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Complete List of Authors:	Klimas, Jan; BC Centre on Substance Use; University of British Columbia, Department of Medicine Gorfinkel, Lauren; BC Centre on Substance Use Giacommuzi, Salvatore; Universitätsklinik Innsbruck-Ambulanz für Abhängigkeitserkrankungen Ruckes, Christian; University Medical Center Mainz, Interdisciplinary Center Clinical Trials Socías, M. Eugenia; BC Centre on Substance Use; University of British Columbia, Department of Medicine Fairbairn, Nadia; BC Centre on Substance Use; University of British Columbia, Department of Medicine Wood, Evan; BC Centre on Substance Use; University of British Columbia, Department of Medicine
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Slow Release Oral Morphine versus Methadone for the Treatment of Opioid Use Disorder: A Systematic Review and Meta-Analysis

Klimas, Jan[1,3], Gorfinkel, Lauren[1], Giacomuzzi, Salvatore[5], Ruckes, Christian[4], Socías, M. Eugenia[1,2], Fairbairn, Nadia[1,2], Wood, Evan[1,2]

1. British Columbia Centre for Substance Use, 400-1045 Howe Street, Vancouver, BC, CANADA, V6Z 1Y6
2. Department of Medicine, University of British Columbia, St. Paul's Hospital, 608-1081 Burrard Street, Vancouver, BC, CANADA, V6Z 1Y6
3. School of Medicine, University College Dublin, Health Sciences Centre, Belfield, Dublin 4, Ireland
4. University Medical Center Mainz, Interdisciplinary Center Clinical Trials (IZKS), Langenbeckstraße 1 · D-55131 Mainz, Germany
5. Universitätsklinik Innsbruck-Ambulanz für Abhängigkeitserkrankungen, Anichstraße 35, 6020 Innsbruck, Austria

JK and LG contributed equally to this paper.

Send correspondence to:

Jan Klimas, PhD, MSc
B.C. Centre on Substance Use
University on British Columbia
400-1045 Howe Street, Vancouver, B.C., V6Z 1Y6
Canada
Tel: (778) 945-7616
Fax: (604) 806-9044
Email: jan.klimas@bccsu.ubc.ca

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ABSTRACT

Objectives: To assess the efficacy of Slow release oral morphine (SROM) as a treatment for opioid use disorder.

Design: Systematic review and meta-analysis of randomized controlled trials.

Methods: We searched three electronic databases for randomized trials published up to May 2018 and reviewed reference lists of published studies. Data were pooled using a random-effects meta-analytic model.

Setting: All four trials were conducted in 17 outpatient secondary care centres.

Participants: Trials were included if their participants met the diagnostic criteria for opioid use disorder, with a treatment arm involving SROM.

Interventions: SROM versus Methadone

Primary and secondary outcome measures: Treatment retention, opioid use and craving.

Results: Among 1315 studies reviewed, four unique randomized trials met inclusion criteria (n = 471), and compared SROM with methadone. In the meta-analysis, we observed no significant differences between SROM and methadone in improving treatment retention (risk ratio [RR] = 0.98; 95% Confidence Interval [CI]: 0.94 - 1.02, p = 0.34), and heroin use (RR = 0.96; 95% CI: 0.61- 1.52, p = 0.86). Craving data was not amenable to meta-analysis but overall implied that SROM reduces heroin cravings to a greater extent than methadone (P < 0.0001, measured using a visual analogue scale; P = 0.010, measured using the heroin craving questionnaire). As well, results implied no significant differences between SROM and methadone on self-reported use of heroin, cocaine, or benzodiazepines. Available data implied no differences in adverse events.

Conclusions: Meta-analysis of existing randomized trials suggests SROM may be as effective in retaining patients in treatment and reducing heroin use as methadone while potentially resulting in less craving. While methadone is effective for many patients, these findings suggest SROM may provide benefits in addressing some of the limitations of methadone and the need to expand uptake and retention of individuals on opioid use disorder treatments.

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Strengths and limitations of this study

- The first meta-analysis of slow release oral morphine.
- We included new studies that increase the validity of the study.
- We included previously unpublished data obtained from primary trials.
- A meta-analysis of craving and adverse events was not possible due to inconsistent reporting of outcome measures across trials

INTRODUCTION

Overdose is the dominant cause of untimely death among people with opioid use disorder, and in 2017, opioid ovrdose was declared a national public health emergency in the U.S. Approximately two million Americans have a diagnosed opioid use disorder,[1] and deaths due to opioid overdoses have nearly doubled since 2006, exceeding 46,000 in 2016.[2] In response, the past decade has witnessed an expansion of pharmaceutical interventions for OUD, including the opioid agonist therapies methadone and buprenorphine/naloxone. Opioid agonist therapy (OAT) is currently the first-line treatment for OUD recommended by the World Health Organization (WHO) and a number of federal health guidelines.[3-5]

While methadone and buprenorphine/naloxone are proven effective,[6 7] they have a known limited ability to attract and retain patients in treatment. For instance, past studies have demonstrated that most individuals who overdose are not on agonist treatment at the time of death, and that, overall, agonist therapies remain sorely underutilised with only a fraction of eligible patients in U.S. accessing these therapies.[8-10] While overall low rates of methadone- and buprenorphine/naloxone-use are partially due to poor access and limited service delivery,[10] the side-effects (e.g., sweating, weight gain), and other limitations of these therapies, also result in low rates of patient retention once individuals initiate therapy.[11] The issues of poor uptake and retention on OAT are particularly urgent in the context of elevated mortality among those not on OAT and the reported dramatic rise in mortality following OAT interruption,[12] as well as increasing overdose rates as a result of the emergence of highly toxic fentanyl analogues in the illicit drug markets of many settings.

In light of increasing recognition that additional forms of opioid agonist therapy are necessary for some persons with OUD, interest in slow release oral morphine (SROM) as an OUD treatment agent has steadily grown.[8 13] A 2013 review by the Cochrane Collaboration reviewed the literature for SROM as treatment for OUD. However, the review was ultimately unable to draw definite conclusions regarding

effectiveness, identifying only three high quality clinical trials.[14] However, some unpublished data were not included in this review, and since the time of its publication, a number of new studies investigating SROM have emerged, including a large international randomized controlled trial from Switzerland and Germany.[15] In light of the known limitations of methadone and buprenorphine/naloxone, these new data on the efficacy of SROM, as well as the need to identify viable OAT options that may be more attractive to patients in the context of the current opioid-related public health emergency, the present systematic review and meta-analysis was conducted to assess the efficacy of slow-release oral morphine as a treatment for opioid use disorder as measured by treatment retention, heroin use, and opioid craving.

METHODS

Data sources and searches

In this report, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[16] Three electronic databases were searched to obtain relevant trials published in the past five years since the date of search of the Cochrane Collaboration review (up to April 2018): the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE. These databases were searched by combining selected MeSH terms and free-text terms related to OUD and SROM. We also searched the following electronic registers for ongoing trials: ClinicalTrials.gov (www.clinicaltrials.gov), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/), Current Controlled Trials (www.controlled-trials.com/), EU Clinical Trials Register (www.clinicaltrialsregister.eu), the Italian Medicines Agency (www.agenziafarmaco.gov.it/en), and Trials (www.trialsjournal.com). References of all relevant papers were reviewed to identify further studies of relevance. Authors of potentially relevant studies were contacted for further unpublished data.

Study Selection

All English-language, scientifically peer-reviewed studies were eligible for inclusion. Studies were included if they met the following criteria: 1) studies were scientifically peer-reviewed; 2) they employed RCT methods (with no requirement for blinding); 3) participants met diagnostic criteria for OUD as defined in the DSM-IV or DSM-V manuals; 4) treatment was defined as SROM with or without an accompanying psychosocial intervention; and 5) control conditions were defined as medication-only, regardless of other concurrent treatment; and 6) outcomes assessed included treatment retention, and/or efficacy (i.e., any measure of change in opioid use).

Outcome Measures

The following outcomes were assessed: 1) Treatment retention, measured using dropout rates; 2) Efficacy, defined as the number of urine drug tests positive for illicit substances (incl. metabolites 6-Monoacetylmorphine [6-MAM] and 6-acetylcodeine [6-A-cod]) during the longest follow-up period in each study (or final weeks of pre-switch phase in case of cross-over trials); 3) Craving reduction, assessed through subjective reduction of scores on opioid-craving scales specific to each study. These outcomes were often assessed multiple times throughout the study period and measured across varied time intervals ranging from 1-24 weeks, depending on study length. Other, less common outcomes, including Quality of Life measures, satisfaction, physical complaints, and mental health were also reported. The level of statistical significance to assess differences between treatment and control groups was set *a priori* at $p < 0.05$.

It is noteworthy that with the new terminology changes to the Diagnostic Statistical Manual (DSM-V), opioid abuse and dependence have been combined into opioid use disorder, which can be labeled as mild, moderate, or severe. Although imprecise, opioid abuse can equate to moderate or severe

OUD, while opioid dependence is similar to the mild subtype.[17 18]

Data extraction

All citations identified by search were independently screened based on title and abstract by two reviewers (LG, AA). Each potentially relevant study was then reviewed in full text and assessed for all inclusion criteria. Any disagreements were resolved by discussion among reviewers (LG, AA) and additional investigators (JK, EW). Relevant data from eligible articles (i.e., socio-demographics, type of interventions, outcomes, etc.) were then extracted.

Quality Assessment

Study quality was assessed according to the criteria indicated in the Cochrane Handbook for Systematic Reviews of Interventions.[16] Each study was assessed for risk of bias in random sequence generation and allocation concealment (i.e., selection bias). Blinding of participants and personnel (i.e., performance bias) and of outcome assessment (i.e., detection bias; objective and subjective outcomes were combined) were measured; however, since blinding was considered unlikely to affect study outcome in this context,[14] open-label studies were included. Incomplete outcome data (i.e., attrition bias) was recorded for each eligible study. Each category of bias was assigned a rating of low, high or unclear risk using protocols from the Cochrane Handbook.

Data Synthesis and Analysis

For the meta-analysis, dichotomous outcome measures (treatment retention, continuous abstinence) were analysed by calculating the risk ratio (RR) for each trial, with uncertainty in each result expressed via 95% confidence intervals (CIs). Continuous outcomes, such as craving, were analysed by calculating the mean difference (MD) between experimental and control groups.

Information on missing data was collected where possible from study authors. If study authors were unable to supply this information, missing data were obtained or calculated from values in the primary

studies according to suggested procedures in the Cochrane Handbook for Systematic Reviews of Interventions.[16]

Given the expected heterogeneity of results among studies due to differences in population and intervention-type, we employed a random-effects meta-analytic model. The I-squared (I^2) statistic was employed to test the presence of heterogeneity between trials, and a sensitivity analysis was undertaken to assess the impact of particular high-risk trials.

RESULTS

We considered all peer-reviewed articles and identified 1315 potentially eligible studies published since the date of search in the previous Cochrane Collaboration review.[14] After removal of duplicates and the application of inclusion criteria (Figure 1), 993 abstracts were screened and only eight reports – out of the 13 full texts reviewed – met all inclusion criteria.[15 19-25] Four reports were excluded due to not meeting inclusion criteria, and one was excluded because the study protocol paper did not report outcome data. Because some trials were the subject of multiple reports, only four unique studies (n = 471) were eligible for quantitative synthesis. We considered data from all available high-quality trials as well as previously unpublished data from trial authors. One study did not report data of interest for this review other than treatment retention.[22]

All participants in the included studies met the DSM-IV or V diagnostic criteria for OUD; mean age 33.1 years; of the three studies that reported on gender,[15 22 23] 24.4% were female. The mean duration of trials was 18 weeks (range 11 to 24 weeks). The mean dose of SROM provided to participants was 506.8 mg/day, and the mean dose of methadone was 67.2 mg/day. All four studies were conducted in an outpatient setting, and assessed SROM *vs.* methadone, with only one study by Giacomuzzi et al.[23]

explicitly stating psychosocial support. This study also assessed buprenorphine in comparison with SROM and methadone.[23]

Quality assessments for each study are presented in Table 1. Three out of four studies were found to be at low risk for selection bias – the final study's selection bias was agreed to be unclear, due to an unspecified randomization technique.[23] There was mixed-risk of bias relating to blinding of participants and outcome assessments; however, as noted by Ferri et al., objective outcomes -such as retention and urine drug screens- are unlikely to be impacted by a lack of blinding.[14] Three of the four included RCTs were therefore open-label.[15 23 24] All four studies were found to be at low risk for attrition bias. Additionally, differences in our risk of bias assessment and the previous Cochrane review were also identified.[14] For the trial by Giacomuzzi et al.,[23] we assessed blinding of outcome assessment to be of high risk while the previous review assigned unclear risk. Blinding of outcome assessment was not possible because the treating physician could terminate patients if three consecutive urine tests were found positive for 6-MAMmam (data from Dr Giacomuzzi).

Treatment retention was assessed via the dropout rate in all studies. Unpublished data regarding treatment retention was obtained from the authors of one study.[23] With respect to measures of opioid use, the number of participants with urine drug tests positive for illicit substances was reported in two studies.[15 24] Unpublished data on positive urine tests was obtained from one study.[23] Measures of craving using various rating scales were used in three studies,[15 22 24] though one did not report the necessary outcome data for meta-analysis to be performed.[22]

Systematic Review Results

A 2013 Cochrane review by Ferri et al. described three trials included in the present analysis.[14] Clark et al.,[24] and Eder et al.,[22] both performed crossover, randomized controlled trials, wherein participants with OUD were randomized to take either SROM or methadone for the first half of the trial period, then

subsequently switched to the other treatment for the second half of the trial period. According to the published conference abstract and M.D. thesis, Clark et al.,[26] conducted a 12-week open-label crossover study that required patients to be taking methadone prior to enrolling (n=9). The authors found SROM to have lower retention than methadone; however, no significant differences were found in regards to heroin use (6-Monoacetylmorphine [6-MAM]) in the last four weeks of treatment, use of other drugs over the study period, dollars spent on heroin in the final week of treatment, mental health and social functioning (as measured by the BASIS-32 Behavior and Symptom Identification Scale), self-reported days of heroin use, or heroin cravings. SROM was found to yield significantly lower scores on subjective opiate withdrawal ($p < 0.001$). Eder et al. conducted a 14-week double-blind crossover study that required participants not to be on any maintenance treatment prior to enrolling in the trial (n=55). No significant differences were found between SROM and methadone on retention rates or illicit drug-use. However, SROM was associated with significantly fewer physical complaints ($p < 0.05$), less craving for heroin, cocaine and alcohol ($p < 0.05$), lower depression scores ($p < 0.001$), and lower anxiety scores ($p < 0.01$). Giacomuzzi et al.,[23] conducted a 24-week, open-label, randomized controlled trial, wherein participants who had OUD and who were previously on methadone (n=120) were randomized to take either SROM, buprenorphine, or to continue methadone treatment. These participants were then compared to an equal number of patients being newly treated for OUD, and thus taking no OUD pharmacotherapy (n=120). Therefore, a total N = 240 was used for this study throughout the manuscript. Overall, Giacomuzzi et al. found SROM to be associated with significantly lower consumption of heroin ($p < 0.001$) and cocaine ($p <0.001$); however, scores on Quality of Life measures such as finances ($p < 0.01$), family ($p < 0.05$), and overall satisfaction ($p < 0.05$) were significantly lower than for methadone or buprenorphine. Analyses of physical complaints on each treatment yielded mixed results.

Beck et al.,[15] conducted a 22-week, randomized, open-label, cross-over study of patients maintained on methadone in Switzerland and Germany (n=157), disseminated via four study reports. First, a non-inferiority study found no significant differences between SROM and methadone in treatment retention (period 1: $p = 0.50$, period 2: $p = 0.19$) or incidence of adverse events ($p = 0.62$). The proportion of heroin-positive urine drug screens (6-Monoacetylmorphine [6-MAM] and 6-acetylcodeine [6-A-cod]) was found to be significantly higher on SROM ($p < 0.001$); however, this difference fell within a pre-specified inferiority margin of 10%, leading the authors to confirm the non-inferiority of SROM compared to methadone. SROM was also found to have significant dose-dependent effects on the number of positive urine drug screens, with higher doses yielding fewer positive screens ($p < 0.05$). A second study similarly confirmed the non-inferiority of SROM to methadone;[27] SROM was associated with higher treatment satisfaction ($p < 0.001$), and fewer adverse mental symptoms ($p < 0.01$). No significant differences were found between number of self-reported days of heroin-, cocaine-, benzodiazepine-, and alcohol-use between SROM and methadone ($p = 0.48$-0.99). A third study reported that heroin-craving scores (as measured by visual analogue scale and brief craving questionnaire) were significantly lower on SROM than on methadone ($p < 0.0001$), and that cocaine-craving were statistically similar between the two treatments ($p = 0.54$).[19] Finally, a fourth study reported on a 24-week extension phase, where all subjects in the initial cross-over trial either continued or were placed back on SROM.[20] This report again found that SROM was associated with fewer cravings for heroin ($p < 0.01$) and statistically similar self-reported drug use ($p = 0.26$-0.54); however, as no control group was present, data from the extension phase was not included in the analyses of this review.

Meta-analysis Results

The meta-analytic results of SROM *vs.* methadone are presented in Figure 2. As one included study was published as a thesis and conference abstract, and contained a small sample size (n = 24), a

sensitivity analysis was run wherein this study's data was excluded. This exclusion did not change the results (Figures 2b and 2d). It was not possible to convert all data reported on outcomes into meta-analysis due to variance in reported data. Because continuous outcomes, such as craving, were reported in less than two studies, a meta-analysis was not performed.

Treatment retention

Acceptability of treatment was measured via participant dropout. Dropouts were assessed in four studies,[15 22-24] with 471 participants [note: unpublished data were sought and obtained from two studies].[15 23] Retention was assessed for the entire duration of the trials. As shown in Figure 2c, the results of the meta-analysis suggest that the mean difference in dropouts was not statistically significant between participants in the SROM *vs.* methadone (RR = 0.98; 95%CI 0.94 - 1.02, p = 0.34), while low heterogeneity between studies was observed.

Efficacy of SROM

As shown in Figure 2a, a three-study meta-analysis,[15 23 24] that included data from 406 participants showed no difference in effectiveness between SROM and methadone in reducing opioid use (RR = 0.96; 95% CI: 0.61- 1.52, p = 0.86). Because other measures of SROM efficacy (i.e., craving) were not reported across all studies or were assessed using different statistical methods, they were not amenable to investigation via meta-analysis. However, two studies indicated that SROM reduces cravings for heroin more than methadone (P < 0.0001, measured using a visual analogue scale; P = 0.010, measured using the heroin craving questionnaire - brief), and that SROM produces no significant differences in self-reported use of illicit drugs.[15 19 24]

DISCUSSION

The results of the present systematic review and meta-analysis indicate that current evidence suggests that SROM is as efficacious in the treatment of OUD as methadone. Building on an earlier review,[14] and with

additional data from more recent trials as well as unpublished data, we were able to pool data on two outcomes: opioid use and retention in treatment. Here, in the meta-analysis, we observed no significant differences between SROM and methadone in improving treatment retention and heroin use. While not amenable to meta-analysis, results from two studies indicated that SROM reduces cravings for heroin more than methadone. These findings are relevant to recent high-level recommendations suggesting the need to consider repurposing existing medications for the treatment of opioid use disorder.[28]

Currently, SROM is available as an alternative to methadone in a range of European jurisdictions,[29 30] as well as in Canada.[4] Our findings concur with the new Canadian National Guidelines on the treatment of OUD, which recommend SROM as a treatment option, and with the findings from earlier systematic reviews though none of them had sufficient data for the calculation of the pooled effects for treatment retention and heroin use.[4 13 31] In particular, our analyses considered new unpublished data that were not included in past reviews, as well as data from a new trial from Switzerland and Germany,[15] thus confirming the apparent non-inferiority of SROM compared to methadone. Although a number of gaps in our understanding of SROM persist (for instance, in the absence of mortality and detailed safety data), the current review underscores the clinical utility and potential for scaling up SROM as an agonist treatment for OUD, relevant beyond European and Canadian settings.

Limitations

The results reported in the present systematic review and meta-analysis are subject to the several limitations. First, the body of evidence regarding the efficacy of SROM in managing OUD is still relatively small. As such, additional research will help to illuminate the role that SROM can play in meeting the needs of specific patient subgroups. For instance, the relative ability of SROM to engage and retain patients with opioid use disorder in the context of the fentanyl epidemic. Second, the methodological quality of the included RCTs was low-to-moderate and the sample sizes were modest. In

terms of comparing SROM to buprenorphine/naloxone, because of the latter's improved safety profile,[12 32] the recently published Canadian guideline recommends staging therapies with buprenorphine/naloxone recommended for first line therapy with methadone or SROM being offered to those unsuccessful with first line treatment.[4] As such, head-to-head comparisons of buprenorphine to SROM may not be warranted. Third, some outcome measures were not uniformly reported across studies and, therefore, were difficult to combine in a meta-analysis. Heroin use was amenable to meta-analysis as it was reported in a consistent manner by three studies.[15 22 24] Fourth, the analysis used some outcome data from the period before cross-over occurred in trials. Therefore, these results are based off of short durations of six to 12 weeks. Finally, with respect to quality, we identified a risk of bias related to inconsistent blinding of participants and unclear blinding of outcomes across studies. Differences in study design and duration were also present. Given these multiple potential sources of possible bias, SROM should remain an area of future study as highlighted above.

CONCLUSIONS

The present meta-analysis demonstrates the consistent pattern in clinical trials evaluating the impact of SROM. Because most OUD patients do not access agonist therapies,[10] and since poor retention in methadone has been linked to heightened mortality and other health outcomes,[12] SROM may have a promising role in OUD treatment, especially given methadone's known side effect profile, the likely attractiveness of SROM to some patients and the apparent reduction in craving when on SROM in comparison to methadone.[8 23] Unless future trials report contradictory findings, the public health crisis presented by illicitly manufactured fentanyl,[2] and the known limitations of existing agonist therapies,[12 31] these data should compel public health agencies and decision makers to support the expanded use and investigation of SROM as a therapeutic tool among people undergoing treatment for OUD.

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Contributorship statement

JK and EW conceived the idea for and designed the study. JK and LG conducted the research and wrote the first draft of the manuscript. GS, CR, EMS, NF contributed to the study design, interpretation of the findings and preparation of the manuscript. All authors reviewed and approved the final version of the manuscript. Ahmed Adam screened the titles, fulltexts and assessed risk of bias in the included studies.

Competing interests

None

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Data sharing statement

Not applicable.

Table 1: Characteristics of included studies

Study/ Country	Design	Participants	Interventions	Outcomes	Risk Rating (A B C D E)
Clark 2002 Australia	Cross-over, Randomized controlled trial, Open-label duration: 12 weeks	N=11 Mean age: 36.5 years Use of heroin: once per week Heroin use disorder and were on methadone	(1) Morphine Flexible starting dose; increased by 50 mg per day following transfer, never exceeded 800 mg/day (2) Methadone Flexible starting dose; reduced by 12 mg per day following transfer	Retention Severity of opiate withdrawal symptoms Heroin or other substance use Severity of dependence Mental health/social functioning	
Eder 2005 Austria	Cross-over, Randomized double blind, double-dummy duration: 14 weeks	N=64 Mean age: 28 years Male: 75% Opioid use disorder (excluded patients already receiving maintenance therapy)	(1) Morphine Starting dose 200 mg/day increased to 800 mg/day by week 1. (2) Methadone Starting dose 40 mg/day increased to 100mg/day by week 1.	Retention Use of illicit substances based on urinalysis Extent of drug cravings Withdrawal symptoms General well being Safety was assessed on the basis of adverse events and clinical and physical examination QoL measured by the Lancashire Quality of Life Profile	
Giacomuzzi 2006 Austria	Randomized controlled trial Open-label duration: 24 weeks	N=120 Mean age: 27 years; Male: 57% Opioid use disorder and were on methadone	(1) Morphine Maintenance dose dependent on severity of withdrawal symptoms (2) Methadone Maintenance dose dependent on severity of withdrawal symptoms (3) Buprenorphine Maintenance dose dependent on severity of withdrawal symptoms	Retention (from personal correspondence) QoL measured by the Lancashire Quality of Life Profile Withdrawal symptoms measured by the Opioid Withdrawal Scale	
Beck 2014 Switzerland and Germany	Cross-over Randomized controlled trial, Open-label, Duration: 22 weeks	N=276 Mean age: 38.1 Male: 81.5% Opioid dependence and were on methadone use disorder	(1) Methadone flexible dosing. Cross over at 11 weeks to morphine (2) Morphine flexible dosing. Cross over at 11 weeks to methadone	Retention (24 weeks) Proportion of positive urine samples per patient (12 weeks) Per treatment for co-consumption of heroin Craving heroin Craving cocaine Self-reported drug use Mental health problems (SCL-27) Positive urine samples Adverse events	

Risk Rating Legend:
A: Random sequence generation (selection bias); B: Allocation concealment (selection bias); C: Blinding of participants and personnel (performance bias); D: Blinding of outcome assessment (detection bias); E: Incomplete outcome data (attrition bias); Amber Circle: Unclear

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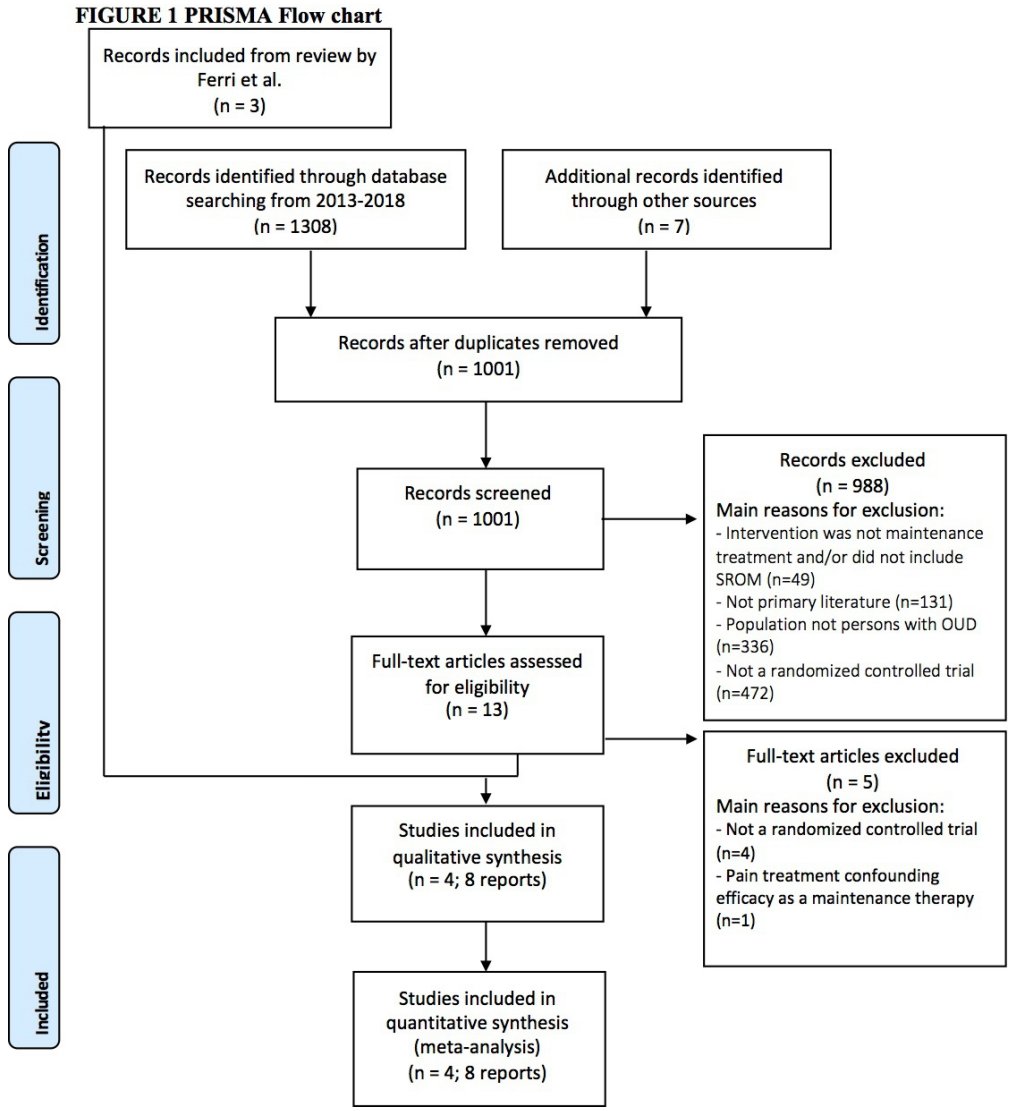

Figure 1 PRISMA Flow chart

189x208mm (150 x 150 DPI)

Figure 2a. Forest plot of the effects of slow release oral morphine (SROM) on heroin use as measured by urine drug tests among persons with opioid use disorders in randomized controlled trials; CI: confidence interval; ITT population.

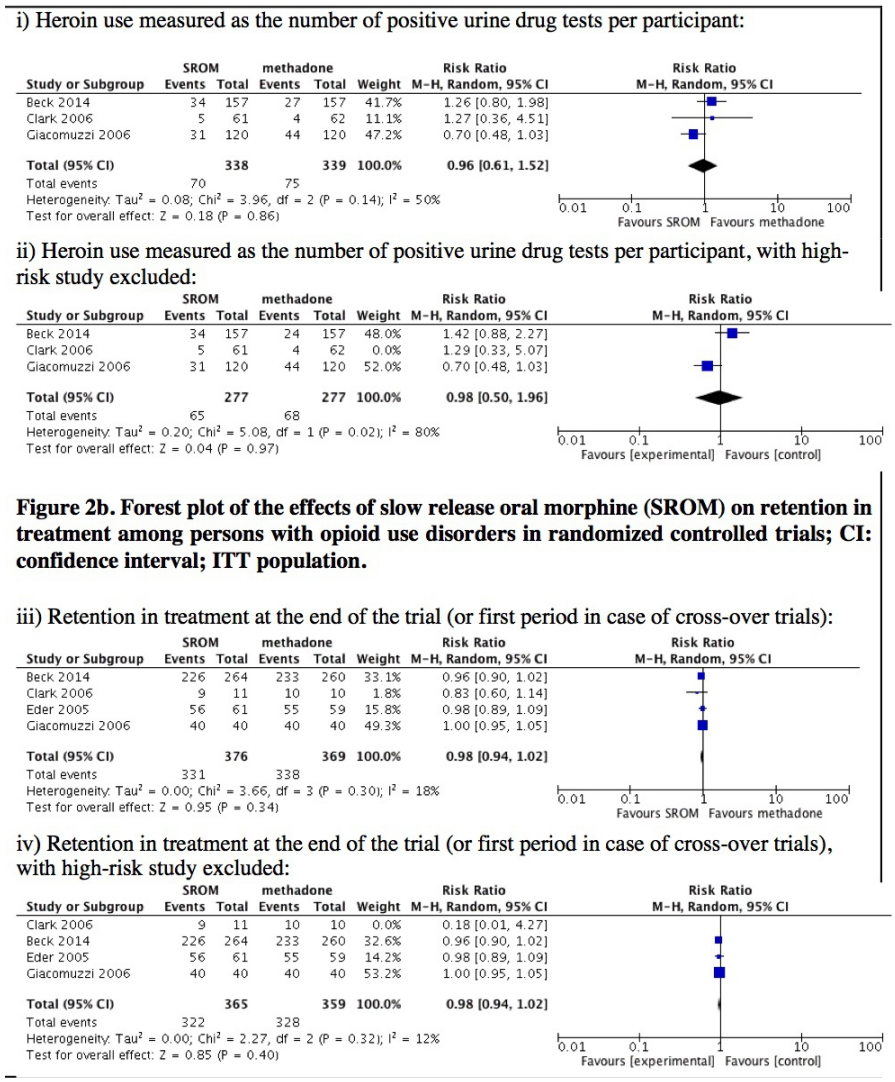

Figure 2b. Forest plot of the effects of slow release oral morphine (SROM) on retention in treatment among persons with opioid use disorders in randomized controlled trials; CI: confidence interval; ITT population.

Forest plot of the effects of slow release oral morphine (SROM)

167x225mm (150 x 150 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	--
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	--
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	--
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	--
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	--
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	--
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

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Slow Release Oral Morphine versus Methadone for the Treatment of Opioid Use Disorder: A Systematic Review and Meta-Analysis

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Slow Release Oral Morphine versus Methadone for the Treatment of Opioid Use Disorder: A Systematic Review and Meta-Analysis

Klimas, Jan[1,3], Gorfinkel, Lauren[1], Giacomuzzi, Salvatore[5], Ruckes, Christian[4], Socías, M. Eugenia[1,2], Fairbairn, Nadia[1,2], Wood, Evan[1,2]

1. British Columbia Centre for Substance Use, 400-1045 Howe Street, Vancouver, BC, CANADA, V6Z 1Y6
2. Department of Medicine, University of British Columbia, St. Paul's Hospital, 608-1081 Burrard Street, Vancouver, BC, CANADA, V6Z 1Y6
3. School of Medicine, University College Dublin, Health Sciences Centre, Belfield, Dublin 4, Ireland
4. University Medical Center Mainz, Interdisciplinary Center Clinical Trials (IZKS), Langenbeckstraße 1 · D-55131 Mainz, Germany
5. Universitätsklinik Innsbruck-Ambulanz für Abhängigkeitserkrankungen, Anichstraße 35, 6020 Innsbruck, Austria

JK and LG contributed equally to this paper.

Send correspondence to:

Jan Klimas, PhD, MSc
B.C. Centre on Substance Use
University on British Columbia
400-1045 Howe Street, Vancouver, B.C., V6Z 1Y6
Canada
Tel: (778) 945-7616
Fax: (604) 806-9044
Email: jan.klimas@bccsu.ubc.ca

Running head: SROM for Opioid Use Disorder
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Tables: 1
Figures: 3
Revised: 8 Dec. 18

ABSTRACT

Objective To assess the efficacy of Slow release oral morphine (SROM) as a treatment for opioid use disorder.

Design Systematic review and meta-analysis of randomized controlled trials (RCT).

Data sources Three electronic databases were searched through May 1st, 2018: the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE. We also searched the following electronic registers for ongoing trials: ClinicalTrials.gov, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), Current Controlled Trials, and the EU Clinical Trials Register.

Eligibility criteria for selecting studies We included RCTs of any duration, assessing the effect of SROM on measures of treatment retention, heroin use and craving in adults who met the diagnostic criteria for opioid use disorder.

Data extraction and synthesis Two independent reviewers extracted data and assessed risk of bias. Data were pooled using the random-effects model and expressed as Risk Ratios (RR) or mean differences (MDs) with 95% CIs. Heterogeneity was assessed (chi-squared statistic) and quantified (I^2 statistic) and a sensitivity analysis was undertaken to assess the impact of particular high-risk trials.

Results Among 1315 studies reviewed, four unique randomized trials met inclusion criteria (n = 471), and compared SROM with methadone. In the meta-analysis, we observed no significant differences between SROM and methadone in improving treatment retention (risk ratio [RR] = 0.98; 95% Confidence Interval [CI]: 0.94 - 1.02, p = 0.34), and heroin use (RR = 0.96; 95% CI: 0.61- 1.52, p = 0.86). Craving data was not amenable to meta-analysis but overall implied that SROM reduces heroin cravings to a greater extent than methadone (P < 0.0001, measured using a visual analogue scale; P = 0.010, measured using the heroin craving questionnaire). As well, results implied no significant differences between SROM and methadone on self-reported use of heroin, cocaine, or benzodiazepines. Available data implied no differences in adverse events.

Conclusions Meta-analysis of existing randomized trials suggests SROM may be generally equal to methadone in retaining patients in treatment and reducing heroin use as methadone while potentially resulting in less craving. While methadone is effective for many patients, these findings suggest SROM may provide benefits in addressing some of the limitations of methadone and the need to expand uptake and retention of individuals on opioid use disorder treatments. The methodological quality of the included RCTs was low-to-moderate.

Word Count: 377

Keywords: opioid use disorder, substance use treatment, oral morphine, meta-analysis
Review registration number: PROSPERO [CRD42018090782]

Strengths and limitations of this study

- The first meta-analysis of slow release oral morphine.
- We included new studies that increase the validity of the study.
- We included previously unpublished data obtained from primary trials.
- A meta-analysis of craving and adverse events was not possible due to inconsistent reporting of outcome measures across trials

INTRODUCTION

Overdose is the dominant cause of untimely death among people with opioid use disorder **(OUD)**, and in 2017, opioid overdose was declared a national public health emergency in the U.S. Approximately two million Americans have a diagnosed opioid use disorder,[1] and deaths due to opioid overdoses have nearly doubled since 2006, exceeding 46,000 in 2016.[2] In response, the past decade has witnessed an expansion of pharmaceutical interventions for OUD, including the opioid agonist therapies methadone and buprenorphine/naloxone. Opioid agonist therapy (OAT) is currently the first-line treatment for OUD recommended by the World Health Organization (WHO) and a number of federal health guidelines.[3-5]

While methadone and buprenorphine/naloxone are proven effective,[6 7] they have a known limited ability to attract and retain patients in treatment. For instance, past studies have demonstrated that most individuals who overdose are not on agonist treatment at the time of death, and that, overall, agonist therapies remain sorely underutilised with only a fraction of eligible patients in U.S. accessing these therapies.[8-10] While overall low rates of methadone- and buprenorphine/naloxone-use are partially due to poor access and limited service delivery,[10] the balance of medication benefits and side-effects (e.g., sweating, weight gain), and other limitations of these therapies (e.g., QTc interval prolongation, sleep disturbance, need for daily visits and supervised urine collection in some settings), also result in low rates of patient retention once individuals initiate therapy.[11-13] The issues of poor uptake and retention on OAT are particularly urgent in the context of elevated mortality among those not on OAT and the reported dramatic rise in mortality following OAT interruption,[14] as well as increasing overdose rates as a result of the emergence of highly toxic fentanyl analogues in the illicit drug markets of many settings.

In light of increasing recognition that a range of additional forms of opioid agonist therapy are necessary for some persons with complex OUD, interest in slow release oral morphine (SROM) as an OUD treatment agent has steadily grown.[8 15] A 2013 review by the Cochrane Collaboration reviewed the literature

for SROM as treatment for OUD. However, the review was ultimately unable to draw definite conclusions regarding effectiveness, identifying only three high quality clinical trials.[16] However, some unpublished data were not included in this review, and since the time of its publication, a number of new studies investigating SROM have emerged, including a large international randomized controlled trial from Switzerland and Germany.[17] In light of the known limitations of methadone, buprenorphine/naloxone and medical heroin,[18] these new data on the efficacy of SROM, as well as the need to identify viable OAT options that may be more attractive to patients in the context of the current opioid-related public health emergency, the present systematic review and meta-analysis was conducted to assess the efficacy of slow-release oral morphine as a treatment for opioid use disorder as measured by treatment retention, heroin use, and opioid craving.

METHODS

Data sources and searches

In this report, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[19] Three electronic databases were searched to obtain relevant trials published in the past five years since the date of search of the Cochrane Collaboration review (up to May 2018): the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE. These databases were searched by combining selected MeSH terms and free-text terms related to OUD and SROM (see search strategy in Appendix). We also searched the following electronic registers for ongoing trials: ClinicalTrials.gov (www.clinicaltrials.gov), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/), Current Controlled Trials (www.controlled-trials.com/), EU Clinical Trials Register (www.clinicaltrialsregister.eu), the Italian Medicines Agency (www.agenziafarmaco.gov.it/en), and Trials (www.trialsjournal.com). References of all relevant papers

were reviewed to identify further studies of relevance. Authors of potentially relevant studies were contacted for further unpublished data.

Study Selection

All English-language, scientifically peer-reviewed studies were eligible for inclusion. Studies were included if they met the following criteria: 1) studies were published in a scientific peer-reviewed journal; 2) they employed RCT methods (with no requirement for blinding); 3) participants met diagnostic criteria for OUD as defined in the DSM-IV or DSM-V manuals; 4) treatment was defined as SROM with or without an accompanying psychosocial intervention; and 5) control conditions were defined as medication-only, regardless of other concurrent treatment; and 6) outcomes assessed included treatment retention, efficacy (i.e., any measure of change in heroin use) and opioid craving.

Outcome Measures

The following outcomes were assessed: 1) Treatment retention, measured using dropout rates; 2) Efficacy, defined as the number of urine drug tests positive for illicit substances (incl. metabolites 6-Monoacetylmorphine [6-MAM] and 6-acetylcodeine [6-A-cod]) during the longest follow-up period in each study (or final weeks of pre-switch phase in case of cross-over trials); 3) Craving reduction, assessed through subjective reduction of scores on opioid-craving scales specific to each study. These outcomes were often assessed multiple times throughout the study period and measured across varied time intervals ranging from 1-24 weeks, depending on study length. Other, less common outcomes, including Quality of Life measures, satisfaction, physical complaints, and mental health were also reported. The level of statistical significance to assess differences between treatment and control groups was set *a priori* at $p < 0.05$.

It is noteworthy that with the new terminology changes to the Diagnostic Statistical Manual (DSM-

V), opioid abuse and dependence have been combined into opioid use disorder, which can be labeled as mild, moderate, or severe. Although imprecise, opioid abuse can equate to moderate or severe OUD, while opioid dependence is similar to the mild subtype.[20 21]

Data extraction

All citations identified by search were independently screened based on title and abstract by two reviewers (LG, AA). Each potentially relevant study was then reviewed in full text and assessed for all inclusion criteria. Any disagreements were resolved by discussion among reviewers (LG, AA) and additional investigators (JK, EW). Relevant data from eligible articles (i.e., socio-demographics, type of interventions, outcomes, etc.) were then extracted.

Quality Assessment

Study quality was assessed according to the criteria indicated in the Cochrane Handbook for Systematic Reviews of Interventions.[19] Each study was assessed for risk of bias in random sequence generation and allocation concealment (i.e., selection bias). Blinding of participants and personnel (i.e., performance bias) and of outcome assessment (that is always possible, i.e., detection bias; objective and subjective outcomes were combined) were measured; however, since blinding was considered unlikely to affect study outcome in this context,[16] open-label studies were included. Incomplete outcome data (i.e., attrition bias) was recorded for each eligible study. Each category of bias was assigned a rating of low, high or unclear risk using protocols from the Cochrane Handbook. There was no deviation from the quality assessment criteria.

Data Synthesis and Analysis

For the meta-analysis, dichotomous outcome measures (treatment retention, continuous abstinence) were analysed by calculating the risk ratio (RR) for each trial, with uncertainty in each result expressed via 95% confidence intervals (CIs). Continuous outcomes, such as craving, were analysed by calculating the

mean difference (MD) between experimental and control groups.

Information on missing data was collected where possible from study authors. If study authors were unable to supply this information, missing data were obtained or calculated from values in the primary studies according to suggested procedures in the Cochrane Handbook for Systematic Reviews of Interventions.[19]

Given the expected heterogeneity of results among studies due to differences in population and intervention type, we employed a random-effects meta-analytic model. The I-squared (I^2) statistic was employed to test the presence of heterogeneity between trials, and a sensitivity analysis was undertaken to assess the impact of particular high-risk trials.

Patient and public involvement: patients and public were not involved.

RESULTS

We considered all peer-reviewed articles and identified 1315 potentially eligible studies published since the date of search in the previous Cochrane Collaboration review.[16] After removal of duplicates and the application of inclusion criteria (Figure 1), 993 abstracts were screened and only eight reports – out of the 13 full texts reviewed – met all inclusion criteria.[17 22-28] Four reports were excluded due to not meeting inclusion criteria, and one was excluded because the study protocol paper did not report outcome data. Because some trials were the subject of multiple reports, only four unique studies (n = 471) were eligible for quantitative synthesis. We considered data from all available high-quality trials as well as previously unpublished data from trial authors. One study did not report data of interest for this review other than treatment retention.[25]

All participants in the included studies met the DSM-IV or V diagnostic criteria for OUD; mean age 33.1 years; of the three studies that reported on gender,[17 25 26] 24.4% were female. The mean duration of

trials was 18 weeks (range 11 to 24 weeks). The mean dose of SROM provided to participants was 506.8 mg/day, and the mean dose of methadone was 67.2 mg/day. All four studies were conducted in an outpatient setting, and assessed SROM *vs.* methadone, with only one study by Giacomuzzi et al.[26] explicitly stating psychosocial support. This study also assessed buprenorphine in comparison with SROM and methadone.[26]

Quality assessments for each study are presented in Table 1. Three out of four studies were found to be at low risk for selection bias – the final study's selection bias was agreed to be unclear, due to an unspecified randomization technique.[26] There was mixed-risk of bias relating to blinding of participants and outcome assessments; however, as noted by Ferri et al., objective outcomes -such as retention and urine drug screens- are unlikely to be impacted by a lack of blinding.[16] Three of the four included RCTs were therefore open-label.[17 26 27] All four studies were found to be at low risk for attrition bias. Additionally, differences in our risk of bias assessment and the previous Cochrane review were also identified.[16] For the trial by Giacomuzzi et al.,[26] we assessed blinding of outcome assessment to be of high risk while the previous review assigned unclear risk. Blinding of outcome assessment was not possible because the treating physician could terminate patients if three consecutive urine tests were found positive for 6-MAMmam (data from Dr Giacomuzzi).

Treatment retention was assessed via the dropout rate in all studies. Unpublished data regarding treatment retention was obtained from the authors of one study.[26] With respect to measures of opioid use, the number of participants with urine drug tests positive for illicit substances was reported in two studies.[17 27] Unpublished data on positive urine tests was obtained from one study.[26] Measures of craving using various rating scales were used in three studies,[17 25 27] though one did not report the necessary outcome data for meta-analysis to be performed.[25]

Systematic Review Results

A 2013 Cochrane review by Ferri et al. described three trials included in the present analysis.[16] Clark et al.,[27] and Eder et al.,[25] both performed crossover, randomized controlled trials, wherein participants with OUD were randomized to take either SROM or methadone for the first half of the trial period, then subsequently switched to the other treatment for the second half of the trial period. According to the published conference abstract and M.D. thesis, Clark et al.,[29] conducted a 12-week open-label crossover study that required patients to be taking methadone prior to enrolling (n=9). The authors found SROM to have lower retention than methadone; however, no significant differences were found in regards to heroin use (6-Monoacetylmorphine [6-MAM]) in the last four weeks of treatment, use of other drugs over the study period, dollars spent on heroin in the final week of treatment, mental health and social functioning (as measured by the BASIS-32 Behavior and Symptom Identification Scale), self-reported days of heroin use, or heroin cravings. SROM was found to yield significantly lower on subjective opiate withdrawal scale (SOWS) scores (by 1.1 on the SOWS scale [95% Confidence Interval {CI} 0.6 to 1.7] $p < 0.001$). Eder et al. conducted a 14-week double-blind crossover study that required participants not to be on any maintenance treatment prior to enrolling in the trial (n=55). No significant differences were found between SROM and methadone on retention rates (103 [94%] patients completed the study) or illicit drug-use (consumption of cocaine was significantly reduced to 23.3% [$p = 0.0083$] by day 21; additional consumption of benzodiazepines remained almost unchanged throughout the study period at approximately 40% (highest [44.7%] on day 10; lowest [32.0%] on day 20); additional consumption of amphetamines was very low, with only two positive urine specimens on day 3). However, SROM was associated with significantly fewer physical complaints (falling from a mean score of 21.7 at baseline to 12.5 at day 21 among patients treated with SROM, $p < 0.05$), less craving for heroin, cocaine and alcohol (data from Visual Analogue Scale presented as charts only, $p < 0.05$), lower depression scores (falling from a mean score of 17.84 at baseline to 10.51 at day 21 among patients treated with SROM, $p < 0.001$),

and lower anxiety scores (data from the State Trait Anxiety Inventory presented as charts only $p < 0.01$). Giacomuzzi et al.,[26] conducted a 24-week, open-label, randomized controlled trial, wherein participants who had OUD and who were previously on methadone (n=120) were randomized to take either SROM, buprenorphine, or to continue methadone treatment. These participants were then compared to an equal number of patients being newly treated for OUD, and thus taking no OUD pharmacotherapy (n=120). Therefore, a total N = 240 was used for this study throughout the manuscript. Overall, Giacomuzzi et al. found SROM to be associated with significantly lower consumption of opioids (unpublished data: methadone 36.7%, buprenorphine 19.2%, SROM 25.8%, $p < 0.001$) and cocaine (unpublished data: methadone 3.3%, buprenorphine 6%, SROM 3.3%, $p <0.001$); however, scores on the Lancashire Quality of Life Profile, such as finances (methadone 4.4, buprenorphine 4.2, SROM 2.6, $p < 0.001$), family (methadone 5.8, buprenorphine 5.1, SROM 3.4, $p < 0.05$), and overall satisfaction (methadone 5.3, buprenorphine 4.9, SROM 4.1, $p < 0.001$), were significantly lower than for methadone or buprenorphine. Analyses of physical complaints on each treatment yielded mixed results.

Beck et al.,[17] conducted a 22-week, randomized, open-label, cross-over study of patients maintained on methadone in Switzerland and Germany (n=157), disseminated via four study reports. First, a non-inferiority study found no significant differences between SROM and methadone in treatment retention (period 1: 88.7% vs. 91.1%; period 2: 82.1% vs. 88.0% for SROM vs. methadone, period 1: $p = 0.50$, period 2: $p = 0.19$) or incidence of adverse events (81% SROM vs. 79% methadone, $p = 0.62$). The proportion of heroin-positive urine drug screens (6-Monoacetylmorphine [6-MAM] and 6-acetylcodeine [6-A-cod]) was found to be significantly higher on SROM (0.20 ± 0.26 SROM vs. 0.15 ± 0.23 methadone, $p < 0.001$); however, this difference fell within a pre-specified inferiority margin of 10%, leading the authors to confirm the non-inferiority of SROM compared to methadone. SROM was also found to have significant dose-dependent effects on the number of positive urine drug screens, with

higher doses yielding fewer positive screens (Pearson's correlation coefficient: −0.1941 for positive 6-MAM and −0.1709 for positive 6-A-cod, $p < 0.05$). A second study similarly confirmed the non-inferiority of SROM to methadone;[30] SROM was associated with higher treatment satisfaction (SROM: 7.6 ± 1.8 vs. methadone: 6.0 ± 2.2, $p < 0.001$), and fewer adverse mental symptoms (SROM: 0.61 ± 0.56 vs. methadone: 0.68 ± 0.60, $p < 0.01$). No significant ($p = 0.48$-0.99) differences were found between number of self-reported days of heroin-(SROM: 6.4 ± 11.7 vs. methadone: 6.4 ± 11.3), cocaine-(SROM: 2.4 ± 6.0 vs. methadone: 2.2 ± 6.2), benzodiazepine-, (SROM: 8.2 ± 17.4 vs. methadone: 7.4 ± 15.8) and alcohol-use (SROM: 14.5 ± 21.7 vs. methadone: 14.5 ± 20.8) between SROM and methadone. A third study reported that heroin-craving scores (as measured by visual analogue scale and brief craving questionnaire) were significantly lower on SROM than on methadone (visual analogue scale: 3.3 ± 2.4 vs. 2.5 ± 2.2; brief craving questionnaire 2.9 ± 1.4 vs. 2.6 ± 1.2 for methadone and SROM respectively, $p < 0.0001$), and that cocaine-craving were statistically similar between the two treatments (visual analogue scale: 1.6 ± 2.0 vs. 1.4 ± 1.9; brief craving questionnaire 2.1 ± 1.2 vs. 2.1 ± 1.2 for methadone and SROM respectively, $p = 0.54$).[22] Finally, a fourth study reported on a 24-week extension phase, where all subjects in the initial cross-over trial either continued or were placed back on SROM.[23] This report again found that SROM was associated with fewer cravings for heroin (visual analogue scale: 2.06 ± 2.33 vs. 2.70 ± 2.63; brief craving questionnaire 2.25 ± 1.30 vs. 2.50 ± 1.43 at the end and start of extension phase respectively, $p < 0.01$) and statistically similar self-reported drug use (Heroin: 0.08 ± 0.18 vs. 0.11 ± 0.21; Cocaine: 0.05 ± 0.17 vs. 0.06 ± 0.18; benzodiazepine: 0.15 ± 0.34 vs. 0.19 ± 0.36; Alcohol: 0.22 ± 0.36 vs. 0.24 ± 0.38 at the end and start of extension phase respectively, $p = 0.26$-0.54); however, as no control group was present, data from the extension phase was not included in the analyses of this review.

Meta-analysis Results

The meta-analytic results of SROM *vs.* methadone are presented in Figure 2. As one included study

was published as a thesis and conference abstract, and contained a small sample size (n = 24), a sensitivity analysis was run wherein this study's data was excluded. This exclusion did not change the results (Figures 2b and 2d). It was not possible to convert all data reported on outcomes into meta-analysis due to variance in reported data. Because continuous outcomes, such as craving, were reported in less than two studies, a meta-analysis was not performed.

Treatment retention

Acceptability of treatment was measured via participant dropout. Dropouts were assessed in four studies,[17 25-27] with 471 participants [note: unpublished data were sought and obtained from two studies].[17 26] Retention was assessed for the entire duration of the trials. As shown in Figure 2c, the results of the meta-analysis suggest that the mean difference in dropouts was not statistically significant between participants in the SROM *vs.* methadone (RR = 0.98; 95%CI 0.94 - 1.02, p = 0.34), while low (18%) heterogeneity between studies was observed.

Efficacy of SROM

As shown in Figure 2a, a three-study meta-analysis,[17 26 27] that included data from 406 participants showed no difference in effectiveness between SROM and methadone in reducing opioid use (RR = 0.96; 95% CI: 0.61- 1.52, p = 0.86, I^2 = 50%). Because other measures of SROM efficacy (i.e., craving) were not reported across all studies or were assessed using different statistical methods, they were not amenable to investigation via meta-analysis. However, two studies indicated that SROM reduces cravings for heroin more than methadone (P < 0.0001, measured using a visual analogue scale; P = 0.010, measured using the heroin craving questionnaire - brief), and that SROM produces no significant differences in self-reported use of illicit drugs.[17 22 27]

DISCUSSION

The results of the present systematic review and meta-analysis indicate that current evidence suggests that SROM may be generally equal to methadone in the treatment of OUD. Building on an earlier review,[16] and with additional data from more recent trials as well as unpublished data, we were able to pool data on two outcomes: opioid use and retention in treatment. Here, in the meta-analysis, we observed no significant differences between SROM and methadone in improving treatment retention and heroin use. While not amenable to meta-analysis, results from two studies indicated that SROM reduces cravings for heroin more than methadone. These findings are relevant to recent high-level recommendations suggesting the need to consider repurposing existing medications for the treatment of opioid use disorder.[31]

Currently, SROM is available as an alternative to methadone in a range of European jurisdictions,[32 33] as well as in Canada.[4] Our findings concur with the new Canadian National Guidelines on the treatment of OUD, which recommend SROM as a treatment option, and with the findings from earlier systematic reviews though none of them had sufficient data for the calculation of the pooled effects for treatment retention and heroin use.[4 15 34] In particular, our analyses considered new unpublished data that were not included in past reviews, as well as data from a new trial from Switzerland and Germany,[17] thus confirming the apparent non-inferiority of SROM compared to methadone. Although a number of gaps in our understanding of SROM persist (for instance, in the absence of mortality and detailed safety data), the current review underscores the clinical utility and potential for scaling up SROM as an agonist treatment for OUD, relevant beyond European and Canadian settings.

Limitations

The results reported in the present systematic review and meta-analysis are subject to the several limitations. First, the body of evidence regarding the efficacy of SROM in managing OUD is still relatively small. As such, additional research will help to illuminate the role that SROM can play in meeting the needs

of specific patient subgroups. For instance, the relative ability of SROM to engage and retain patients with opioid use disorder in the context of the fentanyl epidemic. Second, the methodological quality of the included RCTs was low-to-moderate and the sample sizes were modest. In terms of comparing SROM to buprenorphine/naloxone, because of the latter's improved safety profile,[14 35] the recently published Canadian guideline recommends staging therapies with buprenorphine/naloxone recommended for first line therapy with methadone or SROM being offered to those unsuccessful with first line treatment.[4] As such, head-to-head comparisons of buprenorphine to SROM may not be warranted. Third, some outcome measures were not uniformly reported across studies and, therefore, were difficult to combine in a meta-analysis. Heroin use was amenable to meta-analysis as it was reported in a consistent manner by three studies.[17 25 27] Fourth, the analysis used some outcome data from the period before cross-over occurred in trials. Therefore, these results are based off of short durations of six to 12 weeks. Additionally, while one abstract that met the eligibility criterion of being published in a scientific peer reviewed journal was included, the full results of the RCT were not published in a peer-reviewed journal; nevertheless, the RCT was included in a previous Cochrane systematic review.[18] Finally, with respect to quality, we identified moderate heterogeneity and a risk of bias related to inconsistent blinding of participants and unclear blinding of outcomes across studies. Differences in study design and duration were also present. Given these multiple potential sources of possible bias, SROM should remain an area of future study, where future studies should address the sources of heterogeneity (such as outcome measurement design and study duration) and consider impact on overdose and mortality, as highlighted above.

CONCLUSIONS

The present meta-analysis demonstrates the consistent pattern in clinical trials evaluating the impact of SROM. Because most OUD patients do not access agonist therapies,[10] and since poor retention in

methadone has been linked to heightened mortality and other health outcomes,[14] SROM may have a promising role in OUD treatment, especially given methadone's known side effect profile, the likely attractiveness of SROM to some patients and the apparent reduction in craving when on SROM in comparison to methadone.[8 26] Unless future trials report contradictory findings, the public health crisis presented by illicitly manufactured opioids,[2] and the known limitations of existing agonist therapies,[14 34] these data should inform future investigations of SROM as a therapeutic tool among people undergoing treatment for OUD.

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Contributorship statement

JK and EW conceived the idea for and designed the study. JK and LG conducted the research and wrote the first draft of the manuscript. GS, CR, EMS, NF contributed to the study design, interpretation of the findings and preparation of the manuscript. All authors reviewed and approved the final version of the manuscript. Ahmed Adam screened the titles, fulltexts and assessed risk of bias in the included studies.

Competing interests

None

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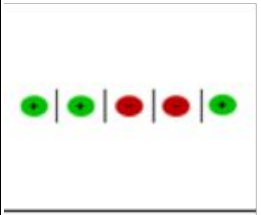
Data sharing statement

No additional data available.

Table 1: Characteristics of included studies

Study/ Country	Design	Participants	Interventions	Outcomes	Risk Rating (A B C D E)
Clark 2002 Australia	Cross-over, Randomized controlled trial, Open-label duration: 12 weeks	N=11 Mean age: 36.5 years Use of heroin: once per week Heroin use disorder and were on methadone	(1) Morphine Flexible starting dose; increased by 50 mg per day following transfer, never exceeded 800 mg/day (2) Methadone Flexible starting dose; reduced by 12 mg per day following transfer	Retention Severity of opiate withdrawal symptoms Heroin or other substance use Severity of dependence Mental health/social functioning	
Eder 2005 Austria	Cross-over, Randomized double blind, double-dummy duration: 14 weeks	N=64 Mean age: 28 years Male: 75% Opioid use disorder (excluded patients already receiving maintenance therapy)	(1) Morphine Starting dose 200 mg/day increased to 800 mg/day by week 1. (2) Methadone Starting dose 40 mg/day increased to 100mg/day by week 1.	Retention Use of illicit substances based on urinalysis Extent of drug cravings Withdrawal symptoms General well being Safety was assessed on the basis of adverse events and clinical and physical examination QoL measured by the Lancashire Quality of Life Profile	
Giacomuzzi 2006 Austria	Randomized controlled trial Open-label duration: 24 weeks	N=120 Mean age: 27 years; Male: 57% Opioid use disorder and were on methadone	(1) Morphine Maintenance dose dependent on severity of withdrawal symptoms (2) Methadone Maintenance dose dependent on severity of withdrawal symptoms (3) Buprenorphine Maintenance dose dependent on severity of withdrawal symptoms	Retention (from personal correspondence) QoL measured by the Lancashire Quality of Life Profile Withdrawal symptoms measured by the Opioid Withdrawal Scale	
Beck 2014 Switzerland and Germany	Cross-over Randomized controlled trial, Open-label, Duration: 22 weeks	N=276 Mean age: 38.1 Male: 81.5% Opioid dependence and were on methadone use disorder	(1) Methadone flexible dosing. Cross over at 11 weeks to morphine (2) Morphine flexible dosing. Cross over at 11 weeks to methadone	Retention (24 weeks) Proportion of positive urine samples per patient (12 weeks) Per treatment for co-consumption of heroin Craving heroin Craving cocaine Self-reported drug use Mental health problems (SCL-27) Positive urine samples Adverse events	

Risk Rating Legend:
A: Random sequence generation (selection bias); B: Allocation concealment (selection bias); C: Blinding of participants and personnel (performance bias); D: Blinding of outcome assessment (detection bias); E: Incomplete outcome data (attrition bias); Amber Circle: Unclear

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SROM as Maintenance Therapy for OUD PRISMA Flow Diagram

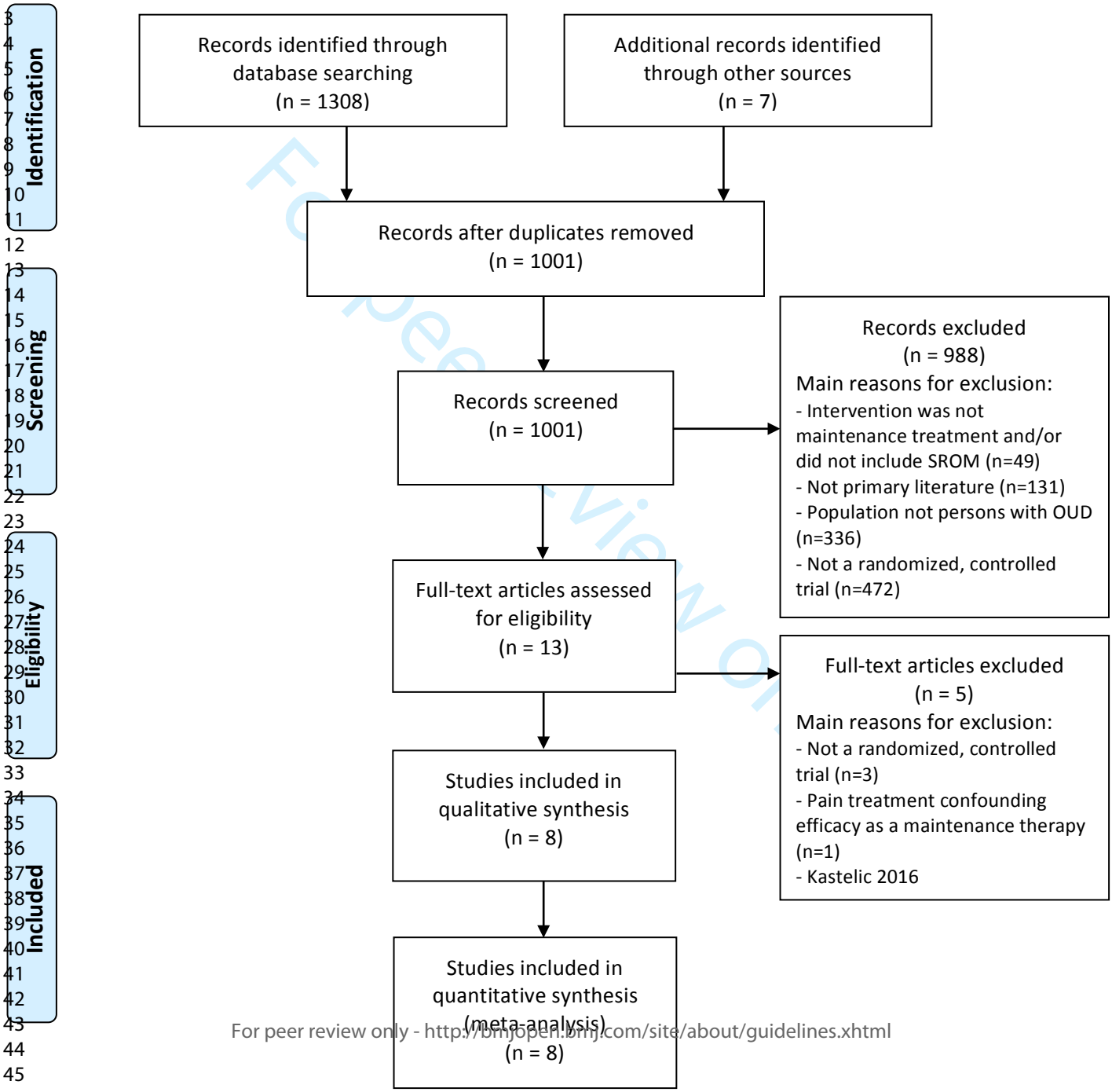
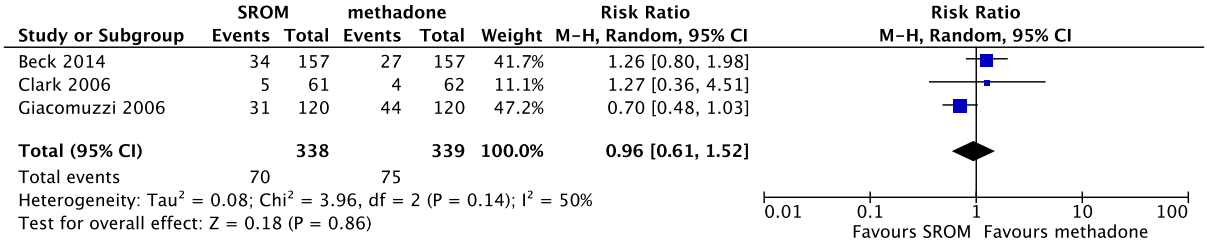


Figure 2a. Forest plot of the effects of slow release oral morphine (SROM) on heroin use as measured by urine drug tests among persons with opioid use disorders in randomized controlled trials; CI: confidence interval; ITT population.

i) Heroin use measured as the number of positive urine drug tests per participant:



ii) Heroin use measured as the number of positive urine drug tests per participant, with high-risk study excluded:

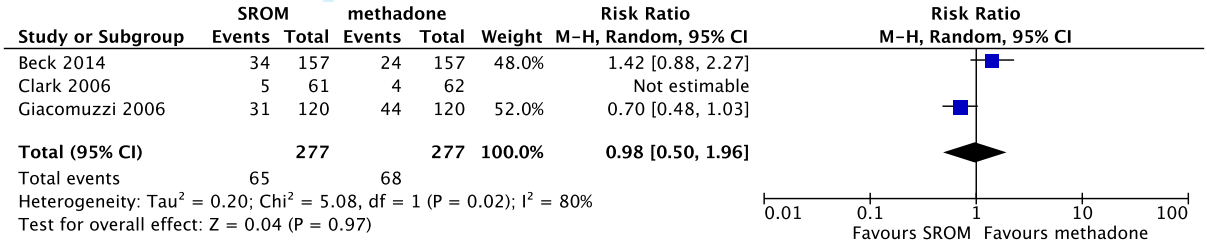
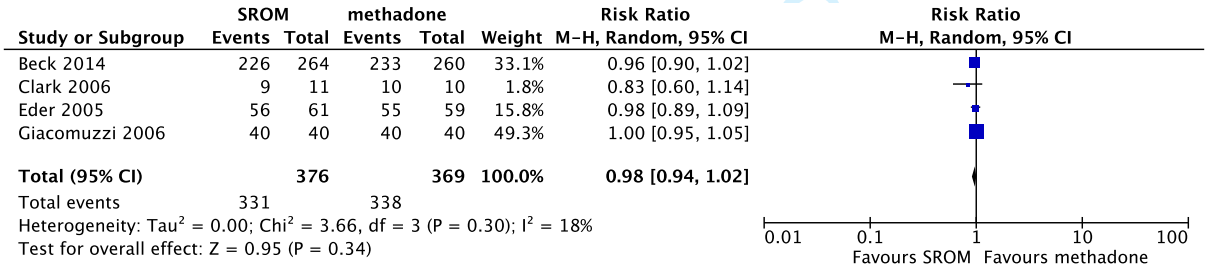


Figure 2b. Forest plot of the effects of slow release oral morphine (SROM) on retention in treatment among persons with opioid use disorders in randomized controlled trials; CI: confidence interval; ITT population.

iii) Retention in treatment at the end of the trial (or first period in case of cross-over trials):

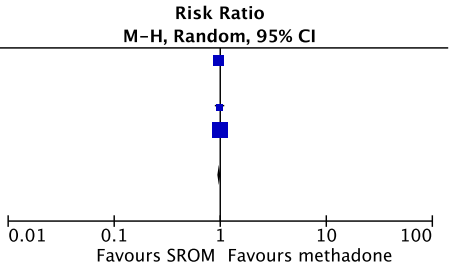


iv) Retention in treatment at the end of the trial (or first period in case of cross-over trials), with high-risk study excluded:

Study or Subgroup	SROM Events	SROM Total	methadone Events	methadone Total	Weight	Risk Ratio M-H, Random, 95% CI
Beck 2014	226	264	233	260	32.6%	0.96 [0.90, 1.02]
Clark 2006	9	11	10	10		Not estimable
Eder 2005	56	61	55	59	14.2%	0.98 [0.89, 1.09]
Giacomuzzi 2006	40	40	40	40	53.2%	1.00 [0.95, 1.05]
Total (95% CI)		**365**		**359**	**100.0%**	**0.98 [0.94, 1.02]**
Total events	322		328			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.27$, df = 2 (P = 0.32); $I^2 = 12\%$

Test for overall effect: Z = 0.85 (P = 0.40)



Slow Release Oral Morphine versus Methadone for the Treatment of Opioid Use Disorder: A Systematic Review and Meta-Analysis

Appendix. MEDLINE Search Strategy:

Database(s): **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to May 1st, 2018		
Search Strategy: Run May 1st		
#	**Searches**	**Results**
1	exp Opioid-Related Disorders/	22650
2	(opiat$ or opioid$ or heroin$ or narcot$ or methadone or buprenorphine).ab,ti.	120510
3	1 or 2	125772
4	(withdraw$ or abstinen$ or abstain$ or abuse$ or abusing or dependen$ or addict$ or overdos$ or 'over-dose' or intoxicat$).ab,ti.	1820666
5	3 and 4	45660
6	exp MORPHINE/	36715
7	morphine.ab,ti.	46588
8	6 or 7	53469
9	randomized controlled trial.pt.	459781
10	controlled clinical trial.pt.	92372
11	randomized.ab,ti.	441959
12	drug therapy.sh.	29544
13	randomly.ab,ti.	290465
14	trial.ab,ti.	500960
15	groups.ab,ti.	1815207
16	9 or 10 or 11 or 12 or 13 or 14 or 15	2650720
17	5 and 8 and 16	1299
18	limit 17 to humans	**613**

BMJ Open

Slow Release Oral Morphine versus Methadone for the Treatment of Opioid Use Disorder: A Systematic Review and Meta-Analysis

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Primary Subject Heading:	Addiction
Secondary Subject Heading:	Mental health
Keywords:	Opioid use disorder, Substance misuse < PSYCHIATRY, Substance use treatment, Oral morphine, meta-analysis

Slow Release Oral Morphine versus Methadone for the Treatment of Opioid Use Disorder: A Systematic Review and Meta-Analysis

Klimas, Jan[1,3], Gorfinkel, Lauren[1], Giacomuzzi, Salvatore[5], Ruckes, Christian[4], Socías, M. Eugenia[1,2], Fairbairn, Nadia[1,2], Wood, Evan[1,2]

1. British Columbia Centre for Substance Use, 400-1045 Howe Street, Vancouver, BC, CANADA, V6Z 1Y6
2. Department of Medicine, University of British Columbia, St. Paul's Hospital, 608-1081 Burrard Street, Vancouver, BC, CANADA, V6Z 1Y6
3. School of Medicine, University College Dublin, Health Sciences Centre, Belfield, Dublin 4, Ireland
4. University Medical Center Mainz, Interdisciplinary Center Clinical Trials (IZKS), Langenbeckstraße 1 · D-55131 Mainz, Germany
5. Universitätsklinik Innsbruck-Ambulanz für Abhängigkeitserkrankungen, Anichstraße 35, 6020 Innsbruck, Austria

JK and LG contributed equally to this paper.

Send correspondence to:

Jan Klimas, PhD, MSc
B.C. Centre on Substance Use
University on British Columbia
400-1045 Howe Street, Vancouver, B.C., V6Z 1Y6
Canada
Tel: (778) 945-7616
Fax: (604) 806-9044
Email: jan.klimas@bccsu.ubc.ca

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ABSTRACT

Objective To assess the efficacy of Slow release oral morphine (SROM) as a treatment for opioid use disorder.

Design Systematic review and meta-analysis of randomized controlled trials (RCT).

Data sources Three electronic databases were searched through May 1st, 2018: the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE. We also searched the following electronic registers for ongoing trials: ClinicalTrials.gov, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), Current Controlled Trials, and the EU Clinical Trials Register.

Eligibility criteria for selecting studies We included RCTs of any duration, assessing the effect of SROM on measures of treatment retention, heroin use and craving in adults who met the diagnostic criteria for opioid use disorder.

Data extraction and synthesis Two independent reviewers extracted data and assessed risk of bias. Data were pooled using the random-effects model and expressed as Risk Ratios (RR) or mean differences (MDs) with 95% CIs. Heterogeneity was assessed (chi-squared statistic) and quantified (I^2 statistic) and a sensitivity analysis was undertaken to assess the impact of particular high-risk trials.

Results Among 1315 studies reviewed, four unique randomized trials met inclusion criteria (n = 471), and compared SROM with methadone. In the meta-analysis, we observed no significant differences between SROM and methadone in improving treatment retention (risk ratio [RR] = 0.98; 95% Confidence Interval [CI]: 0.94 - 1.02, p = 0.34), and heroin use (RR = 0.96; 95% CI: 0.61- 1.52, p = 0.86). Craving data was not amenable to meta-analysis but overall implied that SROM reduces heroin cravings to a greater extent than methadone (P < 0.0001, measured using a visual analogue scale; P = 0.010, measured using the heroin craving questionnaire). As well, results implied no significant differences between SROM and methadone on self-reported use of heroin, cocaine, or benzodiazepines. Available data implied no differences in adverse events.

Conclusions Meta-analysis of existing randomized trials suggests SROM may be generally equal to methadone in retaining patients in treatment and reducing heroin use as methadone while potentially resulting in less craving. While methadone is effective for many patients, these findings suggest SROM may provide benefits in addressing some of the limitations of methadone and the need to expand uptake and retention of individuals on opioid use disorder treatments. The methodological quality of the included RCTs was low-to-moderate.

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Strengths and limitations of this study

- The first meta-analysis of slow release oral morphine.
- We included new studies that increase the validity of the study.
- We included previously unpublished data obtained from primary trials.
- A meta-analysis of craving and adverse events was not possible due to inconsistent reporting of outcome measures across trials

INTRODUCTION

Overdose is the dominant cause of untimely death among people with opioid use disorder **(OUD)**, and in 2017, opioid overdose was declared a national public health emergency in the U.S. Approximately two million Americans have a diagnosed opioid use disorder,[1] and deaths due to opioid overdoses have nearly doubled since 2006, exceeding 46,000 in 2016.[2] In response, the past decade has witnessed an expansion of pharmaceutical interventions for OUD, including the opioid agonist therapies methadone and buprenorphine/naloxone. Opioid agonist therapy (OAT) is currently the first-line treatment for OUD recommended by the World Health Organization (WHO) and a number of federal health guidelines.[3-5]

While methadone and buprenorphine/naloxone are proven effective,[6 7] they have a known limited ability to attract and retain patients in treatment. For instance, past studies have demonstrated that most individuals who overdose are not on agonist treatment at the time of death, and that, overall, agonist therapies remain sorely underutilised with only a fraction of eligible patients in U.S. accessing these therapies.[8-10] While overall low rates of methadone- and buprenorphine/naloxone-use are partially due to poor access and limited service delivery,[10] the balance of medication benefits and side-effects (e.g., sweating, weight gain), and other limitations of these therapies (e.g., QTc interval prolongation, sleep disturbance, need for daily visits and supervised urine collection in some settings), also result in low rates of patient retention once individuals initiate therapy.[11-13] The issues of poor uptake and retention on OAT are particularly urgent in the context of elevated mortality among those not on OAT and the reported dramatic rise in mortality following OAT

interruption,[14] as well as increasing overdose rates as a result of the emergence of highly toxic fentanyl analogues in the illicit drug markets of many settings.

In light of increasing recognition that a range of additional forms of opioid agonist therapy are necessary for some persons with complex OUD, interest in slow release oral morphine (SROM) as an OUD treatment agent has steadily grown.[8 15] A 2013 review by the Cochrane Collaboration reviewed the literature for SROM as treatment for OUD. However, the review was ultimately unable to draw definite conclusions regarding effectiveness, identifying only three high quality clinical trials.[16] However, some unpublished data were not included in this review, and since the time of its publication, a number of new studies investigating SROM have emerged, including a large international randomized controlled trial from Switzerland and Germany.[17] In light of the known limitations of methadone, buprenorphine/naloxone and medical heroin,[18] these new data on the efficacy of SROM, as well as the need to identify viable OAT options that may be more attractive to patients in the context of the current opioid-related public health emergency, the present systematic review and meta-analysis was conducted to assess the efficacy of slow-release oral morphine as a treatment for opioid use disorder as measured by treatment retention, heroin use, and opioid craving.

METHODS

Data sources and searches

In this report, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[19] Three electronic databases were searched to obtain relevant trials published in the past five years since the date of search of the Cochrane Collaboration review (up to May 2018): the Cochrane Central

Register of Controlled Trials, MEDLINE, and EMBASE. These databases were searched by combining selected MeSH terms and free-text terms related to OUD and SROM (see MEDLINE search strategy in Appendix). We also searched the following electronic registers for ongoing trials: ClinicalTrials.gov (www.clinicaltrials.gov), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/), Current Controlled Trials (www.controlled-trials.com/), EU Clinical Trials Register (www.clinicaltrialsregister.eu), the Italian Medicines Agency (www.agenziafarmaco.gov.it/en), and Trials (www.trialsjournal.com). References of all relevant papers were reviewed to identify further studies of relevance. Authors of potentially relevant studies were contacted for further unpublished data.

Study Selection

All English-language, scientifically peer-reviewed studies were eligible for inclusion. Studies were included if they met the following criteria: 1) studies were published in a scientific peer-reviewed journal; 2) they employed RCT methods (with no requirement for blinding); 3) participants met diagnostic criteria for OUD as defined in the DSM-IV or DSM-V manuals; 4) treatment was defined as SROM with or without an accompanying psychosocial intervention; and 5) control conditions were defined as medication-only, regardless of other concurrent treatment; and 6) outcomes assessed included treatment retention, efficacy (i.e., any measure of change in heroin use) and opioid craving.

Outcome Measures

The following outcomes were assessed: 1) Treatment retention, measured using dropout rates; 2) Efficacy, defined as the number of urine drug tests positive for illicit substances (incl. metabolites 6-Monoacetylmorphine [6-MAM] and 6-acetylcodeine [6-A-cod]) during the longest follow-up period in each study (or final weeks of pre-switch phase in case of cross-over trials); 3) Craving reduction, assessed

through subjective reduction of scores on opioid-craving scales specific to each study. These outcomes were often assessed multiple times throughout the study period and measured across varied time intervals ranging from 1-24 weeks, depending on study length. Other, less common outcomes, including Quality of Life measures, satisfaction, physical complaints, and mental health were also reported. The level of statistical significance to assess differences between treatment and control groups was set *a priori* at $p < 0.05$.

It is noteworthy that with the new terminology changes to the Diagnostic Statistical Manual (DSM-V), opioid abuse and dependence have been combined into opioid use disorder, which can be labeled as mild, moderate, or severe. Although imprecise, opioid abuse can equate to moderate or severe OUD, while opioid dependence is similar to the mild subtype.[20 21]

Data extraction

All citations identified by search were independently screened based on title and abstract by two reviewers (LG, AA). Each potentially relevant study was then reviewed in full text and assessed for all inclusion criteria. Any disagreements were resolved by discussion among reviewers (LG, AA) and additional investigators (JK, EW). Relevant data from eligible articles (i.e., socio-demographics, type of interventions, outcomes, etc.) were then extracted.

Quality Assessment

Study quality was assessed according to the criteria indicated in the Cochrane Handbook for Systematic Reviews of Interventions.[19] Each study was assessed for risk of bias in random sequence generation and allocation concealment (i.e., selection bias). Blinding of participants and personnel (i.e., performance bias) and of outcome assessment (that is always possible, i.e., detection bias; objective and subjective outcomes were combined) were measured; however, since blinding was considered unlikely to affect study outcome in this context,[16] open-label studies were included. Incomplete outcome data (i.e.,

attrition bias) was recorded for each eligible study. Each category of bias was assigned a rating of low, high or unclear risk using protocols from the Cochrane Handbook. There was no deviation from the quality assessment criteria.

Data Synthesis and Analysis

For the meta-analysis, dichotomous outcome measures (treatment retention, continuous abstinence) were analysed by calculating the risk ratio (RR) for each trial, with uncertainty in each result expressed via 95% confidence intervals (CIs). Continuous outcomes, such as craving, were analysed by calculating the mean difference (MD) between experimental and control groups.

Information on missing data was collected where possible from study authors. If study authors were unable to supply this information, missing data were obtained or calculated from values in the primary studies according to suggested procedures in the Cochrane Handbook for Systematic Reviews of Interventions.[19]

Given the expected heterogeneity of results among studies due to differences in population and intervention type, we employed a random-effects meta-analytic model. The I-squared (I^2) statistic was employed to test the presence of heterogeneity between trials, and a sensitivity analysis was undertaken to assess the impact of particular high-risk trials.

Patient and public involvement: patients and public were not involved.

RESULTS

We considered all peer-reviewed articles and identified 1315 potentially eligible studies published since the date of search in the previous Cochrane Collaboration review.[16] After deduplication, 1001 records remained for screening based on title and abstract. Of those, 13 records were considered potentially eligible and were screened based on full-text. A total of eight reports from four distinct studies met all inclusion

criteria (Figure 1).[17 22-28] Four reports were excluded due to not meeting inclusion criteria, and one was excluded because the study protocol paper did not report outcome data. Because some trials were the subject of multiple reports, only four unique studies (n = 471) were eligible for quantitative synthesis. We considered data from all available high-quality trials as well as previously unpublished data from trial authors. One study did not report data of interest for this review other than treatment retention.[25]

All participants in the included studies met the DSM-IV or V diagnostic criteria for OUD; mean age 33.1 years; of the three studies that reported on gender,[17 25 26] 24.4% were female. The mean duration of trials was 18 weeks (range 11 to 24 weeks). The mean dose of SROM provided to participants was 506.8 mg/day, and the mean dose of methadone was 67.2 mg/day. All four studies were conducted in an outpatient setting, and assessed SROM *vs.* methadone, with only one study by Giacomuzzi et al.[26] explicitly stating psychosocial support. This study also assessed buprenorphine in comparison with SROM and methadone.[26]

Quality assessments for each study are presented in Table 1. Three out of four studies were found to be at low risk for selection bias – the fourth study's selection bias was agreed to be unclear, due to an unspecified randomization technique.[26] There was mixed-risk of bias relating to blinding of participants and outcome assessments; however, as noted by Ferri et al., objective outcomes -such as retention and urine drug screens- are unlikely to be impacted by a lack of blinding.[16] Three of the four included RCTs were therefore open-label.[17 26 27] All four studies were found to be at low risk for attrition bias. Additionally, differences in our risk of bias assessment and the previous Cochrane review were also identified.[16] For the trial by Giacomuzzi et al.,[26] we assessed blinding of outcome assessment to be of high risk while the previous review assigned unclear risk. Blinding of outcome assessment was not possible because the treating physician could terminate patients if three consecutive urine tests were found positive for 6-MAMmam (data from Dr Giacomuzzi).

Treatment retention was assessed via the dropout rate in all studies. Unpublished data regarding

treatment retention was obtained from the authors of one study.[26] With respect to measures of opioid use, the number of participants with urine drug tests positive for illicit substances was reported in two studies.[17 27] Unpublished data on positive urine tests was obtained from one study.[26] Measures of craving using various rating scales were used in three studies,[17 25 27] though one did not report the necessary outcome data for meta-analysis to be performed.[25]

Systematic Review Results

A 2013 Cochrane review by Ferri et al. described three trials included in the present analysis.[16] Clark et al.,[27] and Eder et al.,[25] both performed crossover, randomized controlled trials, wherein participants with OUD were randomized to take either SROM or methadone for the first half of the trial period, then subsequently switched to the other treatment for the second half of the trial period. According to the published conference abstract and M.D. thesis, Clark et al.,[29] conducted a 12-week open-label crossover study that required patients to be taking methadone prior to enrolling (n=9). The authors found SROM to have lower retention than methadone; however, no significant differences were found in regards to heroin use (6-Monoacetylmorphine [6-MAM]) in the last four weeks of treatment, use of other drugs over the study period, dollars spent on heroin in the final week of treatment, mental health and social functioning (as measured by the BASIS-32 Behavior and Symptom Identification Scale), self-reported days of heroin use, or heroin cravings. SROM was found to yield significantly lower on subjective opiate withdrawal scale (SOWS) scores (by 1.1 on the SOWS scale [95% Confidence Interval [30] 0.6 to 1.7] $p < 0.001$).

Eder et al. conducted a 14-week double-blind crossover study that required participants not to be on any maintenance treatment prior to enrolling in the trial (n=55). No significant differences were found between SROM and methadone on retention rates (103 [94%] patients completed the study) or illicit drug-use (consumption of cocaine was significantly reduced to 23.3% [p = 0.0083] by day 21; additional consumption of benzodiazepines remained almost unchanged throughout the study period at approximately

40% (highest [44.7%] on day 10; lowest [32.0%] on day 20); additional consumption of amphetamines was very low, with only two positive urine specimens on day 3). However, SROM was associated with significantly fewer physical complaints (falling from a mean score of 21.7 at baseline to 12.5 at day 21 among patients treated with SROM, $p < 0.05$), less craving for heroin, cocaine and alcohol (data from Visual Analogue Scale presented as charts only, $p < 0.05$), lower depression scores (falling from a mean score of 17.84 at baseline to 10.51 at day 21 among patients treated with SROM, $p < 0.001$), and lower anxiety scores (data from the State Trait Anxiety Inventory presented as charts only $p < 0.01$).

Giacomuzzi et al.,[26] conducted a 24-week, open-label, randomized controlled trial, wherein participants who had OUD and who were previously on methadone (n=120) were randomized to take either SROM, buprenorphine, or to continue methadone treatment. These participants were then compared to an equal number of patients being newly treated for OUD, and thus taking no OUD pharmacotherapy (n=120). Therefore, a total N = 240 was used for this study throughout the manuscript. Overall, Giacomuzzi et al. found SROM to be associated with significantly lower consumption of opioids (unpublished data: methadone 36.7%, buprenorphine 19.2%, SROM 25.8%, $p < 0.001$) and cocaine (unpublished data: methadone 3.3%, buprenorphine 6%, SROM 3.3%, $p <0.001$); however, scores on the Lancashire Quality of Life Profile, such as finances (methadone 4.4, buprenorphine 4.2, SROM 2.6, $p < 0.001$), family (methadone 5.8, buprenorphine 5.1, SROM 3.4, $p < 0.05$), and overall satisfaction (methadone 5.3, buprenorphine 4.9, SROM 4.1, $p < 0.001$), were significantly lower than for methadone or buprenorphine. Analyses of physical complaints on each treatment yielded mixed results.

Beck et al.,[17] conducted a 22-week, randomized, open-label, cross-over study of patients maintained on methadone in Switzerland and Germany (n=157), disseminated via four study reports. First, a non-inferiority study found no significant differences between SROM and methadone in treatment retention (period 1: 88.7% vs. 91.1%; period 2: 82.1% vs. 88.0% for SROM vs. methadone, period 1: $p =$

0.50, period 2: $p = 0.19$) or incidence of adverse events (81% SROM vs. 79% methadone, $p = 0.62$). The proportion of heroin-positive urine drug screens (6-Monoacetylmorphine [6-MAM] and 6-acetylcodeine [6-A-cod]) was found to be significantly higher on SROM (0.20 ± 0.26 SROM vs. 0.15 ± 0.23 methadone, $p < 0.001$); however, this difference fell within a pre-specified inferiority margin of 10%, leading the authors to confirm the non-inferiority of SROM compared to methadone. SROM was also found to have significant dose-dependent effects on the number of positive urine drug screens, with higher doses yielding fewer positive screens (Pearson's correlation coefficient: −0.1941 for positive 6-MAM and −0.1709 for positive 6-A-cod, $p < 0.05$). A second study similarly confirmed the non-inferiority of SROM to methadone;[31] SROM was associated with higher treatment satisfaction (SROM: 7.6 ± 1.8 vs. methadone: 6.0 ± 2.2, $p < 0.001$), and fewer adverse mental symptoms (SROM: 0.61 ± 0.56 vs. methadone: 0.68 ± 0.60, $p < 0.01$). No significant ($p = 0.48$-0.99) differences were found between number of self-reported days of heroin-(SROM: 6.4 ± 11.7 vs. methadone: 6.4 ± 11.3), cocaine-(SROM: 2.4 ± 6.0 vs. methadone: 2.2 ± 6.2), benzodiazepine-, (SROM: 8.2 ± 17.4 vs. methadone: 7.4 ± 15.8) and alcohol-use (SROM: 14.5 ± 21.7 vs. methadone: 14.5 ± 20.8) between SROM and methadone. A third study reported that heroin-craving scores (as measured by visual analogue scale and brief craving questionnaire) were significantly lower on SROM than on methadone (visual analogue scale: 3.3 ± 2.4 vs. 2.5 ± 2.2; brief craving questionnaire 2.9 ± 1.4 vs. 2.6 ± 1.2 for methadone and SROM respectively, $p < 0.0001$), and that cocaine-craving were statistically similar between the two treatments (visual analogue scale: 1.6 ± 2.0 vs. 1.4 ± 1.9; brief craving questionnaire 2.1 ± 1.2 vs. 2.1 ± 1.2 for methadone and SROM respectively, $p = 0.54$).[22] Finally, a fourth study reported on a 24-week extension phase, where all subjects in the initial cross-over trial either continued or were placed back on SROM.[23] This report again found that SROM was associated with fewer cravings for heroin (visual analogue scale: 2.06 ± 2.33 vs. 2.70 ± 2.63; brief craving questionnaire 2.25 ± 1.30 vs. 2.50 ± 1.43 at the end and start of extension phase respectively, $p < 0.01$) and

statistically similar self-reported drug use (Heroin: 0.08 ± 0.18 vs. 0.11 ± 0.21; Cocaine: 0.05 ± 0.17 vs. 0.06 ± 0.18; benzodiazepine: 0.15 ± 0.34 vs. 0.19 ± 0.36; Alcohol: 0.22 ± 0.36 vs. 0.24 ± 0.38 at the end and start of extension phase respectively, p = 0.26-0.54); however, as no control group was present, data from the extension phase was not included in the analyses of this review.

Meta-analysis Results

Efficacy of SROM

As shown in Figures 2a-I and 2a-ii, a three-study meta-analysis,[17 26 27] that included data from 406 participants showed no difference in effectiveness between SROM and methadone in reducing opioid use (RR = 0.96; 95% CI: 0.61- 1.52, p = 0.86, I^2 = 50%). Because other measures of SROM efficacy (i.e., craving) were not reported across all studies or were assessed using different statistical methods, they were not amenable to investigation via meta-analysis. However, two studies indicated that SROM reduces cravings for heroin more than methadone (P < 0.0001, measured using a visual analogue scale; P = 0.010, measured using the heroin craving questionnaire - brief), and that SROM produces no significant differences in self-reported use of illicit drugs.[17 22 27]

Treatment retention

Acceptability of treatment was measured via participant dropout. Dropouts were assessed in four studies,[17 25-27] with 471 participants [note: unpublished data were sought and obtained from two studies].[17 26] Retention was assessed for the entire duration of the trials. As shown in Figures 2b-iii and 2b-iv, the results of the meta-analysis suggest that the mean difference in dropouts was not statistically significant between participants in the SROM *vs.* methadone (RR = 0.98; 95%CI 0.94 - 1.02, p = 0.34), while low (18%) heterogeneity between studies was observed.

Sensitivity analysis

As one included study was published as a thesis and conference abstract, and contained a small sample

size (n = 24), a sensitivity analysis was run wherein this study's data was excluded. This exclusion did not change the results (Figures 2a-ii and 2b-iv). It was not possible to convert all data reported on outcomes into meta-analysis due to variance in reported data. Because continuous outcomes, such as craving, were reported in less than two studies, a meta-analysis was not performed.

DISCUSSION

The results of the present systematic review and meta-analysis indicate that current evidence suggests that SROM may be generally equal to methadone in the treatment of OUD. Building on an earlier review,[16] and with additional data from more recent trials as well as unpublished data, we were able to pool data on two outcomes: opioid use and retention in treatment. Here, in the meta-analysis, we observed no significant differences between SROM and methadone in improving treatment retention and heroin use. While not amenable to meta-analysis, results from two studies indicated that SROM reduces cravings for heroin more than methadone. These findings are relevant to recent high-level recommendations suggesting the need to consider repurposing existing medications for the treatment of opioid use disorder.[32]

Currently, SROM is available as an alternative to methadone in a range of European jurisdictions,[33 34] as well as in Canada.[4] Our findings concur with the new Canadian National Guidelines on the treatment of OUD, which recommend SROM as a treatment option, and with the findings from earlier systematic reviews though none of them had sufficient data for the calculation of the pooled effects for treatment retention and heroin use.[4 15 35] In particular, our analyses considered new unpublished data that were not included in past reviews, as well as data from a new trial from Switzerland and Germany,[17] thus confirming the apparent non-inferiority of SROM compared to

methadone. Although a number of gaps in our understanding of SROM persist (for instance, in the absence of mortality and detailed safety data), the current review underscores the clinical utility and potential for scaling up SROM as an agonist treatment for OUD, relevant beyond European and Canadian settings.

Limitations

The results reported in the present systematic review and meta-analysis are subject to the several limitations. First, the body of evidence regarding the efficacy of SROM in managing OUD is still relatively small. As such, additional research will help to illuminate the role that SROM can play in meeting the needs of specific patient subgroups. For instance, the relative ability of SROM to engage and retain patients with opioid use disorder in the context of the fentanyl epidemic. Second, the methodological quality of the included RCTs was low-to-moderate and the sample sizes were modest. In terms of comparing SROM to buprenorphine/naloxone, because of the latter's improved safety profile,[14 36] the recently published Canadian guideline recommends staging therapies with buprenorphine/naloxone recommended for first line therapy with methadone or SROM being offered to those unsuccessful with first line treatment.[4] As such, head-to-head comparisons of buprenorphine to SROM may not be warranted. Third, some outcome measures were not uniformly reported across studies and, therefore, were difficult to combine in a meta-analysis. Heroin use was amenable to meta-analysis as it was reported in a consistent manner by three studies.[17 25 27] Fourth, the analysis used some outcome data from the period before cross-over occurred in trials. Therefore, these results are based off of short durations of six to 12 weeks. Additionally, while one abstract that met the eligibility criterion of being published in a scientific peer reviewed journal was included, the full results of the RCT were not published in a peer-reviewed journal; nevertheless, the RCT was included in a previous Cochrane systematic review.[18] Finally, with respect to quality, we identified moderate heterogeneity and a risk of bias related to inconsistent blinding of participants and unclear blinding of outcomes across studies. Differences in study design and duration were also present. Given

these multiple potential sources of possible bias, SROM should remain an area of future study, where future studies should address the sources of heterogeneity (such as outcome measurement design and study duration) and consider impact on overdose and mortality, as highlighted above.

CONCLUSIONS

The present meta-analysis demonstrates the consistent pattern in clinical trials evaluating the impact of SROM. Because most OUD patients do not access agonist therapies,[10] and since poor retention in methadone has been linked to heightened mortality and other health outcomes,[14] SROM may have a promising role in OUD treatment, especially given methadone's known side effect profile, the likely attractiveness of SROM to some patients and the apparent reduction in craving when on SROM in comparison to methadone.[8 26] Unless future trials report contradictory findings, the public health crisis presented by illicitly manufactured opioids,[2] and the known limitations of existing agonist therapies,[14 35] these data should inform future investigations of SROM as a therapeutic tool among people undergoing treatment for OUD.

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Contributorship statement

JK and EW conceived the idea for and designed the study. JK and LG conducted the research and wrote the first draft of the manuscript. GS, CR, EMS, NF contributed to the study design, interpretation of the findings and preparation of the manuscript. All authors reviewed and approved the final version of the manuscript. Ahmed Adam screened the titles, fulltexts and assessed risk of bias in the included studies.

Competing interests

None

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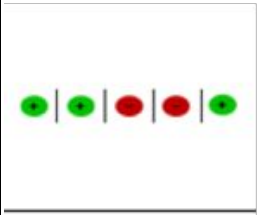
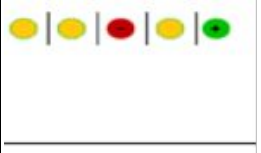
Data sharing statement

The data are extracted from published papers that are available via the individual journal websites.

Table 1: Characteristics of included studies

Study/ Country	Design	Participants	Interventions	Outcomes	Risk Rating (A B C D E)
Clark 2002 Australia	Cross-over, Randomized controlled trial, Open-label duration: 12 weeks	N=11 Mean age: 36.5 years Use of heroin: once per week Heroin use disorder and were on methadone	(1) Morphine Flexible starting dose; increased by 50 mg per day following transfer, never exceeded 800 mg/day (2) Methadone Flexible starting dose; reduced by 12 mg per day following transfer	Retention Severity of opiate withdrawal symptoms Heroin or other substance use Severity of dependence Mental health/social functioning	
Eder 2005 Austria	Cross-over, Randomized double blind, double-dummy duration: 14 weeks	N=64 Mean age: 28 years Male: 75% Opioid use disorder (excluded patients already receiving maintenance therapy)	(1) Morphine Starting dose 200 mg/day increased to 800 mg/day by week 1. (2) Methadone Starting dose 40 mg/day increased to 100mg/day by week 1.	Retention Use of illicit substances based on urinalysis Extent of drug cravings Withdrawal symptoms General well being Safety was assessed on the basis of adverse events and clinical and physical examination QoL measured by the Lancashire Quality of Life Profile	
Giacomuzzi 2006 Austria	Randomized controlled trial Open-label duration: 24 weeks	N=120 Mean age: 27 years; Male: 57% Opioid use disorder and were on methadone	(1) Morphine Maintenance dose dependent on severity of withdrawal symptoms (2) Methadone Maintenance dose dependent on severity of withdrawal symptoms (3) Buprenorphine Maintenance dose dependent on severity of withdrawal symptoms	Retention (from personal correspondence) QoL measured by the Lancashire Quality of Life Profile Withdrawal symptoms measured by the Opioid Withdrawal Scale	
Beck 2014 Switzerland and Germany	Cross-over Randomized controlled trial, Open-label, Duration: 22 weeks	N=276 Mean age: 38.1 Male: 81.5% Opioid dependence and were on methadone use disorder	(1) Methadone flexible dosing. Cross over at 11 weeks to morphine (2) Morphine flexible dosing. Cross over at 11 weeks to methadone	Retention (24 weeks) Proportion of positive urine samples per patient (12 weeks) Per treatment for co-consumption of heroin Craving heroin Craving cocaine Self-reported drug use Mental health problems (SCL-27) Positive urine samples Adverse events	

Risk Rating Legend:
A: Random sequence generation (selection bias); B: Allocation concealment (selection bias); C: Blinding of participants and personnel (performance bias); D: Blinding of outcome assessment (detection bias); E: Incomplete outcome data (attrition bias); Amber Circle: Unclear

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Figure 1. Flowchart of studies

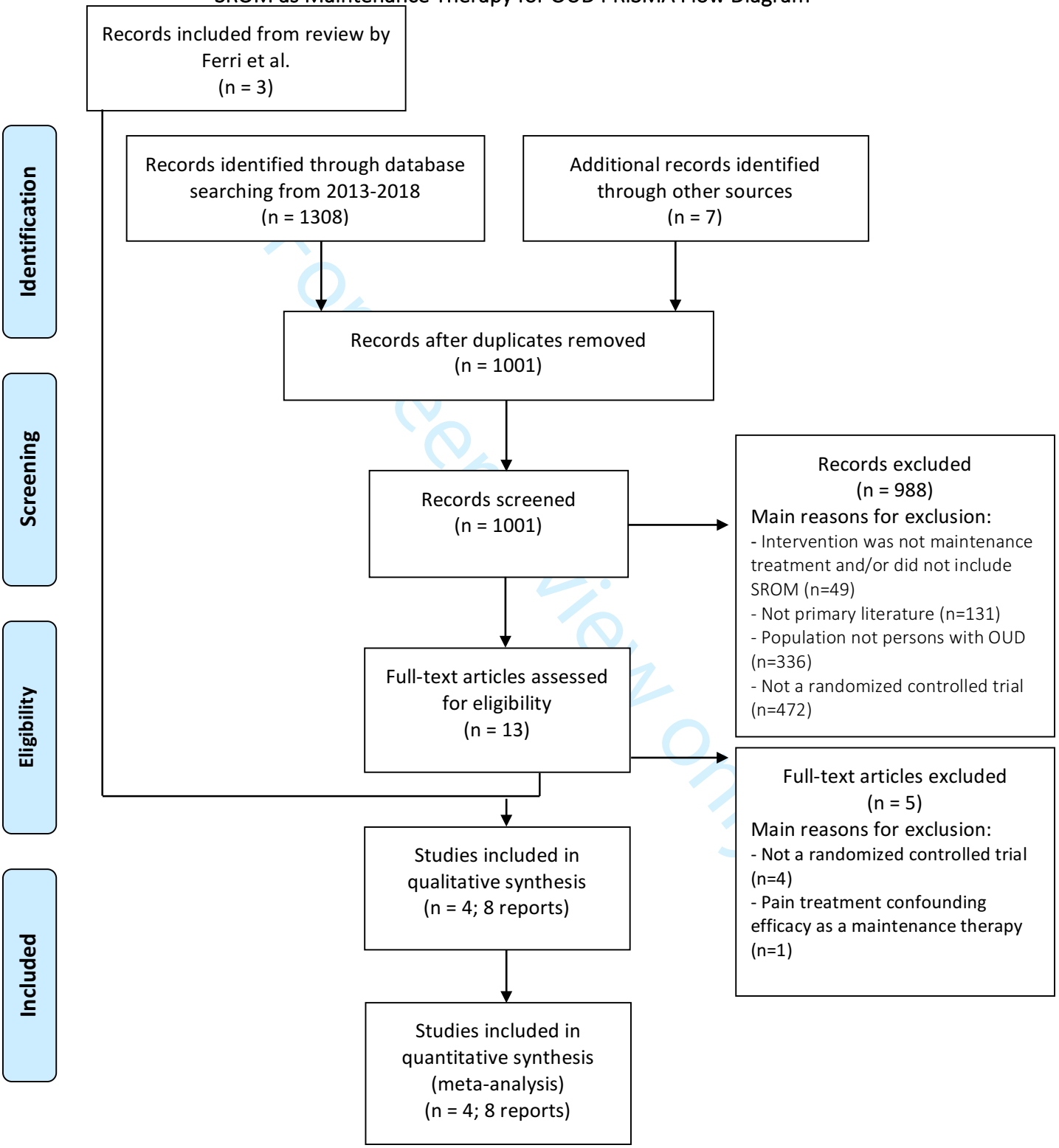
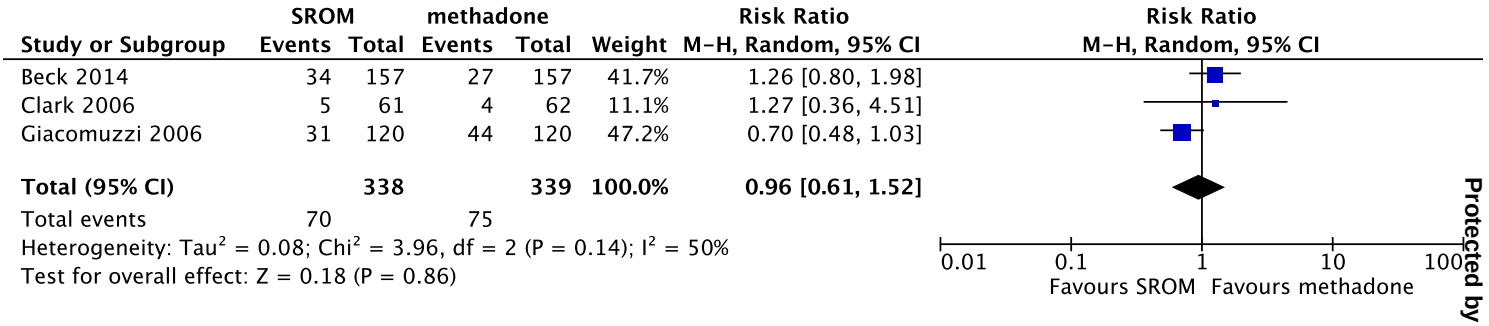


Figure 2a. Forest plot of the effects of slow release oral morphine (SROM) on heroin use as measured by urine drug tests among persons with opioid use disorders in randomized controlled trials; CI: confidence interval; ITT population.

i) Heroin use measured as the number of positive urine drug tests per participant:



ii) Heroin use measured as the number of positive urine drug tests per participant, with high-risk study excluded:

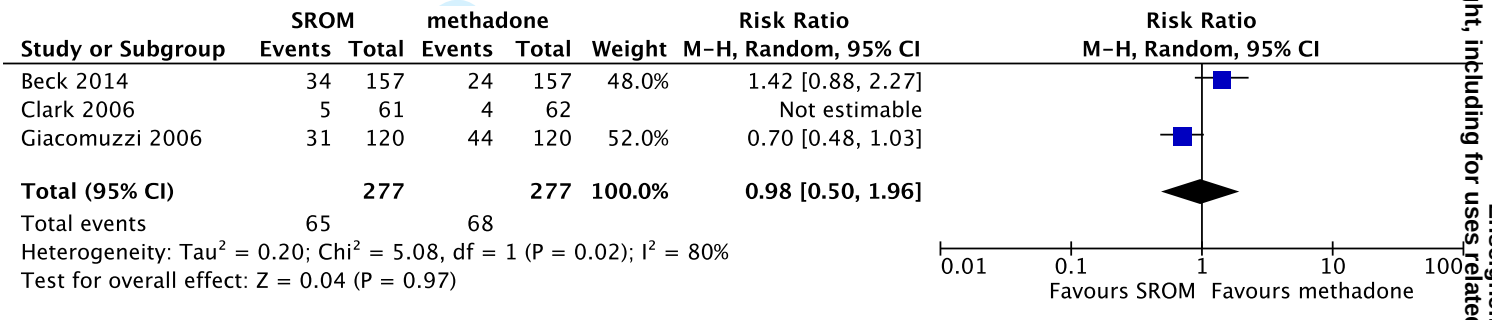
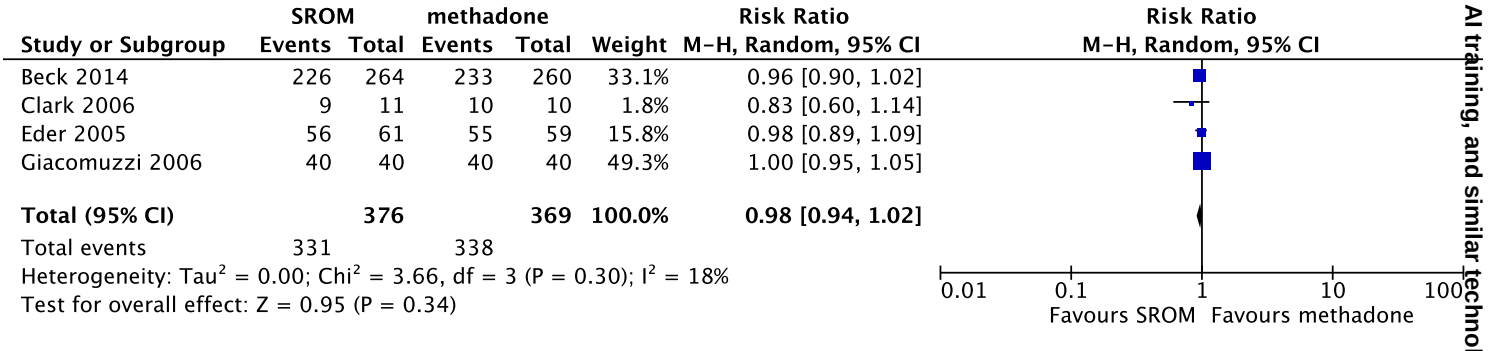
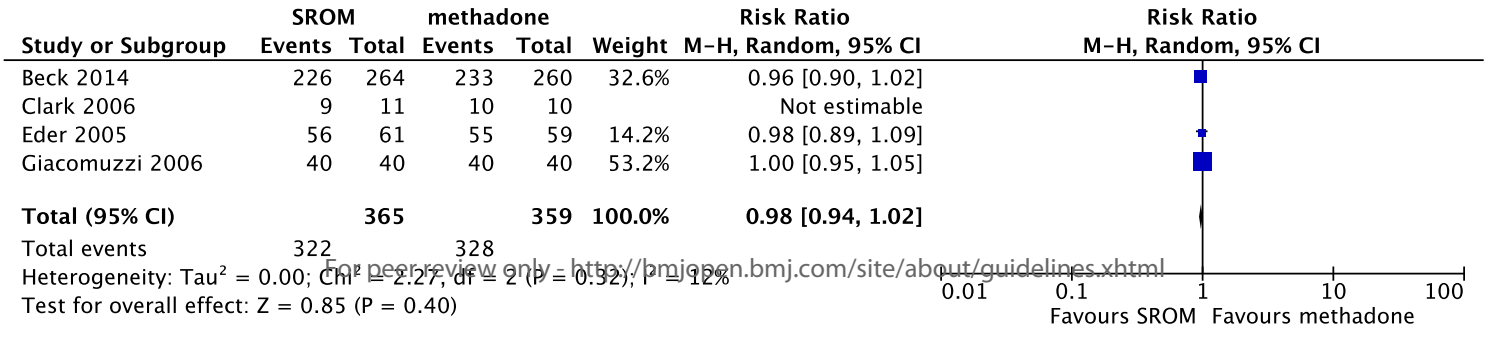


Figure 2b. Forest plot of the effects of slow release oral morphine (SROM) on retention in treatment among persons with opioid use disorders in randomized controlled trials; CI: confidence interval; ITT population.

iii) Retention in treatment at the end of the trial (or first period in case of cross-over trials):



iv) Retention in treatment at the end of the trial (or first period in case of cross-over trials), with high-risk study excluded:



Slow Release Oral Morphine versus Methadone for the Treatment of Opioid Use Disorder: A Systematic Review and Meta-Analysis

Appendix. MEDLINE Search Strategy:

Database(s): **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to May 1st, 2018		
Search Strategy: Run May 1st		
#	**Searches**	**Results**
1	exp Opioid-Related Disorders/	22650
2	(opiat$ or opioid$ or heroin$ or narcot$ or methadone or buprenorphine).ab,ti.	120510
3	1 or 2	125772
4	(withdraw$ or abstinen$ or abstain$ or abuse$ or abusing or dependen$ or addict$ or overdos$ or 'over-dose' or intoxicat$).ab,ti.	1820666
5	3 and 4	45660
6	exp MORPHINE/	36715
7	morphine.ab,ti.	46588
8	6 or 7	53469
9	randomized controlled trial.pt.	459781
10	controlled clinical trial.pt.	92372
11	randomized.ab,ti.	441959
12	drug therapy.sh.	29544
13	randomly.ab,ti.	290465
14	trial.ab,ti.	500960
15	groups.ab,ti.	1815207
16	9 or 10 or 11 or 12 or 13 or 14 or 15	2650720
17	5 and 8 and 16	1299
18	limit 17 to humans	613
19	limit 18 to yr="2013 - 2018"	**143**

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	--
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	--
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	--
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	--
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	17
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	17
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	--
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	--
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

BMJ Open

Slow Release Oral Morphine versus Methadone for the Treatment of Opioid Use Disorder: A Systematic Review and Meta-Analysis

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Primary Subject Heading:	Addiction
Secondary Subject Heading:	Mental health
Keywords:	Opioid use disorder, Substance misuse < PSYCHIATRY, Substance use treatment, Oral morphine, meta-analysis

Slow Release Oral Morphine versus Methadone for the Treatment of Opioid Use Disorder: A Systematic Review and Meta-Analysis

Klimas, Jan[1,3], Gorfinkel, Lauren[1], Giacomuzzi, Salvatore[5], Ruckes, Christian[4], Socías, M. Eugenia[1,2], Fairbairn, Nadia[1,2], Wood, Evan[1,2]

1. British Columbia Centre for Substance Use, 400-1045 Howe Street, Vancouver, BC, CANADA, V6Z 1Y6
2. Department of Medicine, University of British Columbia, St. Paul's Hospital, 608-1081 Burrard Street, Vancouver, BC, CANADA, V6Z 1Y6
3. School of Medicine, University College Dublin, Health Sciences Centre, Belfield, Dublin 4, Ireland
4. University Medical Center Mainz, Interdisciplinary Center Clinical Trials (IZKS), Langenbeckstraße 1 · D-55131 Mainz, Germany
5. Universitätsklinik Innsbruck-Ambulanz für Abhängigkeitserkrankungen, Anichstraße 35, 6020 Innsbruck, Austria

JK and LG contributed equally to this paper.

Send correspondence to:

Jan Klimas, PhD, MSc
B.C. Centre on Substance Use
University on British Columbia
400-1045 Howe Street, Vancouver, B.C., V6Z 1Y6
Canada
Tel: (778) 945-7616
Fax: (604) 806-9044
Email: jan.klimas@bccsu.ubc.ca

Running head: SROM for Opioid Use Disorder
Word Count: 3886
Tables: 1
Figures: 3
Revised: 5 Feb. 19

ABSTRACT

Objective To assess the efficacy of Slow release oral morphine (SROM) as a treatment for opioid use disorder.

Design Systematic review and meta-analysis of randomized controlled trials (RCT).

Data sources Three electronic databases were searched through May 1st, 2018: the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE. We also searched the following electronic registers for ongoing trials: ClinicalTrials.gov, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), Current Controlled Trials, and the EU Clinical Trials Register.

Eligibility criteria for selecting studies We included RCTs of any duration, assessing the effect of SROM on measures of treatment retention, heroin use and craving in adults who met the diagnostic criteria for opioid use disorder.

Data extraction and synthesis Two independent reviewers extracted data and assessed risk of bias. Data were pooled using the random-effects model and expressed as Risk Ratios (RR) or mean differences (MDs) with 95% CIs. Heterogeneity was assessed (chi-squared statistic) and quantified (I^2 statistic) and a sensitivity analysis was undertaken to assess the impact of particular high-risk trials.

Results Among 1315 records screened and four studies reviewed, four unique randomized trials met inclusion criteria (n = 471), and compared SROM with methadone. In the meta-analysis, we observed no significant differences between SROM and methadone in improving treatment retention (risk ratio [RR] = 0.98; 95% Confidence Interval [CI]: 0.94 - 1.02, p = 0.34), and heroin use (RR = 0.96; 95% CI: 0.61- 1.52, p = 0.86). Craving data was not amenable to meta-analysis. Available data implied no differences in adverse events, heroin, cocaine, or benzodiazepine use.

Conclusions Meta-analysis of existing randomized trials suggests SROM may be generally equal to methadone in retaining patients in treatment and reducing heroin use as methadone while potentially resulting in less craving. The methodological quality of the included RCTs was low-to-moderate.

Word Count: 300
Keywords: opioid use disorder, substance use treatment, oral morphine, meta-analysis
Review registration number: PROSPERO [CRD42018090782]

Strengths and limitations of this study

- The first meta-analysis of slow release oral morphine.

- We included new studies that increase the validity of the study.
- We included previously unpublished data obtained from primary trials.
- A meta-analysis of craving and adverse events was not possible due to inconsistent reporting of outcome measures across trials

INTRODUCTION

Overdose is the dominant cause of untimely death among people with opioid use disorder (OUD), and in 2017, opioid overdose was declared a national public health emergency in the U.S. Approximately two million Americans have a diagnosed opioid use disorder,[1] and deaths due to opioid overdoses have nearly doubled since 2006, exceeding 46,000 in 2016.[2] In response, the past decade has witnessed an expansion of pharmaceutical interventions for OUD, including the opioid agonist therapies methadone and buprenorphine/naloxone. Opioid agonist therapy (OAT) is currently the first-line treatment for OUD recommended by the World Health Organization (WHO) and a number of federal health guidelines.[3-5]

While methadone and buprenorphine/naloxone are proven effective,[6 7] they have a known limited ability to attract and retain patients in treatment. For instance, past studies have demonstrated that most individuals who overdose are not on agonist treatment at the time of death, and that, overall, agonist therapies remain sorely underutilised with only a fraction of eligible patients in U.S. accessing these therapies.[8-10] While overall low rates of methadone- and buprenorphine/naloxone-use are partially due to poor access and limited service delivery,[10] the balance of medication benefits and side-effects (e.g., sweating, weight gain), and other limitations of these therapies (e.g., QTc interval prolongation, sleep disturbance, need for daily visits and supervised urine collection in some settings), also result in low rates of patient retention once individuals initiate therapy.[11-13] The issues of poor uptake and retention on OAT are particularly urgent in the context of elevated

mortality among those not on OAT and the reported dramatic rise in mortality following OAT interruption,[14] as well as increasing overdose rates as a result of the emergence of highly toxic fentanyl analogues in the illicit drug markets of many settings.

In light of increasing recognition that a range of additional forms of opioid agonist therapy are necessary for some persons with complex OUD, interest in slow release oral morphine (SROM) as an OUD treatment agent has steadily grown.[8 15] A 2013 review by the Cochrane Collaboration reviewed the literature for SROM as treatment for OUD. However, the review was ultimately unable to draw definite conclusions regarding effectiveness, identifying only three high quality clinical trials.[16] However, some unpublished data were not included in this review, and since the time of its publication, a number of new studies investigating SROM have emerged, including a large international randomized controlled trial from Switzerland and Germany.[17] In light of the known limitations of methadone, buprenorphine/naloxone and medical heroin,[18] these new data on the efficacy of SROM, as well as the need to identify viable OAT options that may be more attractive to patients in the context of the current opioid-related public health emergency, the present systematic review and meta-analysis was conducted to assess the efficacy of slow-release oral morphine as a treatment for opioid use disorder as measured by treatment retention, heroin use, and opioid craving.

METHODS

Data sources and searches

In this report, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[19] Three electronic databases were searched to obtain relevant trials published in the past five years since the date of search of the Cochrane Collaboration review (up to May 2018): the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE. These databases were searched by combining selected MeSH terms and free-text terms related to OUD and SROM (see MEDLINE search strategy in Appendix). We also searched the following electronic registers for ongoing trials: ClinicalTrials.gov (www.clinicaltrials.gov), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/), Current Controlled Trials (www.controlled-trials.com/), EU Clinical Trials Register (www.clinicaltrialsregister.eu), the Italian Medicines Agency (www.agenziafarmaco.gov.it/en), and Trials (www.trialsjournal.com). References of all relevant papers were reviewed to identify further studies of relevance. Authors of potentially relevant studies were contacted for further unpublished data.

Study Selection

All English-language, randomized controlled trials (RCT) were eligible for inclusion. Studies were included if they met the following criteria: 1) studies were published in a scientific peer-reviewed journal (one RCT was published as conference abstract and a corresponding M.D. thesis was provided by authors[20]); 2) they employed RCT methods (with no requirement for blinding); 3) participants met diagnostic criteria for OUD as defined in the DSM-IV or DSM-V manuals; 4) treatment was defined as SROM with or without an accompanying psychosocial intervention; and 5) control conditions were defined as medication-only, regardless of other concurrent treatment; and 6) outcomes assessed included treatment

retention, efficacy (i.e., any measure of change in heroin use) and opioid craving.

Outcome Measures

The following outcomes were assessed: 1) Treatment retention, measured using dropout rates; 2) Efficacy, defined as the number of urine drug tests positive for illicit substances (incl. metabolites 6-Monoacetylmorphine [6-MAM] and 6-acetylcodeine [6-A-cod]) during the longest follow-up period in each study (or final weeks of pre-switch phase in case of cross-over trials); 3) Craving reduction, assessed through subjective reduction of scores on opioid-craving scales specific to each study. These outcomes were often assessed multiple times throughout the study period and measured across varied time intervals ranging from 1-24 weeks, depending on study length. Other, less common outcomes, including Quality of Life measures, satisfaction, physical complaints, and mental health were also reported. The level of statistical significance to assess differences between treatment and control groups was set *a priori* at $p < 0.05$.

It is noteworthy that with the new terminology changes to the Diagnostic Statistical Manual (DSM-V), opioid abuse and dependence have been combined into opioid use disorder, which can be labeled as mild, moderate, or severe. Although imprecise, opioid abuse can equate to moderate or severe OUD, while opioid dependence is similar to the mild subtype.[21 22]

Data extraction

All citations identified by search were independently screened based on title and abstract by two reviewers (LG, AA). Each potentially relevant study was then reviewed in full text and assessed for all inclusion criteria. Any disagreements were resolved by discussion among reviewers (LG, AA) and additional investigators (JK, EW). Relevant data from eligible articles (i.e., socio-demographics, type of interventions, outcomes, etc.) were then extracted.

Quality Assessment

Study quality was assessed according to the criteria indicated in the Cochrane Handbook for Systematic Reviews of Interventions.[19] Each study was assessed for risk of bias in random sequence generation and allocation concealment (i.e., selection bias). Blinding of participants and personnel (i.e., performance bias) and of outcome assessment (that is always possible, i.e., detection bias; objective and subjective outcomes were combined) were measured; however, since blinding was considered unlikely to affect study outcome in this context,[16] open-label studies were included. Incomplete outcome data (i.e., attrition bias) was recorded for each eligible study. Each category of bias was assigned a rating of low, high or unclear risk using protocols from the Cochrane Handbook. There was no deviation from the quality assessment criteria.

Data Synthesis and Analysis

For the meta-analysis, dichotomous outcome measures (treatment retention, continuous abstinence) were analysed by calculating the risk ratio (RR) for each trial, with uncertainty in each result expressed via 95% confidence intervals (CIs). Continuous outcomes, such as craving, were analysed by calculating the mean difference (MD) between experimental and control groups.

Information on missing data was collected where possible from study authors. If study authors were unable to supply this information, missing data were obtained or calculated from values in the primary studies according to suggested procedures in the Cochrane Handbook for Systematic Reviews of Interventions.[19]

Given the expected heterogeneity of results among studies due to differences in population and intervention type, we employed a random-effects meta-analytic model. The I-squared (I^2) statistic was employed to test the presence of heterogeneity between trials, and a sensitivity analysis was undertaken to assess the impact of particular high-risk trials.

Patient and public involvement: patients and public were not involved.

RESULTS

We considered all scientific articles and identified 1315 potentially eligible studies published since the date of search in the previous Cochrane Collaboration review.[16] After deduplication, 1001 records remained for screening based on title and abstract. Of those, 13 records were considered potentially eligible and were screened based on full-text. A total of eight reports from four distinct studies met all inclusion criteria (Figure 1).[17 23-29] Four reports were excluded due to not meeting inclusion criteria, and one was excluded because the study protocol paper did not report outcome data. Because some trials were the subject of multiple reports, only four unique studies (n = 471) were eligible for quantitative synthesis. We considered data from all available high-quality trials as well as previously unpublished data from trial authors. One study did not report data of interest for this review other than treatment retention.[26]

All participants in the included studies met the DSM-IV or V diagnostic criteria for OUD; mean age 33.1 years; of the three studies that reported on gender,[17 26 27] 24.4% were female. The mean duration of trials was 18 weeks (range 11 to 24 weeks). The mean dose of SROM provided to participants was 506.8 mg/day, and the mean dose of methadone was 67.2 mg/day. All four studies were conducted in an outpatient setting, and assessed SROM *vs.* methadone, with only one study by Giacomuzzi et al.[27] explicitly stating psychosocial support. This study also assessed buprenorphine in comparison with SROM and methadone.[27]

Quality assessments for each study are presented in Table 1. Three out of four studies were found to be at low risk for selection bias – the fourth study's selection bias was agreed to be unclear, due to an unspecified randomization technique.[27] There was mixed-risk of bias relating to blinding of participants and outcome assessments; however, as noted by Ferri et al., objective outcomes -such as retention and urine drug screens- are unlikely to be impacted by a lack of blinding.[16] Three of the four included RCTs were therefore open-label.[17 27 28] All four studies were found to be at low risk for attrition bias. Additionally,

differences in our risk of bias assessment and the previous Cochrane review were also identified.[16] For the trial by Giacomuzzi et al.,[27] we assessed blinding of outcome assessment to be of high risk while the previous review assigned unclear risk. Blinding of outcome assessment was not possible because the treating physician could terminate patients if three consecutive urine tests were found positive for 6-MAMmam (data from Dr Giacomuzzi).

Treatment retention was assessed via the dropout rate in all studies. Unpublished data regarding treatment retention was obtained from the authors of one study.[27] With respect to measures of opioid use, the number of participants with urine drug tests positive for illicit substances was reported in two studies.[17 28] Unpublished data on positive urine tests was obtained from one study.[27] Measures of craving using various rating scales were used in three studies,[17 26 28] though one did not report the necessary outcome data for meta-analysis to be performed.[26]

Systematic Review Results

A 2013 Cochrane review by Ferri et al. described three trials included in the present analysis.[16] Clark et al.,[28] and Eder et al.,[26] both performed crossover, randomized controlled trials, wherein participants with OUD were randomized to take either SROM or methadone for the first half of the trial period, then subsequently switched to the other treatment for the second half of the trial period. According to the published conference abstract and M.D. thesis, Clark et al.,[20] conducted a 12-week open-label crossover study that required patients to be taking methadone prior to enrolling (n=9). The authors found SROM to have lower retention than methadone; however, no significant differences were found in regards to heroin use (6-Monoacetylmorphine [6-MAM]) in the last four weeks of treatment, use of other drugs over the study period, dollars spent on heroin in the final week of treatment, mental health and social functioning (as measured by the BASIS-32 Behavior and Symptom Identification Scale), self-reported days of heroin

use, or heroin cravings. SROM was found to yield significantly lower on subjective opiate withdrawal scale (SOWS) scores (by 1.1 on the SOWS scale [95% Confidence Interval 0.6 to 1.7] $p < 0.001$).

Eder et al. conducted a 14-week double-blind crossover study that required participants not to be on any maintenance treatment prior to enrolling in the trial (n=55). No significant differences were found between SROM and methadone on retention rates (103 [94%] patients completed the study) or illicit drug-use (consumption of cocaine was significantly reduced to 23.3% [$p = 0.0083$] by day 21; additional consumption of benzodiazepines remained almost unchanged throughout the study period at approximately 40% (highest [44.7%] on day 10; lowest [32.0%] on day 20); additional consumption of amphetamines was very low, with only two positive urine specimens on day 3). However, SROM was associated with significantly fewer physical complaints (falling from a mean score of 21.7 at baseline to 12.5 at day 21 among patients treated with SROM, $p < 0.05$), less craving for heroin, cocaine and alcohol (data from Visual Analogue Scale presented as charts only, $p < 0.05$), lower depression scores (falling from a mean score of 17.84 at baseline to 10.51 at day 21 among patients treated with SROM, $p < 0.001$), and lower anxiety scores (data from the State Trait Anxiety Inventory presented as charts only $p < 0.01$).

Giacomuzzi et al.,[27] conducted a 24-week, open-label, randomized controlled trial, wherein participants who had OUD and who were previously on methadone (n=120) were randomized to take either SROM, buprenorphine, or to continue methadone treatment. These participants were then compared to an equal number of patients being newly treated for OUD, and thus taking no OUD pharmacotherapy (n=120). Therefore, **a denominator of N=240 is indicated** for this study throughout the manuscript. Overall, Giacomuzzi et al. found SROM to be associated with significantly lower consumption of opioids (unpublished data: methadone 36.7%, buprenorphine 19.2%, SROM 25.8%, $p < 0.001$) and cocaine (unpublished data: methadone 3.3%, buprenorphine 6%, SROM 3.3%, $p <0.001$); however, scores on the Lancashire Quality of Life Profile, such as finances (methadone 4.4, buprenorphine 4.2, SROM 2.6, $p <$

0.001), family (methadone 5.8, buprenorphine 5.1, SROM 3.4, $p < 0.05$), and overall satisfaction (methadone 5.3, buprenorphine 4.9, SROM 4.1, $p < 0.001$), were significantly lower than for methadone or buprenorphine. Analyses of physical complaints on each treatment yielded mixed results.

Beck et al.,[17] conducted a 22-week, randomized, open-label, cross-over study of patients maintained on methadone in Switzerland and Germany (n=157), disseminated via four study reports. First, a non-inferiority study found no significant differences between SROM and methadone in treatment retention (period 1: 88.7% vs. 91.1%; period 2: 82.1% vs. 88.0% for SROM vs. methadone, period 1: $p = 0.50$, period 2: $p = 0.19$) or incidence of adverse events (81% SROM vs. 79% methadone, $p = 0.62$). The proportion of heroin-positive urine drug screens (6-Monoacetylmorphine [6-MAM] and 6-acetylcodeine [6-A-cod]) was found to be significantly higher on SROM (0.20 ± 0.26 SROM vs. 0.15 ± 0.23 methadone, $p < 0.001$); however, this difference fell within a pre-specified inferiority margin of 10%, leading the authors to confirm the non-inferiority of SROM compared to methadone. SROM was also found to have significant dose-dependent effects on the number of positive urine drug screens, with higher doses yielding fewer positive screens (Pearson's correlation coefficient: −0.1941 for positive 6-MAM and −0.1709 for positive 6-A-cod, $p < 0.05$). A second study similarly confirmed the non-inferiority of SROM to methadone;[30] SROM was associated with higher treatment satisfaction (SROM: 7.6 ± 1.8 vs. methadone: 6.0 ± 2.2, $p < 0.001$), and fewer adverse mental symptoms (SROM: 0.61 ± 0.56 vs. methadone: 0.68 ± 0.60, $p < 0.01$). No significant ($p = 0.48$-0.99) differences were found between number of self-reported days of heroin-(SROM: 6.4 ± 11.7 vs. methadone: 6.4 ± 11.3), cocaine-(SROM: 2.4 ± 6.0 vs. methadone: 2.2 ± 6.2), benzodiazepine-, (SROM: 8.2 ± 17.4 vs. methadone: 7.4 ± 15.8) and alcohol-use (SROM: 14.5 ± 21.7 vs. methadone: 14.5 ± 20.8) between SROM and methadone. A third study reported that heroin-craving scores (as measured by visual analogue scale and brief craving questionnaire) were significantly lower on SROM than on methadone (visual analogue scale: 3.3 ± 2.4 vs. 2.5 ± 2.2; brief craving

questionnaire 2.9 ± 1.4 vs. 2.6 ± 1.2 for methadone and SROM respectively, $p < 0.0001$), and that cocaine-craving were statistically similar between the two treatments (visual analogue scale: 1.6 ± 2.0 vs. 1.4 ± 1.9; brief craving questionnaire 2.1 ± 1.2 vs. 2.1 ± 1.2 for methadone and SROM respectively, $p = 0.54$).[23] Finally, a fourth study reported on a 24-week extension phase, where all subjects in the initial cross-over trial either continued or were placed back on SROM.[24] This report again found that SROM was associated with fewer cravings for heroin (visual analogue scale: 2.06 ± 2.33 vs. 2.70 ± 2.63; brief craving questionnaire 2.25 ± 1.30 vs. 2.50 ± 1.43 at the end and start of extension phase respectively, $p < 0.01$) and statistically similar self-reported drug use (Heroin: 0.08 ± 0.18 vs. 0.11 ± 0.21; Cocaine: 0.05 ± 0.17 vs. 0.06 ± 0.18; benzodiazepine: 0.15 ± 0.34 vs. 0.19 ± 0.36; Alcohol: 0.22 ± 0.36 vs. 0.24 ± 0.38 at the end and start of extension phase respectively, $p = 0.26$-0.54); however, as no control group was present, data from the extension phase was not included in the analyses of this review.

Meta-analysis Results

Efficacy of SROM

As shown in Figures 2a-I and 2a-ii, a three-study meta-analysis,[17 27 28] that included data from 406 participants showed no difference in effectiveness between SROM and methadone in reducing opioid use (RR = 0.96; 95% CI: 0.61- 1.52, $p = 0.86$, $I^2 = 50\%$). Because other measures of SROM efficacy (i.e., craving) were not reported across all studies or were assessed using different statistical methods, they were not amenable to investigation via meta-analysis. However, two studies indicated that SROM reduces cravings for heroin more than methadone ($P < 0.0001$, measured using a visual analogue scale; $P = 0.010$, measured using the heroin craving questionnaire - brief), and that SROM produces no significant differences in self-reported use of illicit drugs.[17 23 28]

Treatment retention

Acceptability of treatment was measured via participant dropout. Dropouts were assessed in four

studies,[17 26-28] with 471 participants [note: unpublished data were sought and obtained from two studies].[17 27] Retention was assessed for the entire duration of the trials. As shown in Figures 2b-iii and 2b-iv, the results of the meta-analysis suggest that the mean difference in dropouts was not statistically significant between participants in the SROM *vs.* methadone (RR = 0.98; 95%CI 0.94 - 1.02, $p = 0.34$), while low (18%) heterogeneity between studies was observed.

Sensitivity analysis

As one included study was published as a thesis and conference abstract, and contained a small sample size (n = 24), a sensitivity analysis was run wherein this study's data was excluded. This exclusion did not change the results (Figures 2a-ii and 2b-iv). It was not possible to convert all data reported on outcomes into meta-analysis due to variance in reported data. Because continuous outcomes, such as craving, were reported in less than two studies, a meta-analysis was not performed.

DISCUSSION

The results of the present systematic review and meta-analysis indicate that current evidence suggests that SROM may be generally equal to methadone in the treatment of OUD. Building on an earlier review,[16] and with additional data from more recent trials as well as unpublished data, we were able to pool data on two outcomes: opioid use and retention in treatment. Here, in the meta-analysis, we observed no significant differences between SROM and methadone in improving treatment retention and heroin use. While not amenable to meta-analysis, results from two studies indicated that SROM reduces cravings for heroin more than methadone. These findings are relevant to recent high-level recommendations suggesting the need to consider repurposing existing medications for the treatment of opioid use disorder.[31]

Currently, SROM is available as an alternative to methadone in a range of European jurisdictions,[32 33] as well as in Canada.[4] Our findings concur with the new Canadian National Guidelines on the treatment of OUD, which recommend SROM as a treatment option, and with the findings from earlier systematic reviews though none of them had sufficient data for the calculation of the pooled effects for treatment retention and heroin use.[4 15 16] In particular, our analyses considered new unpublished data that were not included in past reviews, as well as data from a new trial from Switzerland and Germany,[17] thus confirming the apparent non-inferiority of SROM compared to methadone. Although a number of gaps in our understanding of SROM persist (for instance, in the absence of mortality and detailed safety data), the current review underscores the clinical utility and potential for scaling up SROM as an agonist treatment for OUD, relevant beyond European and Canadian settings.

Limitations

The results reported in the present systematic review and meta-analysis are subject to the several limitations. First, the body of evidence regarding the efficacy of SROM in managing OUD is still relatively small. As such, additional research will help to illuminate the role that SROM can play in meeting the needs of specific patient subgroups. For instance, the relative ability of SROM to engage and retain patients with opioid use disorder in the context of the fentanyl epidemic. Second, the methodological quality of the included RCTs was low-to-moderate and the sample sizes were modest. In terms of comparing SROM to buprenorphine/naloxone, because of the latter's improved safety profile,[14 34] the recently published Canadian guideline recommends staging therapies with buprenorphine/naloxone recommended for first line therapy with methadone or SROM being offered to those unsuccessful with first line treatment.[4] As such,

head-to-head comparisons of buprenorphine to SROM may not be warranted. Third, some outcome measures were not uniformly reported across studies and, therefore, were difficult to combine in a meta-analysis. Heroin use was amenable to meta-analysis as it was reported in a consistent manner by three studies.[17 26 28] Fourth, the analysis used some outcome data from the period before cross-over occurred in trials. Therefore, these results are based off of short durations of six to 12 weeks. Additionally, while one included RCT was only published as an abstract in a scientific peer reviewed journal,[20] the full results of the RCT were not published in a peer-reviewed journal; nevertheless, the RCT was included in a previous Cochrane systematic review.[16] Finally, with respect to quality, we identified moderate heterogeneity and a risk of bias related to inconsistent blinding of participants and unclear blinding of outcomes across studies. Differences in study design and duration were also present. Given these multiple potential sources of possible bias, SROM should remain an area of future study, where future studies should address the sources of heterogeneity (such as outcome measurement design and study duration) and consider impact on overdose and mortality, as highlighted above.

CONCLUSIONS

The present meta-analysis demonstrates the consistent pattern in clinical trials evaluating the impact of SROM. Because most OUD patients do not access agonist therapies,[10] and since poor retention in methadone has been linked to heightened mortality and other health outcomes,[14] SROM may have a promising role in OUD treatment, especially given methadone's known side effect profile, the likely attractiveness of SROM to some patients and the apparent reduction in craving when on SROM in comparison to methadone.[8 17 28] Unless future trials report contradictory findings, the public health crisis presented by illicitly manufactured opioids,[2] and the known limitations of existing agonist therapies,[14 35]

these data should inform future investigations of SROM as a therapeutic tool among people undergoing treatment for OUD.

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Contributorship statement

JK and EW conceived the idea for and designed the study. JK and LG conducted the research and wrote the first draft of the manuscript. GS, CR, EMS, NF contributed to the study design, interpretation of the findings and preparation of the manuscript. All authors reviewed and approved the final version of the manuscript.

Competing interests

None

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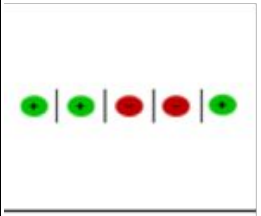
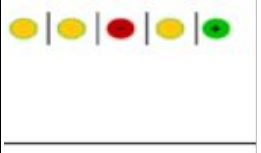
Data sharing statement

The data are extracted from published papers that are available via the individual journal websites.

Table 1: Characteristics of included studies

Study/ Country	Design	Participants	Interventions	Outcomes	Risk Rating (A B C D E)
Clark 2002 Australia	Cross-over, Randomized controlled trial, Open-label duration: 12 weeks	N=11 Mean age: 36.5 years Use of heroin: once per week Heroin use disorder and were on methadone	(1) Morphine Flexible starting dose; increased by 50 mg per day following transfer, never exceeded 800 mg/day (2) Methadone Flexible starting dose; reduced by 12 mg per day following transfer	Retention Severity of opiate withdrawal symptoms Heroin or other substance use Severity of dependence Mental health/social functioning	
Eder 2005 Austria	Cross-over, Randomized double blind, double-dummy duration: 14 weeks	N=64 Mean age: 28 years Male: 75% Opioid use disorder (excluded patients already receiving maintenance therapy)	(1) Morphine Starting dose 200 mg/day increased to 800 mg/day by week 1. (2) Methadone Starting dose 40 mg/day increased to 100mg/day by week 1.	Retention Use of illicit substances based on urinalysis Extent of drug cravings Withdrawal symptoms General well being Safety was assessed on the basis of adverse events and clinical and physical examination QoL measured by the Lancashire Quality of Life Profile	
Giacomuzzi 2006 Austria	Randomized controlled trial Open-label duration: 24 weeks	N=120 Mean age: 27 years; Male: 57% Opioid use disorder and were on methadone	(1) Morphine Maintenance dose dependent on severity of withdrawal symptoms (2) Methadone Maintenance dose dependent on severity of withdrawal symptoms (3) Buprenorphine Maintenance dose dependent on severity of withdrawal symptoms	Retention (from personal correspondence) QoL measured by the Lancashire Quality of Life Profile Withdrawal symptoms measured by the Opioid Withdrawal Scale	
Beck 2014 Switzerland and Germany	Cross-over Randomized controlled trial, Open-label, Duration: 22 weeks	N=276 Mean age: 38.1 Male: 81.5% Opioid dependence and were on methadone use disorder	(1) Methadone flexible dosing. Cross over at 11 weeks to morphine (2) Morphine flexible dosing. Cross over at 11 weeks to methadone	Retention (24 weeks) Proportion of positive urine samples per patient (12 weeks) Per treatment for co-consumption of heroin Craving heroin Craving cocaine Self-reported drug use Mental health problems (SCL-27) Positive urine samples Adverse events	

Risk Rating Legend:
A: Random sequence generation (selection bias); B: Allocation concealment (selection bias); C: Blinding of participants and personnel (performance bias); D: Blinding of outcome assessment (detection bias); E: Incomplete outcome data (attrition bias); Amber Circle: Unclear

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Figure 1. Flowchart of studies

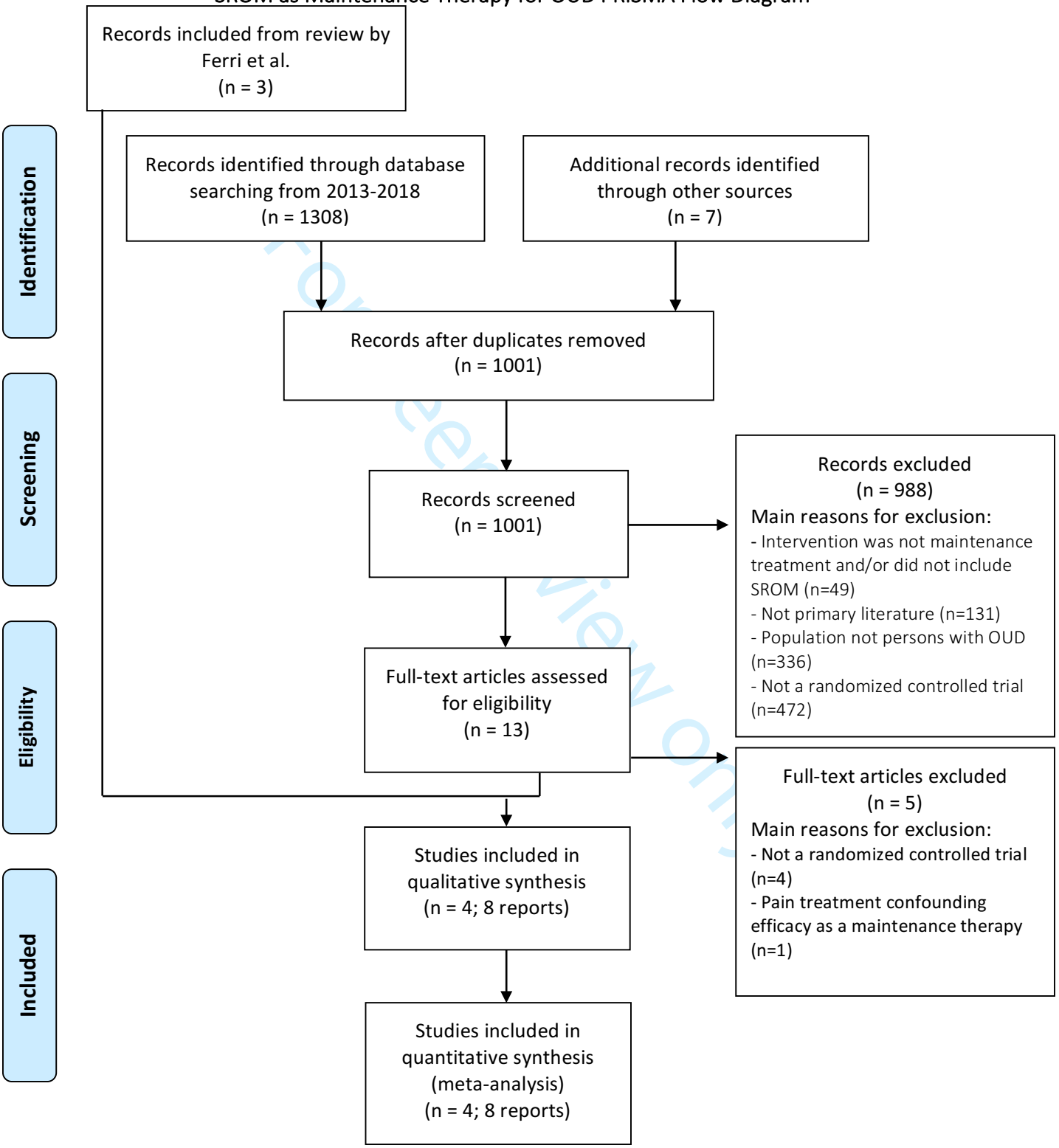
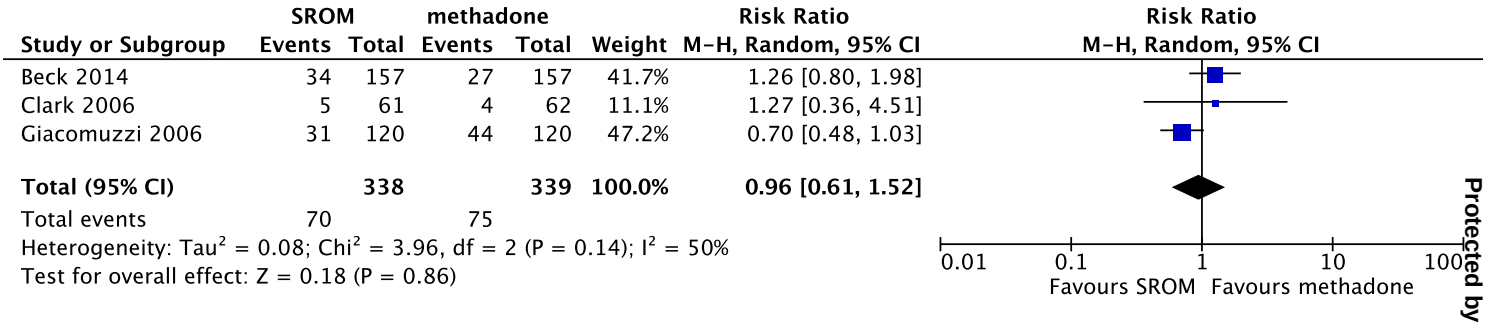


Figure 2a. Forest plot of the effects of slow release oral morphine (SROM) on heroin use as measured by urine drug tests among persons with opioid use disorders in randomized controlled trials; CI: confidence interval; ITT population.

i) Heroin use measured as the number of positive urine drug tests per participant:



ii) Heroin use measured as the number of positive urine drug tests per participant, with high-risk study excluded:

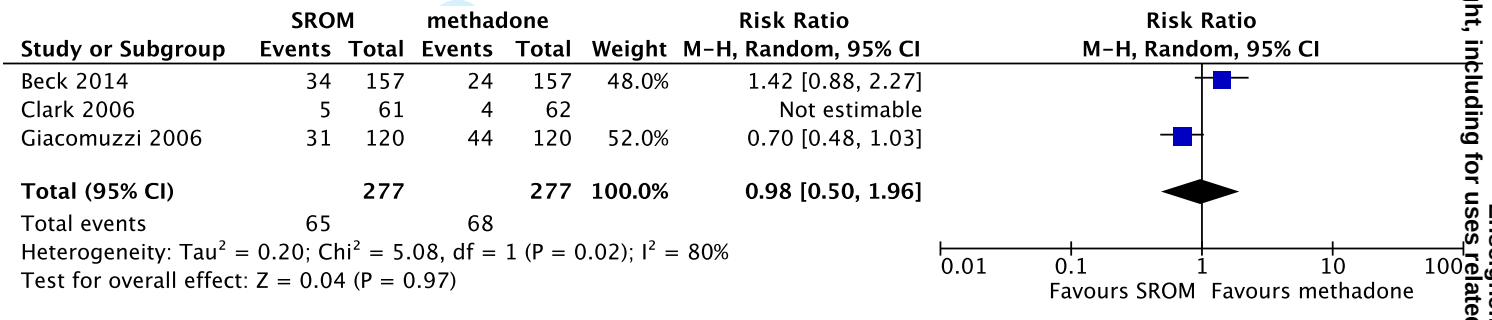
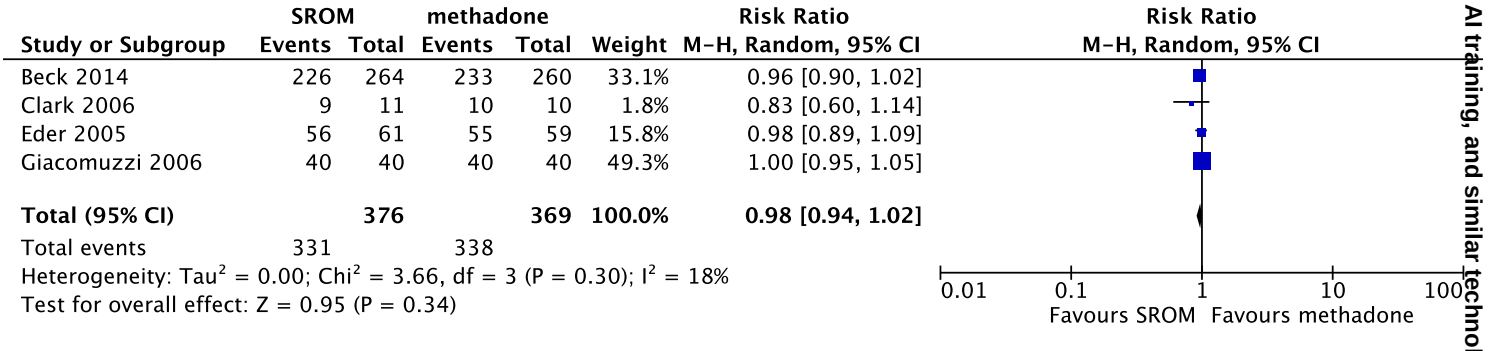
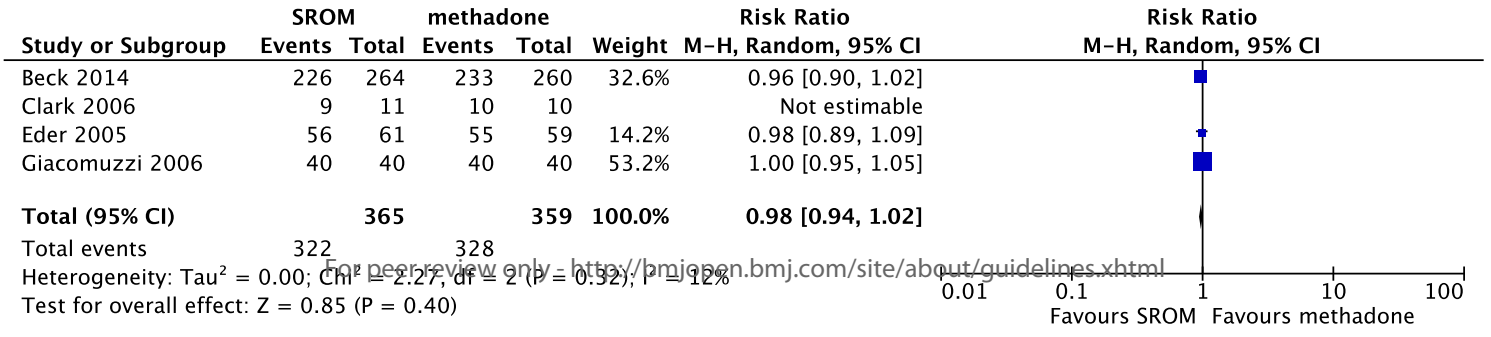


Figure 2b. Forest plot of the effects of slow release oral morphine (SROM) on retention in treatment among persons with opioid use disorders in randomized controlled trials; CI: confidence interval; ITT population.

iii) Retention in treatment at the end of the trial (or first period in case of cross-over trials):



iv) Retention in treatment at the end of the trial (or first period in case of cross-over trials), with high-risk study excluded:



Slow Release Oral Morphine versus Methadone for the Treatment of Opioid Use Disorder: A Systematic Review and Meta-Analysis

Appendix. MEDLINE Search Strategy:

Database(s): **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to May 1st, 2018		
Search Strategy: Run May 1st		
#	**Searches**	**Results**
1	exp Opioid-Related Disorders/	22650
2	(opiat$ or opioid$ or heroin$ or narcot$ or methadone or buprenorphine).ab,ti.	120510
3	1 or 2	125772
4	(withdraw$ or abstinen$ or abstain$ or abuse$ or abusing or dependen$ or addict$ or overdos$ or 'over-dose' or intoxicat$).ab,ti.	1820666
5	3 and 4	45660
6	exp MORPHINE/	36715
7	morphine.ab,ti.	46588
8	6 or 7	53469
9	randomized controlled trial.pt.	459781
10	controlled clinical trial.pt.	92372
11	randomized.ab,ti.	441959
12	drug therapy.sh.	29544
13	randomly.ab,ti.	290465
14	trial.ab,ti.	500960
15	groups.ab,ti.	1815207
16	9 or 10 or 11 or 12 or 13 or 14 or 15	2650720
17	5 and 8 and 16	1299
18	limit 17 to humans	613
19	limit 18 to yr="2013 - 2018"	**143**

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	--
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	--
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	--
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	--
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	17
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	17
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	--
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	--
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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