2601
4.	exp Mortality/ or mortality.mp.	1174420
5.	exp Drug Overdose/ or overdose.mp.	20960
6.	1 or 2 or 3	18276
7.	4 or 5	1191797
8.	6 and 7	1385
9. 1	Limit 9 to English and Humans	1102

EMBASE: inception to June 11, 2019

Order	Search Term	Results
1.	exp methadone treatment/ or methadone.mp. or exp methadone/	34543
2.	buprenorphine.mp. or exp buprenorphine plus naloxone/ or exp buprenorphine/	17718
3.	opioid agonist therapy.mp. or exp hydromorphone/ or exp levacetylmethadol/	699
4.	exp mortality/ or mortality.mp	1413186
5.	exp drug overdose/ or opioid overdose.mp.	25869
6.	1 or 2 or 3	45658
7.	4 or 5	1436157
8.	6 and 7	3481
9.	exp cohort analysis/ or cohort.mp.	902712
10.	8 and 9	318

PsycINFO: inception to June 11, 2019

Order	Search Term	Results
1.	exp Methadone Maintenance/ or exp Methadone/ or methadone.mp.	7858
2.	buprenorphine.mp. or exp Buprenorphine/	2780
3.	opioid agonist.mp.	1048
4.	1 or 2 or 3	10078
5.	mortality.mp. or exp "Death and Dying"/	60500
6.	exp Drug Overdoses/ or opioid overdose.mp.	1774
7.	5 or 6	61836
8.	4 and 7	534

CINAHL: inception to June 11, 2019

Order	Search Term	Results
1.	(MH "Methadone") OR "methadone"	5696
2.	(MH "Buprenorphine") OR "buprenorphine"	3494

3.	"opioid agonist therapy"	157
4.	(MH "Mortality") OR "mortality"	246,139
5.	(MH "Overdose") OR "opioid overdose"	6,086
6.	1 or 2 or 3	7,943
7.	4 or 5	250,896
8.	6 and 7	731

Cochrane CENTRAL Library: inception to June 11, 2019

Order	Search Term	Results
1.	MeSH descriptor: [Analgesics, Opioid] explode all trees	6907
2.	MeSH descriptor: [Methadone] explode all trees	1163
3.	MeSH descriptor: [Buprenorphine] explode all trees	1017
4.	MeSH descriptor: [Mortality] explode all trees	12668
5.	(1 or 2 or 3) and 4	12

ProQuest Dissertations & Theses: inception to June 11, 2019

Order	Search Term	Results
1.	("methadone" OR "buprenorphine") AND "mortality" AND "cohort" AND ("opioid dependence" OR "opioid use disorder")/	430

Allied and Complementary Medicine: inception to June 11, 2019

Order	Search Term	Results
1.	Methadone/ or analgesics opioid/ or methadone.mp.	474
2.	Buprenorphine/ or buprenorphine.mp.	49
3.	1 or 2	499
4.	Mortality/ or mortality.mp.	3086
5.	3 and 4	14

Web of Science: inception to June 11, 2019

Order	Search Term	Results
1.	(methadone or buprenorphine or opioid agonist therapy)	22,814
2.	(mortality)	883,467
3.	1 and 2	1,106

Appendix 2. Reporting checklist for meta-analysis of observational studies based on the MOOSE guidelines.

Segment	Reporting Item	Page Number
Title	Identify the study as a meta-analysis of observational research	1
Abstract	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number (From PRISMA checklist)	2
Background	Problem definition	3
	Hypothesis statement	4
	Description of study outcomes	4
	Type of exposure or intervention used	5
	Type of study designs used	5
	Study population	5
Methods	Qualifications of searchers (e.g., librarians and investigators)	5
	Search strategy, including time period included in the synthesis and keywords	5
	Effort to include all available studies, including contact with authors	5
	Databases and registries searched	5
	Search software used, name and version, including special features used (e.g., explosion)	5
	Use of hand searching (e.g., reference lists of obtained articles)	5
	List of citations located and those excluded, including justification	5
	Method of addressing articles published in languages other than English	5
	Method of handling abstracts and unpublished studies	5
	Description of any contact with authors	5
	Description of relevance or appropriateness of studies gathered for assessing the hypothesis to be tested	5
	Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)	6
	Documentation of how data were classified and coded (e.g., multiple raters, blinding, and interrater reliability)	6
	Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate)	6
	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	6
	Assessment of heterogeneity	6
	Description of statistical methods (e.g., complete description of fixed or random effects models,	6

	justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	
	Provision of appropriate tables and graphics	6
Results	Graphic summarizing individual study estimates and overall estimate	8-9
	Table giving descriptive information for each study included	8-9
	Results of sensitivity testing (e.g., subgroup analysis)	8-9
	Indication of statistical uncertainty of findings	8-9
Discussion	Quantitative assessment of bias (e.g. publication bias)	22-23
	Justification for exclusion (e.g., exclusion of non-English-language citations)	10-13
	Assessment of quality of included studies	10-13
Conclusion	Consideration of alternative explanations for observed results	10-13
	Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review)	10-13
	Guidelines for future research	10-13
	Disclosure of funding source	10-13

Appendix 3. Quality Assessment Scores

Study	Case Ascertainm ent	Measurement	Diagnosis	Estimate	Numerator & Denominator	Numerator & Denominator Epoch	Completeness	Representativeness	Age/Sex	Quality
Gearing et al. 1974 (33)	2	2	0	1	1	1	0	1	1	9
Cushman 1977 (34)	1	1	0	1	1	0	0	1	1	6
Grönbladh et al. 1990 (35)	0	0	0	0	1	1	0	1	1	4
Caplehorn et al. 1994 (36)	1	0	0	1	1	1	0	1	1	6
Caplehorn et al. 1996 (37)	1	1	1	0	0	0	1	1	1	6
Fugelstad et al. 1995 (38)	1	1	1	1	1	1	0	0	0	6
Fugelstad et al. 1998 (39)	0	0	0	1	1	1	2	0	1	6
Risser et al. 2001 (40)	1	1	2	1	1	1	2	1	1	11
Buster et al. 2002 (41)	1	1	1	1	1	1	1	1	0	8
Scherbaum et al. 2002 (42)	1	1	1	1	0	1	1	0	1	7
Esteban et al. 2003 (43)	1	0	1	2	2	1	2	1	1	11
Brugal et al. 2005 (44)	2	1	2	0	0	0	1	2	1	9
Soyka et al. 2006	1	1	1	2	2	1	1	1	1	11

(76)										
Davoli et al. 2007 (46)	1	1	1	2	2	1	1	1	1	11
Fugelstad et al. 2007 (47)	0	0	1	0	0	0	1	0	1	3
Clausen et al. 2008 (48)	0	1	1	1	1	1	1	0	1	7
Degenhardt et al. 2009 (49)	3	2	2	2	2	1	1	3	1	17
Cornish et al. 2010 (50)	0	0	1	2	2	1	2	0	1	9
Peles et al. 2010 (51)	1	1	1	1	1	1	1	1	1	9
Cousins et al. 2011 (52)	2	1	1	1	1	1	1	2	1	11
Huang et al. 2011 (53)	2	0	2	2	2	1	2	2	1	14
Huang et al. 2013 (54)	2	2	2	1	1	1	1	2	1	13
Evans et al. 2015 (55)	2	2	1	1	1	0	2	2	1	12
Kimber et al. 2015 (19)	1	2	1	1	1	1	2	3	1	13
Nosyk et al. 2015 (56)	3	2	2	1	1	1	1	1	1	13
Cousins et al. 2016 (57)	2	1	1	1	1	1	1	2	1	11
Russolillo et al. 2018	3	2	1	2	2	1	3	3	1	18

(58)										
Soyka et al. 2006 (76)	1	1	1	2	2	1	1	1	1	11
Degenhardt et al. 2009 (49)	3	2	2	2	2	1	1	3	1	17
Cornish et al. 2010 (50)	0	0	1	2	2	1	2	0	1	9
Reece 2010 (59)	2	0	1	2	2	1	2	2	1	13
Kimber et al. 2015 (19)	1	2	1	1	1	1	2	3	1	13

Quality Assessment Index

1. Case Ascertainment (/3)
 - a. Were the results on crude mortality clearly specified?
 - i. Yes: 1/1
 - ii. No: 0/1
 - b. Were the results on overdose mortality clearly specified?
 - i. Yes: 1/1
 - ii. No: 0/1
 - c. Were the timelines with respect to opioid agonist therapy clearly specified?
 - i. Yes: 1/1
 - ii. No: 0/1
2. Measurement (/2)
 - a. Was a measurement instrument used to assess exposure of interest?
 - i. Yes: 1/1
 - ii. No: 0/1
 - b. Was a measurement instrument used to assess outcome of interest?
 - i. Yes: 1/1
 - ii. No: 0/1
3. Diagnosis (/2)
 - a. Were eligibility criteria for inclusion in the cohort described in detail?
 - i. Fully described: 2/2
 - ii. Partially described: 1/2
 - iii. No: 0/2
4. Estimate (/2)
 - a. Was the mortality rate clearly reported?
 - i. Yes: 1/1
 - ii. No: 0/1
 - b. Were the time-dependent mortality rates (in/out of opioid agonist therapy) clearly reported?
 - i. Yes: 1/1
 - ii. No: 0/1
5. Numerator & Denominator (/2)
 - a. Were the person years of follow-up reported?
 - i. Yes: 1/1
 - ii. No: 0/1
 - b. Were the number of deaths (overall and overdose-specific) reported?
 - i. Yes: 1/1
 - ii. No: 0/1
6. Numerator & Denominator Epoch (/1)
 - a. Were the mortality estimates and timelines for opioid agonist therapy for the same cohort of individuals (i.e., were the same timelines used)?
 - i. Yes: 1/1
 - ii. No: 0/1
7. Completeness (/3)
 - a. To what extent did the study have complete follow-up for its participants?
 - i. $\geq 70\%$: 3/3
 - ii. $> 50\%$: 2/3
 - iii. Reported but $< 50\%$: 1/3
 - iv. Not reported: 0/3
8. Representativeness (/3)

- Accepted Article
- a. Nationally/internationally representative sample: 3/3
 - b. Regionally representative (e.g., within one province or state): 2/3
 - c. Locally representative (e.g., single hospital/center): 1/3
 - d. Not described: 0/3
9. Age & Sex (/1)
- a. Were the potential confounding effects of age and sex were taken into account by the study?
 - i. Yes: 1/1
 - ii. No: 0/1
10. Quality
- a. Global quality score obtained by summing the scores from other domains (0-19).

Appendix 4. Assessment of Publication Bias for All-Cause Mortality Rates

- Funnel plot for risk of publication bias in crude all-cause mortality rate appeared grossly symmetric.
- Rank Correlation Test for Funnel Plot Asymmetry
 - Kendall's tau = 0.1008, p = 0.4299
- Regression Test for Funnel Plot Asymmetry
 - model: mixed-effects meta-regression model
 - predictor: standard error
 - test for funnel plot asymmetry: z = -0.1516, p = 0.8795
- Estimated number of missing studies on the right side: 0 (SE = 3.3308)
 - Random-Effects Model (k = 32; tau² estimator: REML)
 - tau² (estimated amount of total heterogeneity): 0.6506 (SE = 0.1713)
 - tau (square root of estimated tau² value): 0.8066
 - I² (total heterogeneity / total variability): 99.41%
 - H² (total variability / sampling variability): 168.71

Accepted Article

Appendix 5. Assessment of Publication Bias for Overdose-Specific Mortality Rate

- Funnel plot for risk of publication bias in crude overdose-specific mortality rate appeared grossly symmetric.
- Rank Correlation Test for Funnel Plot Asymmetry
 - Kendall's tau = 0.0476, p = 0.7884
- Regression Test for Funnel Plot Asymmetry
 - model: mixed-effects meta-regression model
 - predictor: standard error
 - test for funnel plot asymmetry: z = -0.5015, p = 0.6160
- Trim & Fill
 - Estimated number of missing studies on the right side: 1 (SE = 2.9218)
 - $\text{Tau}^2 = 0.4691$ (SE = 0.1553), $I^2 = 98.58\%$; $H^2 = 70.32$; $Q(\text{df}=21) = 1139.8436$

Appendix 6. Leave-out-one meta-analysis for all-cause mortality reduction with opioid agonist therapy

Appendix 7. Leave-out-one meta-analysis for overdose-specific mortality reduction with opioid agonist therapy

Appendix 8. Absolute all-cause crude mortality rates within and outside of opioid agonist therapy treatment

All-cause CMR	Est. (per 1000 PY)	95% CI	<i>k</i>	<i>I</i> ²	<i>Q</i>	<i>p</i>
Overall	13.5	10.1-17.9	32	99.41	3520.0315	< .0001
Treatment Class						
Methadone	14.9	10.8-20.5	27	99.49	3285.4341	< .0001
Buprenorphine	7.4	6.3-8.8	5	59.38	7.9869	0.0921
In Treatment						
Overall	8.6	6.4-11.6	32	98.20	976.9908	< .0001
Methadone	9.1	6.5-12.8	27	98.55	931.6551	< .0001
Buprenorphine	6.0	3.9-9.2	5	68.30	14.7081	0.0053
Out of Treatment						
Overall	22.6	16.3-31.3	32	99.31	2685.1150	< .0001
Methadone	26.8	19.1-37.6	27	99.31	2358.0911	< .0001
Buprenorphine	8.6	6.5-11.3	5	79.90	13.9189	< .0001
First Four Weeks in Treatment						
Overall	8.8	5.2-14.9	12	89.53	153.2216	< .0001
Methadone	10.1	5.5-18.3	9	91.99	132.3523	< .0001
Buprenorphine	4.5	2.5-8.1	3	0.00	1.4007	0.4964
First Four Weeks off Treatment						
Overall	31.5	14.6-68.0	12	98.26	686.0263	< .0001
Methadone	32.9	12.1-89.1	9	98.85	622.5066	< .0001
Buprenorphine	26.3	9.1-75.9	3	87.52	14.6525	0.0007
After Four Weeks in Treatment						
Overall	5.0	3.4-7.4	12	97.99	258.3877	< .0001
Methadone	4.8	2.8-8.1	9	98.78	241.8985	< .0001
Buprenorphine	4.7	3.3-6.6	3	47.63	4.1226	0.1273
After Four Weeks off Treatment						
Overall	11.8	7.3-19.2	12	99.38	603.3532	< .0001
Methadone	13.5	7.3-24.9	9	99.53	515.5760	< .0001
Buprenorphine	9.1	8.0-10.3	3	25.15	3.0704	0.2154

CMR = crude mortality rate; 95% CI = 95% confidence interval for estimate; *p* = probability of finding the observed value (or greater) by chance alone (*p* < 0.05 statistically significant); *k* = number of studies reporting selected estimate; *I*² = measure of statistical heterogeneity; *Q* = Cochran's chi-square test of heterogeneity; *p* (*Q*) = corresponding *p*-value for the Cochran's chi-square test of heterogeneity; PY = person years of follow-up; NA = not applicable

Appendix 9. Relative differences in all-cause crude mortality within and outside of opioid agonist therapy treatment

All-cause CMR in/out of treatment	Estimate	95% CI	<i>p</i>	<i>k</i>	<i>I</i> ²	<i>Q</i>	<i>p</i> (<i>Q</i>)
Mortality Rate Difference (MRD)	Per 1000 PY						
Overall	18.2	10.7-25.6	< .0001	32	99.54	523.0815	< .0001
Methadone	21.8	13.3-30.3	< .0001	27	99.58	497.0774	< .0001
Buprenorphine	3.0	-0.1-6.1	0.0581	5	65.01	12.4331	< .0001
MRD: first four weeks							
Overall	63.4	-21.2-148.2	0.1419	12	99.89	222.8883	< .0001
Methadone	79.5	-42.9-201.9	0.2028	9	99.93	217.5059	< .0001
Buprenorphine	12.8	6.5-19.0	< .0001	3	2.03	2.8452	0.2411
MRD: after four weeks							
Overall	10.2	1.7-18.8	0.0190	12	99.62	216.7259	< .0001
Methadone	13.4	2.0-24.7	0.0211	9	99.73	206.1885	< .0001
Buprenorphine	3.2	-1.7-8.0	0.1998	3	87.56	6.2859	0.0432
Mortality Rate Ratio (MRR)							
Overall	2.70	2.25-3.24	< .0001	32	90.00	183.5340	< .0001
Methadone	2.89	2.40-3.50	< .0001	27	90.35	167.4230	< .0001
Buprenorphine	1.62	0.99-2.65	0.0571	5	61.97	12.8583	0.0120
MRR: first four weeks							
Overall	3.57	1.79-7.12	0.0003	12	89.50	129.3119	< .0001
Methadone	3.29	1.37-7.89	0.0078	9	93.21	126.1002	< .0001
Buprenorphine	4.25	2.17-8.33	< .0001	3	0.00	0.2763	0.8710
MRR: after four weeks							
Overall	2.37	1.95-2.87	< .0001	12	83.27	66.6493	< .0001
Methadone	2.50	1.98-3.17	< .0001	9	87.88	60.4455	< .0001
Buprenorphine	1.78	1.01-3.16	0.0479	3	71.12	5.7859	0.0554

CMR = crude mortality rate; 95% CI = 95% confidence interval for estimate; *p* = probability of finding the observed value (or greater) by chance alone (*p* < 0.05 statistically significant); *k* = number of studies reporting selected estimate; *I*² = measure of statistical heterogeneity; *Q* = Cochran's chi-square test of heterogeneity; *p* (*Q*) = corresponding *p*-value for the Cochran's chi-square test of heterogeneity; PY = person years of follow-up; NA = not applicable

Appendix 10. Absolute overdose-specific crude mortality rates within and outside of opioid agonist therapy treatment

Overdose CMR	Est. (per 1000 PY)	95% CI	<i>k</i>	<i>I</i> ²	<i>Q</i>	<i>p</i>
Overall	5.5	4.0-7.4	21	98.55	1086.4248	< .0001
Treatment Class						
Methadone	5.7	4.2-7.8	19	98.66	1024.2360	< .0001
Buprenorphine	3.3	2.8-3.8	2	0.00	0.0002	0.9891
In Treatment						
Overall	2.8	2.1-3.6	21	93.08	313.6804	< .0001
Methadone	2.9	2.2-3.9	19	93.18	272.6096	< .0001
Buprenorphine	2.2	0.7-6.8	2	73.07	3.7140	0.0540
Out of Treatment						
Overall	11.5	7.7-11.71	21	98.86	872.5435	< .0001
Methadone	12.4	8.2-18.8	19	98.88	795.1033	< .0001
Buprenorphine	4.6	3.9-5.4	2	0.00	0.3821	0.5365
First Four Weeks in Treatment						
Overall	3.6	1.6-8.2	5	83.70	16.97	0.0020
Methadone	4.6	2.1-10.0	4	81.37	11.43	0.0096
Buprenorphine	1.0	0.2-3.8	1	NA	0.00	1.00
First Four Weeks off Treatment						
Overall	8.3	3.0-23.2	5	91.67	37.0783	< .0001
Methadone	7.6	2.0-29.3	4	92.56	37.0582	< .0001
Buprenorphine	10.8	6.8-17.1	1	NA	0.00	1.00
After Four Weeks in Treatment						
Overall	1.9	1.6-2.3	5	55.23	8.9218	0.0631
Methadone	2.0	1.6-2.5	4	55.23	6.9723	0.0728
Buprenorphine	1.5	1.0-2.1	1	NA	0.00	1.00
After Four Weeks off Treatment						
Overall	4.2	3.0-5.8	5	87.65	17.1815	0.0018
Methadone	4.1	2.6-6.6	4	86.56	16.7453	0.0008
Buprenorphine	4.2	3.5-5.0	1	NA	0.00	1.00

CMR = crude mortality rate; 95% CI = 95% confidence interval for estimate; *p* = probability of finding the observed value (or greater) by chance alone (*p* < 0.05 statistically significant); *k* = number of studies reporting selected estimate; *I*² = measure of statistical heterogeneity; *Q* = Cochran's chi-square test of heterogeneity; *p* (*Q*) = corresponding *p*-value for the Cochran's chi-square test of heterogeneity; PY = person years of follow-up; NA = not applicable

Appendix 11. Relative differences in overdose-specific crude mortality within and outside of opioid agonist therapy treatment

Overdose CMR in vs. out of treatment	Estimate	95% CI	<i>p</i>	<i>k</i>	<i>I</i> ²	<i>Q</i>	<i>p (Q)</i>
Mortality Rate Difference (MRD)	Per 1000 PY						
Overall	9.9	5.4-14.4	< .0001	21	99.36	339.7977	< .0001
Methadone	11.1	6.3-15.9	< .0001	19	99.34	333.8455	< .0001
Buprenorphine	1.0	-5.0-7.0	0.7338	2	63.88	2.7686	0.0961
MRD: first four weeks							
Overall	4.5	-2.8-11.9	0.2238	5	88.19	26.1832	< .0001
Methadone	3.6	-6.1-13.3	0.4706	4	90.84	15.8177	0.0012
Buprenorphine	9.8	4.7-14.9	0.0002	1	NA	0	1.00
MRD: after four weeks							
Overall	2.2	0.8-3.7	0.0030	5	86.04	20.2233	0.0005
Methadone	2.1	0.1-4.1	0.0351	4	87.37	19.4751	0.0002
Buprenorphine	2.8	1.9-3.7	< .0001	1	NA	0	1.00
Mortality Rate Ratio (MRR)							
Overall	3.88	2.74-5.51	< .0001	21	93.55	169.6250	< .0001
Methadone	4.06	2.80-5.88	< .0001	19	94.19	167.4642	< .0001
Buprenorphine	1.80	0.27-12.10	0.5438	2	51.75	2.0724	0.1500
MRR: first four weeks							
Overall	2.42	0.67-8.74	0.1765	5	84.98	22.1676	0.0002
Methadone	1.72	0.43-6.82	0.4408	4	85.42	17.0547	0.0007
Buprenorphine	11.26	2.61-48.52	0.0012	1	NA	0	1.00
MRR: after four weeks							
Overall	2.19	1.46-3.27	0.0001	5	77.60	14.7889	0.0052
Methadone	2.02	1.22-3.33	0.0062	4	80.02	14.1115	0.0028
Buprenorphine	2.89	1.93-4.33	< .0001	1	NA	0	1.00

CMR = crude mortality rate; 95% CI = 95% confidence interval for estimate; *p* = probability of finding the observed value (or greater) by chance alone (*p* < 0.05 statistically significant); *k* = number of studies reporting selected estimate; *I*² = measure of statistical heterogeneity; *Q* = Cochran's chi-square test of heterogeneity; *p (Q)* = corresponding *p*-value for the Cochran's chi-square test of heterogeneity; PY = person years of follow-up; NA = not applicable

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