



2017

Alternative opioid agonists in the treatment of opioid dependence

A systematic review

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Key messages

Opioid maintenance treatment can help people with opioid dependence to improve their lives. The treatment is effective, but people often experience side effects. Sometimes it may help to change the medication used in treatment.

In this review, we have looked at treatment with slow release oral morphine and levomethadone. These treatments are compared to the three medications used in Norway: buprenorphine with naloxone, buprenorphine or methadone.

We found six relevant studies - three for slow release oral morphine and three for levomethadone. All compared these treatments with methadone. Almost all studies examined effect on use of illicit drugs and at least some possible adverse effects. Some studies reported if people stayed in treatment or how satisfied they were. No studies examined effect on crime.

When treatment with either slow release oral morphine or levomethadone was compared to treatment with methadone for opioid maintenance treatment, the researchers did not find evidence that these have different effects. However, the evidence is too limited and uncertain to conclude whether the treatments are equivalent.

Title:
Alternative opioid agonists in the treatment of opioid dependence

Type of publication:
Systematic review
A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.

Doesn't answer everything:
- Excludes studies that fall outside of the inclusion criteria
- No health economic evaluation
- No recommendations

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Brittelise Bakstad, Gabrielle Welle-Strand, both Norwegian Directorate of Health

Executive summary

Background

The Norwegian Directorate of Health revises the national guideline for the treatment of opioid dependence. Opioid Maintenance Treatment (OMT) has become the dominant form of treatment for people with opioid dependence. The current Norwegian OMT guideline recommends buprenorphine with naloxone as the first choice of medication, secondly buprenorphine monoformulation or methadone. However, all OMT drugs have several side effects. There is a need to diversify the possible medications available. The objective of this report is to assess the effect of using slow-released oral morphine or levomethadone in OMT for opioid dependence compared with the three medications used today.

Method

We first searched for systematic reviews and found one systematic review on treatment with slow-release oral morphine. We decided to use this as a basis with updated search for new primary studies. Subsequently, we searched for primary studies in Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL and PsycInfo through June 2016. Two people independently examined 2210 references and assessed 15 articles in full-text. We included three studies on treatment with slow-release oral morphine and three studies on levomethadone. The relevant study population was adults receiving OMT for opioid dependence. The intervention was either treatment with slow-release oral morphine or levomethadone. Control was treatment with methadone, buprenorphine or buprenorphine with naloxone. Relevant outcomes were retention in treatment, patient satisfaction, use of opioids and other addictive drugs, adverse effects and crime. We looked for randomized controlled trials or controlled studies with both pre- and post-measurements. Two reviewers independently assessed risk of bias. One person retrieved data from the studies, analysed and assessed our confidence in the effect estimates, and another person checked the data and analyses. We used the GRADE-methodology (Grading of Recommendations Assessment, Development, and Evaluation) to indicate our certainty in the effect estimates. The certainty may be high, medium, low, or very low.

Results

We found six relevant studies conducted in Germany, Switzerland, Austria and Netherlands. All studies recruited persons with long-term opioid dependence who had received OMT for some years. We considered that all studies had unclear risk of bias.

Three studies, with in total 460 recruited participants, compared receiving slow-release oral morphine with receiving methadone. One of these also compared treatment with buprenorphine. We found that when people are treated with slow-release oral morphine as compared to methadone:

- There is probably little or no difference in retention in treatment (Relative risk 0.97, 95% confidence interval 0.90 - 1.04, moderate certainty).
- There may be little or no difference in the use of illicit opioids and drugs as measured in urine and self-reported (low certainty).
- About 4 of 5 participants in these studies experienced at least one side effect (any severity) during treatment with slow-release oral morphine or methadone. Two of the studies reported that the overall prevalence of serious adverse events was 4% and 0% respectively. One person, treated with methadone at the time of event, died of an overdose. There may be little or no difference in the occurrence of adverse events between these treatments, but we have low to very low certainty in these estimates.
- The evidence is too uncertain to estimate effect on patient satisfaction.
- We found no studies that looked at effect on crime.

The evidence is sparse regarding the effect of treatment with slow-release oral morphine as compared to buprenorphine.

Further three studies compared receiving levomethadone with receiving methadone among 141 recruited participants. We could not calculate effect on retention in treatment when people were treated with levomethadone compared to methadone. The evidence is too uncertain to estimate the effect on any differences in patient satisfaction, use of both illicit opioids and other drugs, and in the prevalence of adverse events (very low certainty evidence). We found no studies that looked at effect on crime.

Discussion

The evidence is more comprehensive for slow-release oral morphine than for levomethadone. Most of the studies compared the alternative treatment to treatment with methadone. All the included studies had weaknesses in how the studies were performed and presented. Due to these weaknesses, we assessed the certainty in most of the evidence of effect as low or very low. Low certainty in evidence of effect does not mean that the treatments are ineffective or differ, but that the available evidence is insufficient to reliably estimate the true comparative effect.

Only one of the studies related their design and interpretation of findings to features of equivalence and non-inferiority study designs. The other studies provided insufficient information to judge the effects against equivalence and non-inferiority margins.

Overall, when the evidence is viewed across all the presented outcomes, the studies do not indicate any major differences in effects of treatment with slow-release oral morphine or levomethadone as compared to methadone for OMT. However, the evidence is too uncertain and limited to conclude whether the treatments are equivalent or non-inferior to standard treatments.

Conclusion

When treatment with either slow release oral morphine or levomethadone for OMT was compared to treatment with methadone, we did not find evidence suggesting substantially different effects between treatments. However, the evidence is too limited and uncertain to conclude whether the treatments are equivalent.

Hovedbudskap (norsk)

Legemiddelassistert rehabilitering kan hjelpe mennesker med opioidavhengighet til å forbedre livene sine. Behandlingen er effektiv, men pasientene opplever ofte bivirkninger. Noen ganger kan det hjelpe å bytte til et annet legemiddel.

I denne oversikten har vi sett på behandling med langtidsvirkende morfin eller levometadon. Disse behandlingene er sammenliknet med de tre legemidlene som brukes i Norge: buprenorfin med nalokson, buprenorfin eller metadon.

Vi fant seks relevante studier – tre for langtidsvirkende morfin og tre for levometadon. Alle sammenlignet disse behandlingene med metadon. Nesten alle studiene undersøkte effekten på bruk av ulovlige stoffer og enkelte mulige bivirkninger. Noen studier har rapportert om personene ble værende i behandling og hvor fornøyde de var. Ingen studier undersøkte effekt på kriminalitet.

Når behandling med enten langtidsvirkende morfin eller levometadon ble sammenlignet med behandling med metadon i legemiddelassistert rehabilitering, fant ikke forskerne holdepunkter for at disse har ulike effekter. Dokumentasjon er imidlertid for begrenset og usikker til å kunne konkludere med at behandlingene er likeverdige.

Tittel:

Alternative opioidagonister i behandling av opioidavhengighet

Publikasjonstype:

Systematisk oversikt

En systematisk oversikt er resultatet av å

- innhente
- kritisk vurdere og
- sammenfatte

relevante forskningsresultater ved hjelp av forhåndsdefinerte og eksplisitte metoder.

Svarer ikke på alt:

- Ingen studier utenfor de eksplisitte inklusjonskriteriene
- Ingen helseøkonomisk evaluering
- Ingen anbefalinger

Hvem står bak denne publikasjonen?

Kunnskapssenteret har gjennomført oppdraget etter forespørsel fra Helsedirektoratet

Når ble litteratursøket utført?

Søk etter studier ble avsluttet i juni 2016.

Interne fagfeller:

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Brittelise Bakstad, Gabrielle Welle-Strand, position, begge Helsedirektoratet

Sammendrag (norsk)

Innledning

Helsedirektoratet reviderer den nasjonale faglige retningslinjen for behandling av opioidavhengighet. Legemiddelassistert rehabilitering (LAR) har blitt den dominerende behandlingen for mennesker med opioidavhengighet. Dagens retningslinje for LAR anbefaler at buprenorfin med nalokson er førstevalg som medikament, sekundært buprenorfin monopreparat eller metadon. Imidlertid har alle LAR-legemidler flere bivirkninger. Det er derfor behov for å utvide antall tilgjengelige medikamenter. Formålet med denne rapporten er å se på effekt av å bruke langtidsvirkende morfin eller levometadon i LAR for opioidavhengighet sammenliknet med de tre legemidlene som benyttes i dag.

Metode

Vi søkte først etter systematiske oversikter og fant en systematisk oversikt på behandling med langtidsvirkende morfin. Vi besluttet å bruke denne som basis for et oppdatert søk etter primærstudier. Deretter søkte vi etter primærstudier i Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL og PsycInfo til juni 2016. To personer leste uavhengig av hverandre 2210 referanser og vurderte 15 artikler i fulltekst. Vi inkluderte tre studier på behandling med langtidsvirkende morfin og tre studier med levometadon. Den aktuelle studiepopulasjonen var voksne som fikk LAR for opioidavhengighet. Intervensjonen var enten behandling med langtidsvirkende morfin eller levometadon. Kontroll var behandling med metadon, buprenorfin eller buprenorfin med nalokson. Relevante utfall var retensjon i behandling, pasienttilfredshet, bruk av opioider, andre rusmidler og vanedannende legemidler, uønskede effekter og kriminalitet. Vi så etter randomiserte, kontrollerte studier eller kontrollerte studier med både før og etter målinger. To personer vurderte uavhengig av hverandre risiko for systematiske skjevheter. En person hentet data fra studiene, analyserte og vurderte tillit til dokumentasjonen og en person kvalitetssjekket dette. Vi benyttet GRADE-metodikken (Grading of Recommendations Assessment, Development and Evaluation) for å angi tilliten til effektestimaterne. Tilliten kan være høy, moderat, lav eller svært lav.

Resultat

Vi fant seks studier gjennomført i Tyskland, Sveits, Østerrike og Nederland. Alle de rekrutterte personene hadde vært opioidavhengige lenge. De fleste hadde fått LAR i noen år. Vi vurderte at alle studiene hadde uklar risiko for systematiske skjevheter.

Tre studier, med totalt 460 deltakere, sammenliknet det å få langtidsvirkende morfin med å få metadon i LAR. En av disse sammenliknet også behandling med buprenorfin.

Vi fant at når personer behandles med langtidsvirkende morfin sammenlignet med metadon:

- Er det trolig liten eller ingen forskjell i andel som gjennomfører behandlingen (Relativ risiko 0.97, 95% konfidensintervall 0.90 - 1.04, moderat tillit til resultatet)
- Er det muligens liten eller ingen forskjell i bruk av illegale opioider, andre rusmidler og vanedannende medikamenter målt ved urinprøver og selv-rapportert bruk (lav tillit til resultatet).
- Omtrent 4 av 5 deltakere i studiene opplevde minst en bivirkning (enhver alvorlighetsgrad) mens de mottok behandling med langtidsvirkende morfin eller metadon. To av studiene rapporterte at total forekomst av alvorlige uønskede hendelser/bivirkninger var henholdsvis 4 % og 0 %. En person, som fikk behandling med metadon på det tidspunktet, døde av en overdose. Det er muligens liten eller ingen forskjell i forekomst av uønskede hendelser, men vi har lav til svært lav tillit til estimatene.
- Dokumentasjonen er for usikker til å anslå effekt på pasienttilfredsheten.
- Vi fant ingen studier som studerte effekt på kriminalitet.

Det er svært lite dokumentasjonen med hensyn til effekter av behandlingen med langtidsvirkende morfin sammenliknet med buprenorfin.

Ytterligere tre studier sammenliknet det å få levometadon med å få metadon blant 141 rekrutterte deltakere. Vi kunne ikke beregne om det var noen effekt på andel som gjennomfører behandlingen når pasienter behandles med levometadon sammenlignet med metadon. Dokumentasjonen er for usikker til å anslå mulig effekt på forskjeller mellom behandlingene i pasienttilfredshet, bruk av illegale opioider og medikamenter, og forekomsten av bivirkninger (svært lav tillit til dokumentasjon av effekt). Vi fant ingen studier som undersøkte effekt på kriminalitet.

Diskusjon

Dokumentasjonen er mer omfattende for langtidsvirkende morfin enn for levometadon. De fleste av studiene sammenlignet den alternative behandlingen med metadonbehandling. Alle de inkluderte studiene hadde svakheter i hvordan studiene ble utført og presentert. På grunn av disse svakhetene, vurderte vi tilliten til resultatene som lav eller svært lav. Lav tillit til resultatene betyr verken at behandlingene er ineffektive eller at de er forskjellige, men at den tilgjengelige dokumentasjonen er utilstrekkelig til å estimere den sanne relative effekten på en god måte.

Kun én av studiene relaterte design og fortolkning av funnene til relevante særtrekk ved ekvivalens- og ikke-underlegenhetsstudier. De andre studiene oppga ikke tilstrekkelig informasjon til å bedømme effekten mot likeverdighets- og ikke-underlegenhetsmarginer.

Overordnet, når dokumentasjonen sees på tvers av alle resultatene, indikerer ikke disse studiene at det er store forskjeller i effekt for behandling med langtidsvirkende morfin eller levometadon sammenlignet med metadon for LAR. Imidlertid er dokumentasjonen for usikker og begrenset til å konkludere om behandlingene er likeverdige eller ikke dårligere enn standard behandling.

Konklusjon

Når behandling med enten langtidsvirkende morfin eller levometadon i LAR ble sammenliknet med behandling med metadon, fant vi ikke holdepunkter for at effektene er svært ulike. Dokumentasjon er imidlertid for begrenset og usikker til å kunne konkludere med at behandlingene er likeverdige.

Preface

The Norwegian Directorate of Health revises the national guideline for the treatment of opioid dependence. This systematic review is part of the evidence base for this revision. In Norway, opioid maintenance treatment (OMT) of opioid dependence primarily uses the medications methadone, buprenorphine or buprenorphine with naloxone. The Directorate of Health commissioned this report to provide a summary of the evidence on the effects of alternative opioids for OMT treatment.

The project group consisted of:

- Project leader: Senior researcher Annhild Mosdøl
- Researcher Kristoffer Yunpeng Ding
- Senior Advisor Laila Hov

All project group members are from the Knowledge Centre for the Health Services at Norwegian Institute of Public Health. Laila Hov is currently at Diakonova University College.

Thanks to Brynjar Fure and Liv Merete Reinart for internal peer review and Brittelise Bakstad and Gabrielle Welle-Strand for external peer review of both the protocol and report.

All authors and reviewers have filled out a conflict of interest forms. None reported conflicts of interest.

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Introduction

The international classification systems of diseases, ICD 10 and DSM-V, define opioid dependence as an illness. Opioid maintenance treatment (OMT) has become the dominant form of treatment for people with opioid dependence. The medications used in these programmes are similar to or identical with the abused substance (substitution therapy). These will, when used in a controlled manner, relieve cravings and withdrawal symptoms of the abused opioid. Non-prescribed use of opioids is costly for both the individuals, their families and the society. Mortality is high among opioid dependent persons, even among those who receive OMT treatment. In 2015, 127 deaths were reported among people in the Norwegian OMT program, a prevalence of 1.7 per 100 patient-years (1).

The Norwegian National guidelines for OMT to opioid dependent persons recommend buprenorphine with naloxone as the first choice of medication for new patients. Other recommended medications are buprenorphine monoformulation or methadone (2). At the end of 2015, the OMT programme in Norway had 7498 registered patients. Of these, 39% received methadone, 36% buprenorphine and 24% buprenorphine with naloxone (1).

All OMT medications have potential side effects. Common side effects for methadone are weight gain, sweating, and sleepiness. Some people find the side effects to be a significant problem, leading to low patient satisfaction with treatment. Patient interest groups in particular have called for a wider range of alternative medications offered for opioid dependence. The Norwegian Directorate of Health commissioned this systematic review of alternative opioids for OMT treatment. They specified two relevant alternative medications: slow-release oral morphine and levomethadone. Heroin assisted treatment will not be considered in this review. A wider range of possible OMT-medications may contribute to a greater degree of individual support and patient satisfaction, which is emphasized in the OMT guidelines (2). Changes in recommended intervention in a national guideline must, among other considerations, be informed by scientific evidence about the effects, side effects and other relevant outcomes (3).

Morphine is an opioid with analgesic effect, but can also induce experiences of euphoria and reduced tension. This substance is highly addictive and can cause serious breathing problems when overdosed. Slow-release oral morphine has been developed for chronic pain management. The capsules are formulated with a coating so that morphine is released over a prolonged period. This provides a relatively stable blood concentration over a period of 12 to 24 hours. Slow-release oral morphine has been tested as a possible alternative medication for persons who respond poorly to or have low tolerance for the medications commonly used in the OMT programmes (4-6). For instance the OMT

programmes in Austria and Australia use slow-release oral morphine as one alternative medication. A Cochrane review from 2013 found three studies that compared the effects of slow-release oral morphine with other medications used in OMT programmes. They found that the documentation was too sparse to conclude about the comparative effects of slow-release oral morphine in relation to other medications used in OMT programmes. Their outcomes were the number of participants who followed the treatment (retention in treatment), misuse of opioids and adverse events (7).

Methadone is an opioid agonist that binds to all opioid receptors in the brain. The methadone molecule has two mirror-isomeric forms. One form, levomethadone¹, has higher affinity for opioid receptors and accounts for the main opioid effect of methadone. The other methadone isomer is called S-methadone. The mixture of both forms can be called racemic methadone². A common problem with drugs like methadone³ is that the patients develop tolerance. This means that the person needs a larger dose of a medication over time to maintain the original effect. Treatment with levomethadone instead of methadone may reduce the tendency to develop methadone tolerance (8). Levomethadone is used as an OMT medication for instance in Germany. The other methadone isomer (S-methadone) carry higher risk of inducing cardiac arrhythmias, in addition to having lower opioid effect. Levomethadone may therefore have a different side effects profile than methadone. Both methadone and levomethadone are highly addictive and may cause fatal respiratory depression if overdosed. Levomethadone is twice as potent as racemic methadone, so the risk of overdose may be higher.

The overarching goal of this review is to provide evidence for consideration in the discussion about offering patients in OMT a wider choice of alternative medication. Thus, it is for instance desirable that these medications have equally good effectiveness, have no more side effects, and are generally liked by the users. In other words, we would like the alternative treatments “to be as good as” standard treatments. This question is best explored in *equivalence trials*. Yet, we may also accept alternative treatments “not to be any worse than” standard treatments, preferably explored in *non-inferiority trials*. Equivalence and non-inferiority trials are similar, but have distinct features in the design and statistical analyses (9, 10). This distinction was not made in our review protocol, nor is it likely that all relevant studies take these features into account.

The objective of this report is to assess the effect of using slow-released oral morphine or levomethadone for OMT in relation to the three medications used in the Norwegian OMT programme today; buprenorphine with naloxone, buprenorphine or methadone.

¹ Levomethadone (the chosen term in this report) can denoted by several other names, for instance L-methadone, R-(-)-methadone or lavamethodone.

² Racemic methadone contains both isomeric forms. Another common name is D,L-methadone.

³ Unless otherwise stated, the term methadone means racemic methadone in this report.

Method

We conducted a systematic review based on the methods described in the Norwegian Knowledge Centre's [methodological handbook](#) (11) and the [Cochrane Handbook for Systematic Reviews of Interventions](#) (12). Literature searches were performed and results presented for slow-release oral morphine and levomethadone separately.

Inclusion criteria

Study designs: Systematic reviews, Randomized controlled trials (RCTs), including cluster-randomized trials, Controlled studies with both pre- and post-measurements

Population: Persons, 18 years or older receiving OMT for opioid dependence

Intervention: Treatment with slow-release oral morphine (12 or 24 hour form) or levomethadone

Comparison: Treatment with methadone, buprenorphine or buprenorphine with naloxone

Outcome:

- Retention in treatment
- Patient satisfaction
- The use of opioids (self-reported or measurements in urine or other biological samples)
- Use of other addictive drugs (self-reported or measurements in urine or other biological samples)
- Adverse events (side effects, overdose, mortality)
- Crime

Language: We had no language restrictions in the search. The project group could read English, Norwegian, Swedish, Danish and Chinese and colleagues with different language skills were available.

Exclusion criteria:

- Conference abstracts and other publication formats where results are not presented in full-text.

Literature search

Librarian Gyri Hval Straumann conducted the literature searches and another librarian reviewed these. Appendix 1 contains all search strategies.

We first searched for relevant systematic reviews published during the last 5 years (after 1.1.2011) with search filters for systematic reviews in the following databases:

- Epistemonikos
- Cochrane Library (CDSR, DARE, HTA)
- MEDLINE (Ovid) and PubMed [sb]
- Embase (Ovid)

As described in the introduction, we knew about two older systematic reviews on the effect of slow-release oral morphine in OMT (6, 7). As described in the protocol, we decided to use the systematic review on slow-release oral morphine from Cochrane Collaboration (5) as a basis for an update search for new primary studies. This systematic review has slightly wider study inclusion criteria than our systematic review. We found no systematic reviews on levomethadone for OMT and conducted a systematic review of primary studies.

We searched for primary studies in the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE (Ovid) and PubMed [sb]
- Embase (Ovid)
- CINAHL (EBSCO)
- PsycInfo

In addition, we searched some trial registries and the reference lists of included studies for relevant studies.

Article selection

Annhild Mosdøl (AM) and either Laila Hov (LH) or Kristoffer Yunpeng Ding (KYD) carried out the selection of studies independently of each other, first based on titles and abstracts, subsequently in full-text according to the inclusion criteria.

Assessment of risk of bias in included studies

AM and KYD assessed risk of bias using the tool from the Cochrane handbook for systematic reviews (12) to assess the quality of the data, independently of each other. This is a change from the study protocol. The protocol specified that the risk of bias domains developed by [Cochrane Effective Practice and Organisation of Care Group](#) (13) should be used. These domains are more open for different types of study designs. We changed the risk of bias tool because all included studies were RCTs.

Data extraction

AM extracted information and data from the included studies and KYD controlled the information. We present author, year, country, title, number of participants in the study population, intervention and control intervention (drug type, dosage and administration), as well as the outcomes measured, and the results.

Analyses

The studies are organised according to comparisons made. We decided if meta-analysis was appropriate based on similarity in population, study design, intervention and control intervention, outcomes and data formats across studies. Decisions were guided by the Cochrane Handbook for Systematic Reviews of Interventions (12). The meta-analysis was conducted in the software Review Manager 5.3. We used the “random-effects” method. Results from meta-analysis are presented in forest-plots and tables. We planned to analyse RCTs separately from other study designs. When comparisons, outcomes or data formats were too different for meta-analysis, we present the data descriptively in tables and text. Dichotomous outcomes are presented as risk ratio (RR) with 95% confidence intervals (95% CI), and continuous outcomes as mean differences (MD) with 95% CI when available. We had planned to convert outcomes measured on different scales to standardized mean differences (SMD).

Assessment of quality of evidence

AM and KYD assessed the quality of the overall evidence for each of the outcomes using the GRADE methodology (Grading of Recommendations Assessment, Development and Evaluation) (14). The grading provides an assessment of the confidence we have in the effect estimates. We describe our confidence in the effect estimates as high, medium, low or very low (Table 1).

Table 1: GRADE categories, symbols used and their interpretation to rate the certainty in the evidence of effect.

Category	Symbol	Interpretation
High certainty	⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty	⊕⊕⊕○	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty	⊕⊕○○	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty	⊕○○○	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Results for slow-release oral morphine

Description of studies

Results of literature search

The search for systematic reviews published during the last five years returned 545 assumed unique references. Based on assessment of the title and summary, one previously known systematic review (7) met our inclusion criteria. We updated the information from this review with a search for new primary studies (Figure 1).

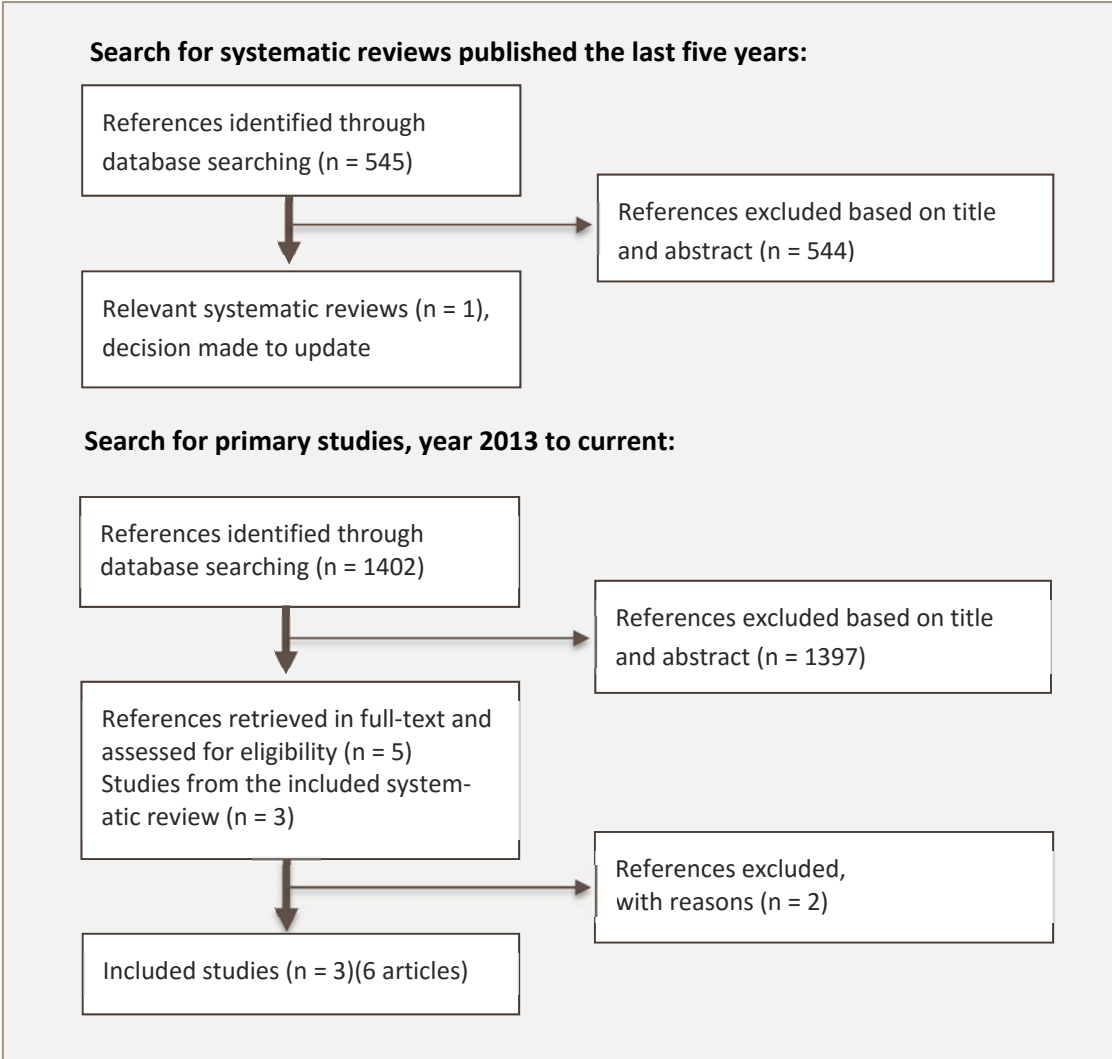


Figure 1: Study flow diagram for slow-release oral morphine.

The search for primary studies returned 1402 references. We selected five of these references for further assessment in full-text. In addition, we considered all three studies from the systematic review. Two studies from the systematic review fulfilled the inclusion criteria, while the third study was only a conference abstract (exclusion criteria). One new study from the literature search (presented in four publications) fulfilled the inclusion criteria.

Included studies

We included three studies, one multi-centre study from Germany and Switzerland (15-18) and two studies from Austria (19, 20), published between 2005 and 2014. All three were randomised controlled trials, two of them (15, 19) with a crossover design. Table 2 summarizes the treatment procedures in the three studies, while Appendix 2 contains further details.

Table 2: Description of the treatment given in the intervention groups and comparison groups in the included studies.

Author year (reference)	Treatment in intervention group	Treatment in comparison group
Beck 2014 (15-18)	RCT with crossover design. Before the trial, all participants were treated with methadone in an OMT programme. Participants were randomised to receive slow-release oral morphine for 11 weeks followed by methadone for 11 weeks, or vice versa. No washout phase between drugs. Each period started with a 1-week adjustment phase, followed by a 10-week treatment phase. Flexible dosing was permitted depending on individual needs.	
	<i>Last follow up end of trial (week 22)*.</i>	
Eder 2005 (19)	RCT with crossover design. Participants were novel to an OMT programme. Participants were randomised to receive slow-release morphine for 7 weeks followed by methadone for 7 weeks, or vice versa. No washout phase between drugs. Each period started with a 1-week adjustment phase, followed by a 6-week treatment phase with a fixed dose.	
	<i>Last follow up towards end of trial (week 12).</i>	
Giacomuzzi 2009 (20)	Before the trial, all participants were in an OMT programme. Open-label, flexible dosing regimen of slow-release oral morphine. Increasing doses during 8 days induction depending on the severity of withdrawal symptoms and the person's opinion. Stable dose thereafter for 6 months.	Alternative treatment 1: Open-label, flexible dosing regimen of methadone. Alternative treatment 2: Open-label, flexible dosing regimen of sublingual buprenorphine. Induction dose adjustments and trial procedures for alternative 1 and 2 otherwise as for slow-release morphine.
	<i>Follow up end of trial (6 months).</i>	

** After 22 weeks, all participants in this study were offered slow-release oral morphine for 26 weeks. We do not present these data as this phase has no control condition (observational data).*

In the standard RCT study by Giacomuzzi and co-authors (20), participants receiving slow-release oral morphine were compared with participants receiving either methadone or sublingual buprenorphine. Each treatment arm had 40 participants. All were previously in an OMT programme. In the smallest crossover trial (19), participants

were novel to an OMT programme, while in the other crossover trial participants had been under treatment for several years (15). Both studies (15, 19) randomised participants to receive treatment with slow-release oral morphine first and then methadone; or the other way around. Each was either 7 weeks (19) or 11 weeks (15). The study by Eder et al. (19) included 64 participants. The multi-centre trial presented by Beck et al. (15-18) included in total 276 participants. Results for all participants were presented in intention-to-treat analyses (ITT). These study authors also presented several of the results only for the 157 participants who followed the study protocol procedures, described as the per protocol population (PP population)⁴. All the studies recruited both men and women, but included a higher proportion of men (from 57% to 88% men). Participants in the two Austrian studies had mean age in the late 20-ies, while mean age in the multi-centre study was 38 years. All participants had a history of long-standing opioid dependence, mainly heroin use in two of the studies (15, 19) and while morphine misuse was most common in the third (20). The articles otherwise provide limited information about the socioeconomic characteristics or circumstances of the study populations.

Excluded studies

We excluded two of the eight references assessed in full-text. See Appendix 3 for the list of excluded studies with reasons for exclusion.

Risk of bias for included studies

Based on an overall assessment, we considered that all three studies had unclear risk of bias overall, but high risk of bias for some outcomes. One of the studies had unclear description of the randomisation procedures (20). The two crossover trials (15, 19) described appropriate procedures to generate and conceal allocation to treatment groups, but the second phase of the crossover trial treatment allocation was neither random nor concealed. The crossover trials had also not sufficiently corrected the statistical analyses for the effect of paired data, arising when participants undergo both treatments in a sequence. In two of the studies (15, 20), participants and staff were not blinded to treatment, but some of the outcome assessments were blinded. For the third study, authors described that drugs were administered blindly and that they had changed the taste of drugs to keep the alternative treatment blinded. However, it is unclear how capsules versus oral solution were concealed. Appendix 2 presents further details and judgements for each domain.

⁴ The PP population included participants who completed both crossover treatment periods (11 weeks) within a specified time-frame of ≥ 70 days and ≤ 84 days, who had urine-analyses for ≥ 9 of 11 weeks per crossover period and no discontinuation of study medication for more than 5 consecutive days

Intervention effects of slow-release oral morphine

Results from the study by Beck et al. were presented in four papers (15-18), but we only extracted data from the two (15, 18) reporting on our pre-specified outcomes. Giacomuzzi et al. (20) presented the data in a manner where the results of treatment with slow-release oral morphine could not directly be compared to the two groups treated with methadone or sublingual buprenorphine respectively. Eder et al. (19) presented many of the results as graphs only, presenting few results as numbers and in part insufficient data to analyse the comparative effect of treatments. It was only possible to combine outcomes in meta-analysis for one outcome - retention in treatment.

Two studies, both crossover trials, presented retention in treatment. Figure 2 illustrates this outcome for each phase separately in the meta-analyses. The effect estimates from Figure 2 with corresponding 95% CI are presented again in Table 3, with GRADE-assessment for our certainty in the effect estimates for this outcomes. Other results are presented narratively, by describing results presented for each outcome.

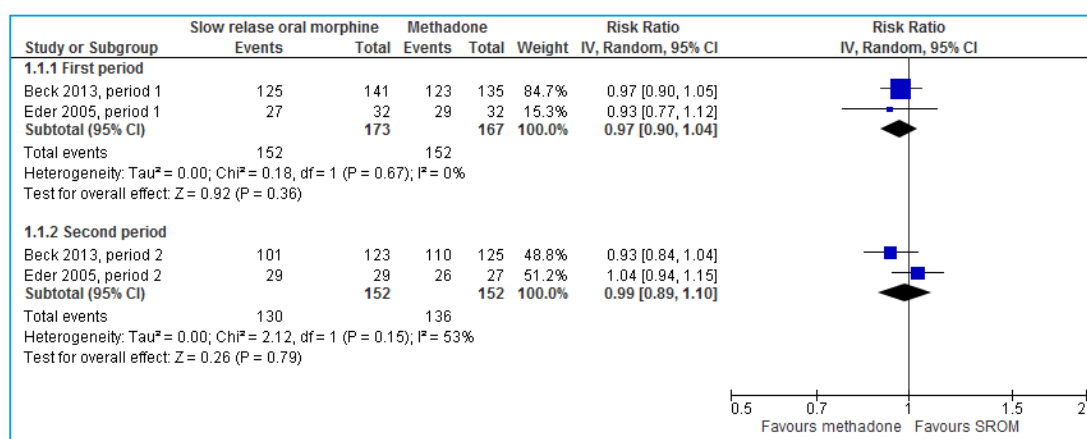


Figure 2: Retention in treatment when receiving slow-release oral morphine compared to receiving methadone for participants in OMT treatment (two periods in crossover trials). IV: Inverse variance; CI: Confidence interval; SROM: Slow-release oral morphine.

For the outcome retention in treatment, we considered that our certainty in the effect estimates was moderate for the first phase of the crossover trials, and low for the second phase (see footnotes under Table 3 for reasons and Appendix 4 for judgements relating to each domain). When our certainty in the evidence of effect is moderate, the true effect is likely, but not certain, to be close to the estimate of the effect. For most other outcomes, we found low certainty in the evidence of effect, meaning that the true effect may be substantially different from described effect estimate. For some outcomes, we are very uncertain whether the effect estimate represents the true effect. It is advisable not to present the numerical values of such outcomes to express the effect of the intervention. The main reasons for low certainty in the evidence of effect were that results for many outcomes were based on only one or few studies with relatively few participants; no blinding of treatment; and inappropriate statistical analyses of the crossover trial. For outcomes rated as very low confidence, additional factors were self-reported outcomes in a non-blinded study and insufficient data available from the authors to analyse any effect estimates.

Table 3: Summary of findings for treatment with slow-release oral morphine compared to methadone or buprenorphine for people in OMT treatment (table continues next page).

Outcomes (follow up)	Anticipated absolute effects (95 % CI)		Relative effect (95 % CI)	No of participants (Studies)	Quality of evidence (GRADE)
	Treatment with slow-release oral morphine	Treatment with methadone or buprenorphine			
Retention in treatment (registered)					
First period of crossover (7 or 11 weeks treatment)	910 per 1 000	883 per 1 000 (819 to 947)	RR 0.97 (0.90 - 1.04)	340 (2 RCTs)	⊕⊕⊕○ MODERATE ¹
Second period of crossover (7 or 11 weeks treatment)	895 per 1 000	886 per 1 000 (796 to 984)	RR 0.99 (0.89 - 1.10)	304 (2 RCTs)	⊕⊕○○ LOW ^{1,2}
Patient satisfaction (self-rated, questionnaires)					
Treatment satisfaction score (during trial 2x11 weeks crossover)	Pooled score (higher score = more satisfied) 7.6 (SD 1.8) under SROM and 6.0 (SD 2.2) under methadone, p<0.001. Sequence effect p = 0.82, carry-over effect p = 0.81, period effect p<0.01.			157 (1 RCT)	⊕○○○ VERY LOW ^{1,3,4,5}
Quality of life score (end of 6 months trial)	Score 4.1 (SD 1.7) for SROM, 5.3 (SD 1.5) for methadone and 4.9 (SD 1.4) for buprenorphine. No relevant statistical test presented.			120 (1 RCT)	⊕○○○ VERY LOW ^{1,3,4,5,6}
Use of illicit opioids (urine samples and self-reports)					
Urine samples (during trial 2x11 weeks crossover)	Proportion of heroin-positive urine samples per participant in PP population: 0.20 under SROM vs. 0.15 under methadone, difference 0.05 (95% CI: 0.02, 0.08; p = 0.0008. Within pre-defined non-inferiority margin). Reported as statistically not significantly different between treatments in ITT population (n=276).			157 (1 RCT)	⊕⊕○○ LOW ^{1,3,5}
Self-reported (during trial 2x11 weeks crossover)	Proportion of days self-reported use of heroin per patient in PP population: 0.08 (SD 0.15) under SROM vs. 0.08 (SD 0.15) under methadone. Reported as statistically not significantly different between treatments.			157 (1 RCT)	⊕○○○ VERY LOW ^{1,3,4,5}
Use of illicit drugs (urine samples and self-reports)					
Urine samples (during trials, up to 6 months)	Shortest crossover trial: Positive urine samples for cocaine, benzodiazepine and amphetamine reported as not significantly different between treatments. Longest crossover trial: Proportion of positive urine samples per participant in PP population. Cocaine: 0.13 (SD 0.27) under SROM vs. 0.15 (SD 0.27) under methadone. Benzodiazepines 0.36 (SD 0.42) under SROM vs. 0.39 (SD 0.42) under methadone. Reported as not significantly different. Standard RCT: Authors indicate more prevalent use of benzodiazepines in SROM group compared to methadone and buprenorphine (p = 0.02). Non numbers presented.			341 (3 RCTs)	⊕⊕○○ LOW ^{1,3,5}
Self-reported (during trial 2x11 weeks crossover)	Proportion of days self-reported use per participants in PP population of cocaine 0.03 (SD 0.10) under SROM vs. 0.03 (SD 0.08) under methadone; of benzodiazepines 0.11 (SD 0.23) under SROM vs. 0.10 (SD 0.21) under methadone. Reported as not significantly different.			157 (1 RCT)	⊕○○○ VERY LOW ^{1,3,4,5}

Population: Persons 18 years or older receiving OMT for opioid dependence.




Setting: Austria, Germany and Switzerland. Outpatient clinics.

Intervention: Treatment with slow-release oral morphine.

Comparison: Treatment with methadone or buprenorphine (standard treatment in Norway).

Outcomes (follow up)	Anticipated absolute effects (95 % CI)		Relative effect (95 % CI)	No of participants (Studies)	Quality of evidence (GRADE)
	Treatment with slow-release oral morphine	Treatment with methadone or buprenorphine			

Adverse effects (reported events)

All adverse events (during trials, up to 6 months)	Shortest crossover trial: At least one side effect reported by 82 % of participants when receiving SROM and 76 % when receiving methadone. Reported as statistically not significantly different. Some apparent variation between treatments, but no appropriate analyses comparing treatments presented. Longest crossover trial: At least one adverse event reported by 81 % of participants when receiving SROM and 79 % when receiving methadone (p = 0.61) in ITT population. Standard RCT: Authors reported the prevalence of several adverse symptoms and events, some with apparent variation between the three treatments, but presented no appropriate analyses comparing treatments presented.		460 (3 RCTs)		LOW 1, 3, 5, 6
Serious adverse events (during trials, up to 22 weeks)	Shortest crossover trial: Authors reported that no serious adverse events were registered during the trial. Longest crossover trial: At least one serious adverse event reported by 3 % of participants when receiving SROM and 4 % when receiving methadone (p = 0.12) in ITT population.		340 (2 RCTs)		LOW 1, 3, 5, 6
Mortality (during trial 2x11 weeks crossover)	One death (overdose). The participant was treated with methadone at event.		276 (1 RCT)		VERY LOW 1, 6

Crime (registered)

- No studies reported outcomes on crime

1. One to three studies with relatively few participants.

2. Allocation to treatment is not random in second part of crossover trial, i.e. bears resemblance to a non-randomised controlled trial. Downgraded one point.

3. Unclear risk of bias.

4. Self-reported outcome in non-blinded study.

5. Not sufficiently adjusted for paired data, arising when participants undergo both treatments in a sequence.

6. Insufficient data to analyse effect.

RR: Relative risk; CI: Confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; RCT: Randomised controlled trial; SROM: Slow-release oral morphine; PP population: Per protocol population; ITT population: Intention-to-treat analyses, i.e. all recruited participants.

The documentation in Table 3 shows the effect of treatment with slow-release oral morphine compared to either methadone or buprenorphine for people in OMT treatment for opioid dependence. In summary, we found that:

- Retention in treatment is probably little or no different when patients are treated with slow-release oral morphine compared to methadone (moderate certainty)
- The evidence is too uncertain to estimate whether patient satisfaction differs when people are treated with slow-release oral morphine compared to methadone (very low certainty evidence).

- Use of both illicit opioids and drugs (most data for benzodiazepines) may be little or no different when people are treated with slow-release oral morphine compared to methadone (low certainty).
- About 4 of every 5 participants experienced at least one side effect (any severity) during treatment with slow-release oral morphine or methadone. The overall occurrence of any adverse events may be little or no different when people are treated with slow-release oral morphine compared to methadone (low certainty).
- Two of the studies reported that the overall prevalence of serious adverse events were 4% and 0% respectively. One person, treated with methadone at the time of event, died of an overdose. The evidence is too uncertain to estimate the comparative effects of the two treatments on serious adverse events, specific side effects and mortality.
- The evidence is sparse for treatment with slow-release oral morphine compared to buprenorphine.
- We found no studies that looked at effects on crime.

Results for levomethadone

Description of studies

Results of literature search

The search for systematic reviews published the last five years returned 29 assumed unique references. Based on assessment of titles and summaries, none of the systematic reviews met our inclusion criteria. The search for primary studies returned 234 references. We selected six of these for further assessment in full-text. Three studies (presented in four articles) met our inclusion criteria (Figure 3).

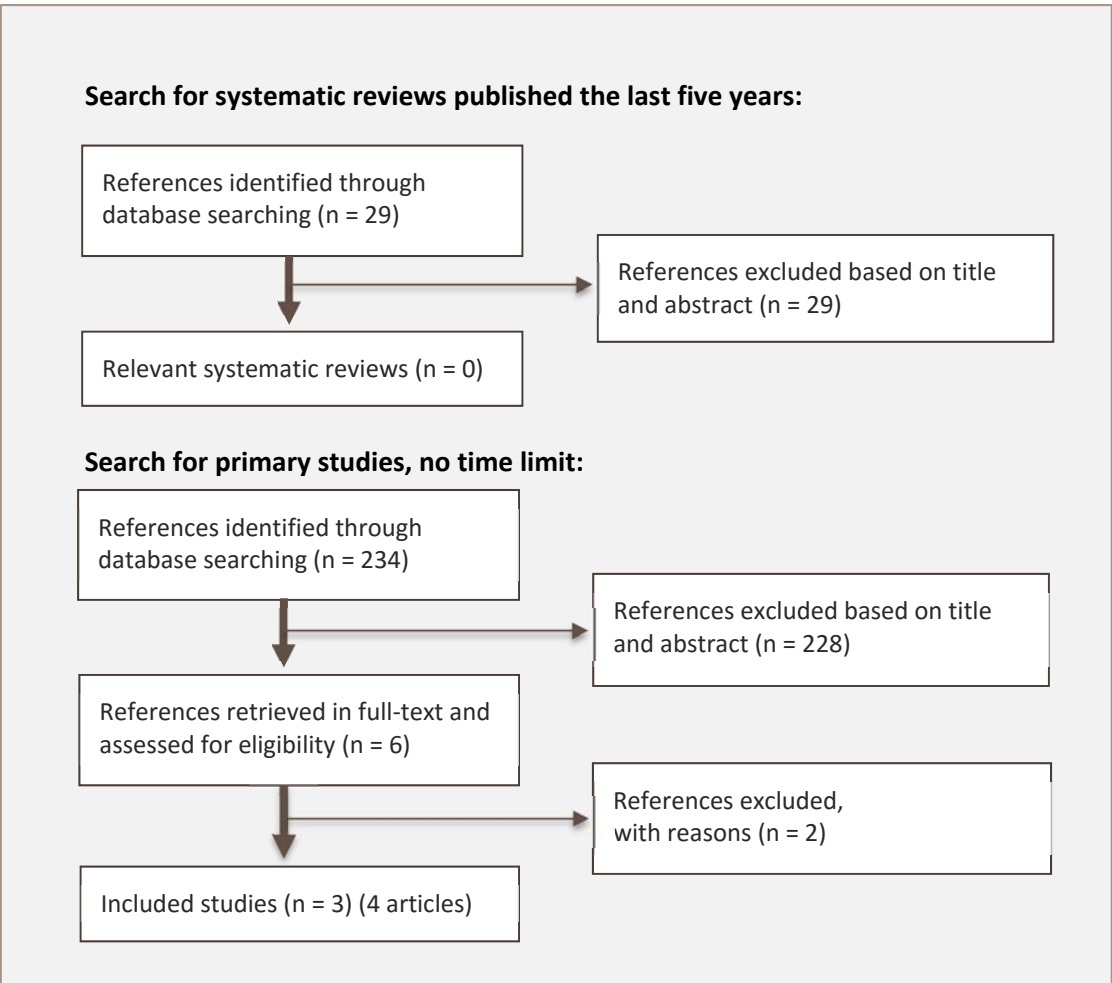


Figure 3: Study flow diagram for levomethadone.

Included studies

We included three studies, two from Germany (21-23) and one from the Netherlands (24), published between 1998 and 2005. All three were randomised controlled trials, one of them (22, 23) with a crossover design. Table 4 summarizes the treatment procedures in the three studies, while Appendix 2 contains further details.

Table 4: Description of the treatment given in the intervention groups and comparison groups in the included studies

Author year (reference)	Treatment in intervention group	Treatment in comparison group
Scherbaum 1998 (21)	Before the trial, participants were treated with levomethadone. During the baseline week, participants received fixed individual dose levomethadone as before. Followed by two weeks trial period with continued fixed individual dose of levomethadone. <i>Last follow up end of trial (week 3)*</i>	Before the trial, participants were treated with levomethadone. During the baseline week, participants received fixed individual dose levomethadone as before. Followed by two weeks trial period with double dose (compared to pre-trial levomethadone) of methadone.
Verthein 2005 (22, 23)	Trial with crossover design. Before the trial started, 22% of participants were treated with levomethadone and 78% with methadone. Participants were randomised, separately by pre-trial medication, to receive either levomethadone or methadone for 4 weeks (i.e. 50% changed from their pre-trial medication). After the fourth week, participants switched to the opposite medication for another 4 weeks of trial. No washout phase between medications. <i>Last follow up end of trial (week 8).</i>	
de Vos 1998 (24)	Participants were previously treated with levomethadone. Levomethadone dose maintained for all 22 days of trial. Individual dose adjustments as needed. <i>Last follow up end of trial (week 3).</i>	Previous levomethadone dose maintained for 8 days, then methadone at double dose of levomethadone. Individual dose adjustments as needed.

** After 2 weeks trial, all participants in this study were offered methadone. We do not present these data as this phase has no control condition (observational data).*

In all the studies, levomethadone was the standard OMT medication for opioid dependence in the resident country and methadone was the experimental medication. All participants were previous patients in an OMT programme. In the two standard RCTs (21, 24), a total of 26 and 40 participants, respectively, were randomised to receive treatment with levomethadone or methadone for 2 or 3 weeks. The crossover study randomised 75 participants to receive 4 weeks treatment with levomethadone first and then 4 weeks with methadone; or the other way around. All the studies recruited both men and women, but included a higher proportion of men (from 60 % to 87 % men). Mean age of participants were in the 30-ies for all studies. The articles otherwise provide limited information about the socioeconomic characteristics or circumstances of the study populations.

Excluded studies

We excluded two of the six references assessed in full-text. See Appendix 3 for the list of excluded studies with reasons for exclusion.



Risk of bias for included studies

Based on an overall assessment, we considered that all three studies had unclear risk of bias. All had unclear description of the randomisation procedures. In the second phase of the crossover trial, treatment allocation is neither random nor concealed. The crossover trial had not sufficiently corrected the statistical analyses for the effect of paired data. The two standard RCTs lacked information on participant flow and track of drop-outs. Appendix 2 presents further details and judgements for each domain.

Intervention effects of levomethadone

Results from the study by Verthein et al. were presented in two papers (22, 23) but we were only able to use data from one (22) reporting on our pre-specified outcomes in sufficient detail. All three studies reported many of the results in graphs only, presenting few results as numbers and insufficient data to analyse the comparative effects of treatments. None of the studies provided specific data on participant flow that could be used to estimate retention in treatment for each treatment. It was not possible to combine outcomes in meta-analysis. All results are presented narratively, by describing results presented for each outcome. Table 5 presents these results with GRADE-assessment for our certainty in the evidence of effect for each outcomes.

Table 5: Summary of findings for treatment with levomethadone compared to methadone for participants in OMT treatment.

Population: Persons, 18 years or older receiving OMT for opioid dependence. Setting: Germany, Netherlands. Outpatient clinics. Intervention: Treatment with levomethadone (standard treatment in the countries the studies were conducted). Comparison: Treatment with methadone (current standard treatment in Norway).					
Outcomes (follow up)	Anticipated absolute effects (95 % CI)		Relative effect (95 % CI)	No of participants (Studies)	Quality of evidence (GRADE)
	Treatment with levomethadone	Treatment with methadone			
Retention in treatment					
-	None of the studies reported on retention.		-	-	-
Patient satisfaction (Self-reported/-assessed)					
Patient satisfaction (end of trial, 2-8 weeks)	Smallest RCT: Reported as no statistically significant differences on participants' satisfaction with clinical effects. Crossover trial: Reported as no observed effect of changing the substitution medication on measures of psychological well-being.		94 (2 RCTs)	 VERY LOW 1, 2, 3	
Use of illicit opioids (urine samples and self-reports)					
Urine samples (end of trial, 2-8 weeks)	Two RCTs: Provided little or no information on prevalence of positive urine samples between groups. Crossover trial: Reported as no observed effect of changing the substitution medication on prevalence of positive urine samples.		124 (3 RCTs)	 VERY LOW 1, 2, 3	

Population: Persons, 18 years or older receiving OMT for opioid dependence.


Setting: Germany, Netherlands. Outpatient clinics.

Intervention: Treatment with levomethadone (standard treatment in the countries the studies were conducted).


Comparison: Treatment with methadone (current standard treatment in Norway).

Outcomes (follow up)	Anticipated absolute effects (95 % CI)		Relative effect (95 % CI)	No of participants (Studies)	Quality of evidence (GRADE)
	Treatment with levomethadone	Treatment with methadone			

Use of illicit drugs (urine samples and self-reports)

Urine samples (end of trial, 2-8 weeks)	Two RCTs: Provided little or no information on prevalence of positive urine samples between groups. Crossover trial: Reported as no observed effect of changing the substitution medication on prevalence of positive urine samples.		124 (3 RCTs)		VERY LOW ^{1, 2, 3}
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Adverse effects

All adverse events (end of trial, 2-8 weeks)	Smallest RCT: No statistically significant differences for somatic and psychological complaints and withdrawal checklists. Largest RCT: No statistically significant differences in craving. Crossover trial: No statistically significant differences in score for opioid side-effects between treatment groups at end of week 4 (period 1, p = 0.174) or week 8 (period 2, p = 0.095).		124 (3 RCTs)		VERY LOW ^{1, 2, 3}
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Crime

-	None of the studies reported outcomes on crime.	-	-
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1. Unclear risk of bias.

2. Small studies and few events. Short trial duration.

3. No or insufficient data to estimate effect.

RR: Relative risk; CI: Confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; RCT: Randomised controlled trial.

The documentation in Table 5 shows the effects of treatment with levomethadone compared to methadone for people in OMT treatment for opioid dependence. In summary, we found that:

- The evidence is too uncertain to estimate whether patient satisfaction, use of both illicit opioids and drugs, and prevalence of adverse events differs between treatments (very low certainty).
- We could not calculate effect on retention in treatment when people are treated with levomethadone compared to methadone.
- We found no studies that looked at effects on crime.

Discussion

Key findings summary

We found that when people are treated with slow-release oral morphine as compared to methadone there may be little or no difference in:

- retention in treatment (moderate certainty)
- use of illicit opioids and drugs (low certainty)
- overall occurrence of adverse events (low certainty)

The evidence is too uncertain to estimate effect on patient satisfaction. We found no studies that looked at effect on crime. The evidence is sparse regarding the effect of treatment with slow-release oral morphine as compared to buprenorphine.

We could not calculate effect on retention in treatment when people are treated with levomethadone compared to methadone. The evidence is too uncertain to estimate the comparative effect of levomethadone versus methadone on patient satisfaction, use of both illicit opioids and drugs, and prevalence of adverse events (very low certainty evidence). We found no studies that looked at effect on crime.

Our confidence in these results

The background for this commission from the Directorate of Health was a wish for a wider selection of alternative medications in the OMT programme. It is desirable that new medications are “as good as” or “not any worse than” standard treatments. These types of questions are best answered by equivalence trials or non-inferiority trials (9, 10). Traditional significance testing assesses how likely the observed or larger effect in the sample data is if the true effect is no difference between the experimental groups (the null hypothesis). In a trial, a low p-value (low likelihood of the null hypothesis) implies that we can assume that one treatment is superior over the other. In equivalence trials or non-inferiority trials the question is opposite, meaning that traditional significance testing is inappropriate. Studies aiming to establish equivalence or non-inferiority should pre-define values for the estimated effects that are considered clinically “close enough” to be considered equal. If this margin is defined in both directions (upper and lower boundaries), it is called the equivalence margin. If the margin is one-sided towards a lower effect threshold, it is called a non-inferiority margin (10).

Only the newest of the included studies defined their study and discussed their findings in relation to features of a non-inferiority study design (15). For this study, they defined a non-inferiority margin of 10% between treatments with slow release oral morphine and methadone as appropriate. All the outcomes we have reported from their

study were within this non-inferiority margin. We had not defined equivalence and non-inferiority margins in the protocol for this review. It would have been possible to discuss review findings in relation to such margins post hoc, but the included studies provided very little information regarding the effects and uncertainty of findings overall. Many of the results were presented as graphs without actual values and measures of dispersion, or differences between groups were commented using only p-values or described as statistically non-significant. Thus, the included studies have limited evidence to contribute to the question whether the treatments in this review were equal or non-inferior to standard treatment. Although we found as many as six relevant studies, three for slow release oral morphine and three for levomethadone, the overall amount of evidence is limited. Some of the studies were small and followed the participants for a very short period of time (only 2-8 weeks for the studies of levomethadone).

We judged that all the included studies have unclear risk of bias in the results based on how the studies were carried out and described. Several of the studies had unclear description of how groups were allocated to treatments. The best described studies were two of the crossover trials (15, 19). However, in the second crossover phase of the study, treatment allocation was neither random nor concealed. The effect of this on the results is unclear. The crossover trials had furthermore not sufficiently corrected for the effect of paired data for participants in the statistical analyses. Such lack of statistical correction will underestimate the uncertainty of effect estimates (i.e. will produce too narrow confidence intervals or too low p-values).

All the studies of levomethadone administered the drugs double blinded (21-24), but two of the studies on slow release oral morphine were open label studies (15, 20). Beck et al. argued for a non-blind design because “intrinsic pharmacological differences of morphine and methadone mean that these persons are experienced in perceiving specific drug effects, either from prior illicit consumption or from previous maintenance treatment,[...]” (15). For the third study (19), the authors describe that drugs were administered blindly with taste modification to match the alternative treatment, but it is unclear how capsules versus oral solution were concealed. The possible bias on effects due to the non-blind design, for instance if participants have preferences for one drug or the other, is difficult to predict. We therefore consider that the magnitude and direction of bias on results due to no or uncertain blinding is unclear.

Overall, when the evidence is viewed across all the presented outcomes, the studies do not indicate any major differences in effect of treatment with slow-release oral morphine or levomethadone as compared to methadone. However, the study limitations described above led us generally to assess the certainty effect estimates as low or very low. Low certainty in effect estimates does not mean that the interventions are ineffective or different, but that the available evidence is insufficient to reliably estimate the true comparative effect.

Strengths and weaknesses of this systematic review

We searched widely in international databases for primary studies. There is always a small chance that relevant studies are not included, particularly new studies that were not yet indexed when the search was conducted. The last search for relevant studies

was in June 2016. The strength of a systematic review is the extensive and systematic process of collecting, evaluating and analysing all research related to an issue. Two people did this independently of one another. We documented the process so that others can verify the assessments. We were open to include different controlled study designs, but we found only RCTs, including three trials with crossover design. RCT is a good design to assess the comparative effects of interventions.

Generalisability of findings

The included studies were from countries with comparable care for opioid dependent persons and health care systems as in Norway, i.e. Germany, Switzerland, Austria and Netherlands. The findings from this systematic review are therefore considered to be transferrable to a Norwegian context.

All three studies on levomethadone were done in countries where this medication was a standard OMT medication, while methadone was the experimental treatment, i.e. the opposite of the situation in Norway. We do not believe that this is a major limitation for the transferability of the results. The evidence gives some insight into the comparative effectiveness and safety of using levomethadone for MAT. However, the long-standing tradition using this medication in several European countries means that there is experience-based knowledge from the clinical field that may be relevant to the upcoming revision of the Norwegian guideline.

Consistency with other studies or reviews

We found no systematic reviews of the comparative effectiveness of levomethadone with any of the other medications used in Norway.

The systematic review from Ferri et al. (7), published in 2013, concluded that the evidence was insufficient to assess the effectiveness of slow release oral morphine for MAT. Since then, one relatively large multi-centre study had been published. The study by Beck et al. (15) is larger than all previous studies combined and has been performed with a good level of scientific rigour. Thus, this study dominates the combined evidence for slow release oral morphine in the current systematic review. Still, due to the limitations of the evidence as discussed above, the evidence is too uncertain and limited to conclude that slow release oral morphine is equivalent to the current treatment options.

Implication of results

In our systematic review, we do not make any recommendations about the future revised guideline. We have summarized the available scientific evidence related to the specified questions and judged our certainty in the effect estimates. When the Directorate of Health shall revise the OMT guideline they will integrate research-based knowledge about treatment effects with experience-based knowledge from the clinical

field and with patient needs and preferences. In addition, they need to consider the balance between benefits and harms, the Norwegian context and impact assessments, prioritization of resources, values, economic considerations, laws and regulations (3, 25).

Identified knowledge gaps

We need more evidence in order to sufficiently assess the effects of using slow-released oral morphine or levomethadone for opioid maintenance treatment for opioid dependence compared to treatment using buprenorphine with naloxone, buprenorphine or methadone.

If it is decided to run new trials, these should be designed to:

- examine equivalence or non-inferiority of the treatment options.
- have longer follow up period.

New trials should measure and report the following important outcome measures:

- Retention in treatment
- Patient satisfaction
- The use of opioids
- Use of other addictive drugs
- Adverse effects
- Crime

Conclusion

When treatment with either slow release oral morphine or levomethadone was compared to treatment with methadone, we did not find evidence that these have different effects. However, the evidence is too uncertain to conclude whether the treatments are equivalent.

References

1. Waal H, Bussesund K, Clausen T, Skeie I, Håseth A, Lillevold PH. Statusrapport 2015. Mot grensene for vekst og nytte? Oslo: Senter for rus- og avhengighetsforskning, Nasjonalt kompetansesenter for tverrfaglig spesialisert rusbehandling 2016.
2. Helsedirektoratet. Nasjonal retningslinje for legemiddelassistert rehabilitering ved opioidavhengighet. Oslo: Helsedirektoratet; 2010.
3. Veileder for utvikling av kunnskapsbaserte retningslinjer. Oslo: Helsedirektoratet; 2012.
4. Bond AJ, Reed KD, Beavan P, Strang J. After the randomised injectable opiate treatment trial: post-trial investigation of slow-release oral morphine as an alternative opiate maintenance medication. *Drug and alcohol review*. 2012;31(4):492-8.
5. Kastelic A, Dubajic G, Strbad E. Slow-release oral morphine for maintenance treatment of opioid addicts intolerant to methadone or with inadequate withdrawal suppression. *Addiction (Abingdon, England)*. 2008;103(11):1837-46.
6. Jegu J, Gallini A, Soler P, Montastruc JL, Lapeyre-Mestre M. Slow-release oral morphine for opioid maintenance treatment: a systematic review. *British journal of clinical pharmacology*. 2011;71(6):832-43.
7. Ferri M, Minozzi S, Bo A, Amato L. Slow-release oral morphine as maintenance therapy for opioid dependence. *Cochrane Database of Systematic Reviews*. 2013(6).
8. Gutwinski S, Schoofs N, Stuke H, Riemer TG, Wiers CE, Bermpohl F. Opioid tolerance in methadone maintenance treatment: comparison of methadone and levomethadone in long-term treatment. *Harm reduction journal*. 2016;13:7.
9. Gjersvik P, Hem E, Jacobsen GW, Bretthauer M. [What should non-inferiority studies be called in Norwegian?]. *Tidsskrift for den Norske lægeforening : tidsskrift for praktisk medicin, ny række*. 2014;134(8):852-3.
10. Walker E, Nowacki AS. Understanding Equivalence and Noninferiority Testing. *Journal of General Internal Medicine*. 2011;26(2):192-6.
11. Nasjonalt kunnskapscenter for helsetjenesten. Slik oppsummerer vi forskning. Håndbok for Nasjonalt kunnskapscenter for helsetjenesten. 3.2. reviderte utg. Oslo: Nasjonalt kunnskapscenter for helsetjenesten; 2013.
12. Higgins J, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration; 2011.
13. Effective Practice and Organisation of Care (EPOC). Suggested risk of bias criteria for EPOC reviews. EPOC Resources for review authors. Oslo: Norwegian Knowledge Centre for the Health Services; 2014 [Available from: <http://epocoslo.cochrane.org/epoc-specific-resources-review-authors>]
14. GRADE working group. GRADE guidelines - best practices using the GRADE framework [Available from: http://www.gradeworkinggroup.org/publications/ICE_series.htm].
15. Beck T, Haasen C, Verthein U, Walcher S, Schuler C, Backmund M, et al. Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone. *Addiction (Abingdon, England)*. 2014;109(4):617-26.

16. Hammig R, Kohler W, Bonorden-Kleij K, Weber B, Lebentrau K, Berthel T, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment of opioid dependence. *Journal of substance abuse treatment*. 2014;47(4):275-81.
17. Falcato L, Beck T, Reimer J, Verthein U. Self-reported cravings for heroin and cocaine during maintenance treatment with slow-release oral morphine compared with methadone: a randomized, crossover clinical trial. *Journal of clinical psychopharmacology*. 2015;35(2):150-7.
18. Verthein U, Beck T, Haasen C, Reimer J. Mental symptoms and drug use in maintenance treatment with slow-release oral morphine compared to methadone: results of a randomized crossover study. *European addiction research*. 2015;21(2):97-104.
19. Eder H, Jagsch R, Kraigher D, Primorac A, Ebner N, Fischer G. Comparative study of the effectiveness of slow-release morphine and methadone for opioid maintenance therapy. *Addiction (Abingdon, England)*. 2005;100(8):1101-9.
20. Giacomuzzi S, Kemmler G, Ertl M, Riemer Y. Opioid addicts at admission vs. slow-release oral morphine, methadone, and sublingual buprenorphine maintenance treatment participants. *Substance use & misuse*. 2006;41(2):223-44.
21. Scherbaum N, Finkbeiner T, Leifert K, Gastpar M. The efficacy of L-methadone and racemic methadone in substitution treatment for opiate addicts--a double-blind comparison. *Pharmacopsychiatry*. 1996;29(6):212-5.
22. Verthein U, Ullmann R, Lachmann A, Düring A, Koch B, Meyer-Thompson HG, et al. The effects of racemic D,L-methadone and L-methadone in substituted patients--a randomized controlled study. *Drug and alcohol dependence*. 2005;80(2):267-71.
23. Verthein U, Reimer J, Ullmann R, Haasen C. [Psychological state during substitution treatment with Levomethadone and d,1-Methadone - a double-blind, randomised, cross-over study]. *Sucht*. 2007;53(1):32-41.
24. De Vos JW, Geerlings P, Van Wilgenburg H, Leeuwing R. Methadone maintenance therapy; pharmacotherapeutic aspects. [Dutch]. *Tijdschrift voor Alcohol, Drugs en Andere Psychotrope Stoffen*. 1993;19(1):16-22.
25. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ*. 2016;353.

Appendices

Appendix 1: Search strategy

Search for systematic reviews, slow-release oral morphine

Database: PubMed, searched 22.06.16

#14,"Search systematic[sb] AND (#9) Filters: Publication date from 2013/01/01 to 2016/12/31",15,04:05:54

#13,"Search systematic[sb] AND (#9)",37,04:05:37

#9,"Search (((("Opioid-Related Disorders"[Mesh]) OR ((opiat*[tiab] or opioid*[tiab] or heroin*[tiab] or narcot*[tiab] or methadone[tiab] buprenorphine[tiab]))) AND ((withdraw*[tiab] or abstinen*[tiab] or abstain*[tiab] or abuse*[tiab] or abusing[tiab] or dependen*[tiab] or addict*[tiab] or overdos*[tiab] or "over-dose"[tiab] or intoxicat*[tiab]))) AND ("Morphine"[Mesh]) OR morphine[tiab])",3641,04:04:59

#8,"Search ("Morphine"[Mesh]) OR morphine[tiab]",50943,04:04:17

#7,"Search morphine[tiab]",44838,04:04:00

#6,"Search "Morphine"[Mesh]",35536,04:03:45

#5,"Search (((("Opioid-Related Disorders"[Mesh]) OR ((opiat*[tiab] or opioid*[tiab] or heroin*[tiab] or narcot*[tiab] or methadone[tiab] buprenorphine[tiab]))) AND ((withdraw*[tiab] or abstinen*[tiab] or abstain*[tiab] or abuse*[tiab] or abusing[tiab] or dependen*[tiab] or addict*[tiab] or overdos*[tiab] or "over-dose"[tiab] or intoxicat*[tiab])))",16115,04:03:18

#4,"Search 4. (withdraw*[tiab] or abstinen*[tiab] or abstain*[tiab] or abuse*[tiab] or abusing[tiab] or dependen*[tiab] or addict*[tiab] or overdos*[tiab] or "over-dose"[tiab] or intoxicat*[tiab])",529270,04:02:55

#3,"Search ("Opioid-Related Disorders"[Mesh]) OR ((opiat*[tiab] or opioid*[tiab] or heroin*[tiab] or narcot*[tiab] or methadone[tiab] buprenorphine[tiab]))",22551,04:02:38

#2,"Search (opiat*[tiab] or opioid*[tiab] or heroin*[tiab] or narcot*[tiab] or methadone[tiab] buprenorphine[tiab])",3489,04:02:24

#1,"Search "Opioid-Related Disorders"[Mesh]",20539,04:02:05

Database: Embase 1974 to 2016 June 21, searched 22.06.16

1 exp opiate addiction/ (12211)

2 (opioid* or heroin* or narcot* or methadone or buprenorphine).ti,ab. (124987)

3 1 or 2 (129288)

4 (withdraw* or abstinen* or abstain* or abuse* or abusing* or dependen* or addict* or overdos* or over-dose or intoxicat*).ti,ab. (1949783)

- 5 3 and 4 (46842)
- 6 morphine.ti,ab. (56288)
- 7 exp morphine/ (91371)
- 8 srom.ti,ab. (90)
- 9 or/6-8 (100472)
- 10 5 and 9 (11232)
- 11 limit 10 to ("reviews (maximizes sensitivity)" and yr="2013 -Current") (559)

Database: Epistemonikos, searched 22.06.16

srom (systematic reviews, 2013-2016) : 1

slow-release (systematic reviews, 2013-2016) : 2

Database: Cochrane Database of Systematic Reviews, searched 22.06.16

Manual search through all publications by Cochrane Drugs and Alcohol Group

Database: DARE, HTA (Cochrane Library), searched 22.06.16

- #1 MeSH descriptor: [Opioid-Related Disorders] explode all trees 1388
- #2 (opiat* or opioid* or heroin* or narcot* or methadone or buprenorphin) 19320
- #3 #1 or #2 19325
- #4 (withdraw* or abstinen* or abstain* or abuse* or abusing or dependen* or addict* or overdos* or "over-dose" or intoxicat*) 83761
- #5 #3 and #4 5814
- #6 srom:ti,ab 13
- #7 morphine:ti,ab,kw 8456
- #8 MeSH descriptor: [Morphine] explode all trees 3717
- #9 #6 or #7 or #8 8461
- #10 #5 and #9 Publication Year from 2013 to 2016, in Other Reviews and Technology Assessments 1

Search for systematic reviews, levomethadone

Database: PubMed, searched 22.06.16

#2,"Search systematic[sb] AND (#1) Filters: Publication date from 2011/01/01 to 2016/12/31",0

#1,"Search (levomethadone[Title/Abstract] OR levamethadone[Title/Abstract] OR levadone[Title/Abstract] OR levothyl[Title/Abstract] OR l-polamidon[Title/Abstract] OR l-polamivet[Title/Abstract] OR l-methadone[Title/Abstract] OR ""levo methadone""[Title/Abstract]) Search systematic[sb] AND (#1) Filters: Publication date from 2011/01/01 to 2016/12/31",15

Database: Embase 1974 to 2016 June 21, searched 22.06.16

- 1 levomethadone/ (366)
- 2 (levomethadone or levamethadone or levadone or levothyl or l-polamidon or l-polamivet or l-methadone or levo methadone).ti,ab. (232)
- 3 1 or 2 (501)
- 4 limit 3 to ("reviews (maximizes sensitivity)" and yr="2011 -Current") (27)

Database: Cochrane Library (CDSR, DARE, HTA), searched 22.06.16

#1 (levomethadone or levamethadone or levadone or levothyl or l-polamidon or l-polamivet or l-methadone or "levo methadone") Publication Year 2011- 2016, in Cochrane Reviews (Reviews and Protocols), Other Reviews and Technology Assessments 3

Database: Epistemonikos, searched 22.06.16

(title:(levomethadone OR levamethadone OR levadone OR levothyl OR l-polamidon OR l-polamivet OR l-methadone OR "levo methadone") AND abstract:(levomethadone OR levamethadone OR levadone OR levothyl OR l-polamidon OR l-polamivet OR l-methadone OR "levo methadone")) 0

Search for primary studies, slow-release oral morphine

Database: PubMed, searched 28.06.16

#20,"Search (((((((("Opioid-Related Disorders"[Mesh]) OR (((opiat*[tiab] or opioid*[tiab] or heroin*[tiab] or narcot*[tiab] or methadone[tiab] buprenorphine[tiab]))) AND (((withdraw*[tiab] or abstinen*[tiab] or abstain*[tiab] or abuse*[tiab] or abusing[tiab] or dependen*[tiab] or addict*[tiab] or overdos*[tiab] or "over-dose"[tiab] or intoxicat*[tiab]))) AND (("Morphine"[Mesh]) OR morphine[tiab]))) AND (((((((drug therapy [sh]) OR randomized controlled trial[pt]) OR controlled clinical trial[pt]) OR multicenter study[pt]) OR (randomis*[tiab] or randomiz*[tiab] or randomly[tiab] or groups[tiab]) OR (trial[ti] or multicenter[ti] or multi center[ti] or multicentre[ti] or multi centre[ti])) OR (intervention*[tiab] or controlled[tiab] or control group[tiab] or control groups[tiab] or compare[tiab] or compared[tiab] or quasiexperiment*[tiab] or quasi experiment*[tiab] or evaluat*[tiab] or effect*[tiab] or impact*[tiab])) Filters: Publication date from 2013/01/01 to 2017/12/31",273,08:21:27

#19,"Search (((((((("Opioid-Related Disorders"[Mesh]) OR (((opiat*[tiab] or opioid*[tiab] or heroin*[tiab] or narcot*[tiab] or methadone[tiab] buprenorphine[tiab]))) AND (((withdraw*[tiab] or abstinen*[tiab] or abstain*[tiab] or abuse*[tiab] or abusing[tiab] or dependen*[tiab] or addict*[tiab] or overdos*[tiab] or "over-dose"[tiab] or intoxicat*[tiab]))) AND (("Morphine"[Mesh]) OR morphine[tiab]))) AND (((((((drug therapy [sh]) OR randomized controlled trial[pt]) OR controlled clinical trial[pt]) OR multicenter study[pt]) OR (randomis*[tiab] or randomiz*[tiab] or randomly[tiab] or groups[tiab]) OR (trial[ti] or multicenter[ti] or multi center[ti] or multicentre[ti] or multi centre[ti])) OR (intervention*[tiab] or controlled[tiab] or control group[tiab] or control groups[tiab] or compare[tiab] or compared[tiab] or quasiexperiment*[tiab] or quasi experiment*[tiab] or evaluat*[tiab] or effect*[tiab] or impact*[tiab]))",2683,08:15:26

#18,"Search (((((((drug therapy [sh]) OR randomized controlled trial[pt]) OR controlled clinical trial[pt]) OR multicenter study[pt]) OR (randomis*[tiab] or randomiz*[tiab] or randomly[tiab] or groups[tiab]) OR (trial[ti] or multicenter[ti] or multi center[ti] or multicentre[ti] or multi centre[ti])) OR (intervention*[tiab] or controlled[tiab] or con-

trol group[tiab] or control groups[tiab] or compare[tiab] or compared[tiab] or quasiexperiment*[tiab] or quasi experiment*[tiab] or evaluat*[tiab] or effect*[tiab] or impact*[tiab])",10835339,08:15:01

#17,"Search intervention*[tiab] or controlled[tiab] or control group[tiab] or control groups[tiab] or compare[tiab] or compared[tiab] or quasiexperiment*[tiab] or quasi experiment*[tiab] or evaluat*[tiab] or effect*[tiab] or impact*[tiab]",9370773,08:13:31

#16,"Search trial[ti] or multicenter[ti] or multi center[ti] or multicentre[ti] or multi centre[ti]",180439,08:11:49

#15,"Search randomis*[tiab] or randomiz*[tiab] or randomly[tiab] or groups[tiab]",2028485,08:11:28

#14,"Search multicenter study[pt]",198776,08:11:15

#13,"Search controlled clinical trial[pt]",499567,08:11:06

#12,"Search randomized controlled trial[pt]",413932,08:10:55

#11,"Search drug therapy [sh]",1848215,08:10:29

#10,"Search (((("Opioid-Related Disorders"[Mesh]) OR ((opiat*[tiab] or opioid*[tiab] or heroin*[tiab] or narcot*[tiab] or methadone[tiab] buprenorphine[tiab]))) AND (((withdraw*[tiab] or abstinen*[tiab] or abstain*[tiab] or abuse*[tiab] or abusing[tiab] or dependen*[tiab] or addict*[tiab] or overdos*[tiab] or "over-dose"[tiab] or intoxicat*[tiab]))) AND ("Morphine"[Mesh]) OR morphine[tiab])",3642,08:09:59

#9,"Search ("Morphine"[Mesh]) OR morphine[tiab]",50956,08:08:33

#8,"Search morphine[tiab]",44850,08:08:22

#7,"Search "Morphine"[Mesh]",35541,08:08:09

#6,"Search (((("Opioid-Related Disorders"[Mesh]) OR ((opiat*[tiab] or opioid*[tiab] or heroin*[tiab] or narcot*[tiab] or methadone[tiab] buprenorphine[tiab]))) AND (((withdraw*[tiab] or abstinen*[tiab] or abstain*[tiab] or abuse*[tiab] or abusing[tiab] or dependen*[tiab] or addict*[tiab] or overdos*[tiab] or "over-dose"[tiab] or intoxicat*[tiab])))",16121,08:07:08

#5,"Search ((withdraw*[tiab] or abstinen*[tiab] or abstain*[tiab] or abuse*[tiab] or abusing[tiab] or dependen*[tiab] or addict*[tiab] or overdos*[tiab] or "over-dose"[tiab] or intoxicat*[tiab]))",1670707,08:06:35

#4,"Search ("Opioid-Related Disorders"[Mesh]) OR (((opiat*[tiab] or opioid*[tiab] or heroin*[tiab] or narcot*[tiab] or methadone[tiab] buprenorphine[tiab])))",22561,08:06:13

#3,"Search ((opiat*[tiab] or opioid*[tiab] or heroin*[tiab] or narcot*[tiab] or methadone[tiab] buprenorphine[tiab]))",3492,08:05:58

#2,"Search "Opioid-Related Disorders"[Mesh]",20547,08:05:43

Database: Embase 1974 to 2016 June 27, searched 28.06.16

1 exp opiate addiction/ (12226)

2 (opioid* or heroin* or narcot* or methadone or buprenorphine).ti,ab. (125086)

3 1 or 2 (129391)

4 (withdraw* or abstinen* or abstain* or abuse* or abusing* or dependen* or addict* or overdos* or over-dose or intoxicat*).ti,ab. (1951419)

5 3 and 4 (46876)

6 morphine.ti,ab. (56322)

- 7 exp morphine/ (91418)
- 8 srom.ti,ab. (92)
- 9 or/6-8 (100528)
- 10 5 and 9 (11239)
- 11 exp crossover procedure/ (47603)
- 12 exp double blind procedure/ (131904)
- 13 exp single blind procedure/ (22363)
- 14 exp clinical trial/ (1099592)
- 15 exp randomized controlled trial/ (410384)
- 16 (randomis* or randomiz* or randomly or trial or intervention? or effect? or impact? or multicenter or multi center or multicentre or multi centre or controlled or control group? or quasiexperiment* or quasi experiment* or double blind* or single blind* or assign* or allocat* or volunteer* or crossover or cross over).ti,ab. (7837964)
- 17 or/11-16 (8208459)
- 18 10 and 17 (7795)
- 19 limit 18 to yr="2013 -Current" (1337)

Database: Central, searched 28.06.16

- #1 MeSH descriptor: [Opioid-Related Disorders] explode all trees 1388
- #2 (opiat* or opioid* or heroin* or narcot* or methadone or buprenorphin) 19320
- #3 #1 or #2 19325
- #4 (withdraw* or abstinen* or abstain* or abuse* or abusing or dependen* or addict* or overdos* or "over-dose" or intoxicat*) 83761
- #5 #3 and #4 5814
- #6 srom:ti,ab 13
- #7 morphine:ti,ab,kw 8456
- #8 MeSH descriptor: [Morphine] explode all trees 3717
- #9 #6 or #7 or #8 8461
- #10 #5 and #9 Publication Year from 2013 to 2016, in Trials112

Database: ClinicalTrials.gov (www.clinicaltrials.gov), searched 28.06.16

Slow-release morphine: 13

Database: World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)(apps.who.int/trialsearch/), searched 28.06.16

Slow-release morphine: 8

Database: Current Controlled Trials (www.controlled-trials.com/), searched 28.06.16

Slow-release morphine: 8

Database: EU Clinical Trials Register (www.clinicaltrialsregister.eu), searched 28.06.16

Slow-release morphine: 4

Database: Trials (www.trialsjournal.com), searched 28.06.16

Slow-release morphine: 176

Search for primary studies, levomethadone

Database: PubMed, searched 30.06.16

"Search ((levomethadone[Title/Abstract] OR levamethadone[Title/Abstract] OR levadone[Title/Abstract] OR levorphanol[Title/Abstract] OR l-polamidon[Title/Abstract] OR l-polamivet[Title/Abstract] OR l-methadone[Title/Abstract] OR ""levo methadone""[Title/Abstract])) AND ((((((drug therapy [sh]) OR randomized controlled trial[pt]) OR controlled clinical trial[pt]) OR multicenter study[pt]) OR (randomis*[tiab] or randomiz*[tiab] or randomly[tiab] or groups[tiab])) OR (trial[ti] or multicenter[ti] or multicentre[ti] or multi centre[ti])) OR (intervention*[tiab] or controlled[tiab] or control group[tiab] or control groups[tiab] or compare[tiab] or compared[tiab] or quasiexperiment*[tiab] or quasi experiment*[tiab] or evaluat*[tiab] or effect*[tiab] or impact*[tiab])) Filters: Publication date from 1990/01/01 to 2017/12/31",91,02:53:03

Database: Embase 1974 to 2016 June 29, searched 30.06.16

- 1 levomethadone/ (366)
- 2 (levomethadone or levamethadone or levadone or levorphanol or l-polamidon or l-polamivet or l-methadone or levo methadone).ti,ab. (232)
- 3 1 or 2 (501)
- 4 exp crossover procedure/ (47729)
- 5 exp double blind procedure/ (131975)
- 6 exp single blind procedure/ (22380)
- 7 exp clinical trial/ (1100072)
- 8 exp randomized controlled trial/ (410685)
- 9 (randomis* or randomiz* or randomly or trial or intervention? or effect? or impact? or multicenter or multi centre or multicentre or multi centre or controlled or control group? or quasiexperiment* or quasi experiment* or double blind* or single blind* or assign* or allocat* or volunteer* or crossover or cross over).ti,ab. (7844788)
- 10 or/4-9 (8215393)
- 11 3 and 10 (238)
- 12 limit 11 to yr="1990 -Current" (181)

Database: Central, searched 30.06.16

#1 (levomethadone or levamethadone or levadone or levorphanol or l-polamidon or l-polamivet or l-methadone or "levo methadone") Publication Year 1990 - 2016, in Trials 19

Database: ClinicalTrials.gov (www.clinicaltrials.gov), searched 30.06.16

Levomethadone: 3

Levamethadone: 0

Levo methadone: 4

Leva methadone: 0

Database: World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/), searched 30.06.16

Levomethadone: 2

Levamehadone: 0
Levo methadone: 0
Leva methadone: 0

Database: Current Controlled Trials (www.controlled-trials.com/), searched 30.06.16

Levomethadone : 0
Levamehadone : 0
Levo methadone : 1
Leva methadone : 0

Database: EU Clinical Trials Register (www.clinicaltrialsregister.eu), searched 30.06.16

Levomethadone : 2
Levamehadone : 0
Levo methadone : 0
Leva methadone : 0

Database: Trials (www.trialsjournal.com), searched 30.06.16

Levomethadone : 16
Levamehadone : 0
Levo methadone : 6
Leva methadone : 0

Appendix 2: Characteristics of included studies and risk of bias

Slow-release oral morphine: Beck 2013 (15-18)

Study design	<p>Randomised controlled trial. 2x2 crossover (2x11 weeks). The study was extended 25 weeks where all patients received slow-release oral morphine. We do not report these results as this phase has no control condition (observational data).</p> <p><i>Study objective:</i> “to validate the effectiveness of SROM in opioid-dependent patients treated previously with methadone in a randomized crossover design, aiming to show non-inferiority of SROM over methadone with flexible dosing”.</p>
Country	<p>Multi-centre trial in Germany (10 treatment centres) and Switzerland (4 treatment centres).</p>
Participants	<p><i>Inclusion criteria:</i> A diagnosis of opioid-dependence according to DSM-ICV criteria, aged ≥ 18 years with permanent residence, and in a methadone treatment programme ≥ 26 weeks on a methadone dose ≥ 50 mg/day at inclusion. Capability to act responsibly and no intention of dose reductions during trial. Women required having a negative pregnancy test, new tests every 4 weeks, and using hormonal contraception during trial (if relevant).</p> <p><i>Exclusion criteria:</i> Persons with acute somatic illnesses or other clinically significant mental health problems, known contraindications for opioids, pending imprisonment at time of inclusion, baseline QTc-interval >450 msec or long QT-syndrome (heart rhythm disturbances), and pregnant /breastfeeding. Treatment-naïve patients or patients unsatisfied with pre-treatment.</p> <p><i>Included sample:</i> 276 patients were enrolled, 141 randomised to treatment sequence morphine/methadone and 135 to treatment sequence methadone/morphine. 81.5% men, mean age 38.1 years, mean 3.85 years in maintenance treatment, mean pre-trial last dose of methadone 98.0 mg/day, mean age at first heroin consumption 20.3 years. Of the 276 participants, 157 complied sufficiently with the study to be considered as the per protocol (PP) population. The PP population included patients who completed both crossover treatment periods (11 weeks) within a specified time-frame of ≥ 70 days and ≤ 84 days, who had urinalyses for ≥ 9 of 11 weeks per cross-over period and no discontinuation of study medication for more than 5 consecutive days. All patients were included in Intention-to-treat (ITT) analyses. There were no significant differences in baseline characteristics between PP and ITS populations, nor the two study arms.</p>
Intervention and comparison (crossover)	<p>Patients were randomised to receive slow-release morphine for 11 weeks, follow by methadone for 11 weeks, or vice versa. No washout phase between drugs. Each period started as a 1-week adjustment phase, followed by 10 weeks treatment phase. Flexible dosing was permitted depending on a patient’s individual needs. Observed oral intake in clinic for at least 3 days per week. Patients and providers were not blinded to type of drug.</p> <p>Methadone was switched to SROM in a ratio of 1:6–1:8 of the previous methadone dose. SROM given as capsules (Bard Pharmaceuticals, Cambridge, UK or Mundipharma Gesellschaft m.b.H., Vienna, Austria).</p> <p>SROM was switched to methadone in a ratio of 8:1–6:1 of the previous SROM dose. In Switzerland, methadone solution given as 1% solution (Amino AG, Neuenhof, Switzerland) and in Germany as 0.5% solution (Eptadone oral solution; Molteni Farmaceutici, Scandicci, Italy).</p>
Outcomes	<p><i>Retention in treatment:</i> Registered participant flow (15)</p>

	<p><i>Patient satisfaction:</i> Assessed by visual analogue scale scoring from 0 (not satisfied at all) to 10 (deeply contented) (18)</p> <p><i>Use of opioids:</i> Urine samples (weekly), self-reports (number of days used per crossover period) (15)</p> <p><i>Use of illicit drugs:</i> Urine samples (weekly), self-reports (number of days used per crossover period) (15)</p> <p><i>Adverse effects:</i> Recording of all adverse events as well as by periodic evaluation of vital signs and physical examinations. (15)</p> <p><i>Crime:</i> Not reported.</p> <p>This study also present results for numerous outcomes in four publications (15-18).</p>	
Follow up	Repeat measurements throughout the trial. Last follow up end of trial (week 22). <i>After 22 weeks crossover trial, all patients in this study were offered slow-release oral morphine for 26 weeks. We do not present these data as this phase has no control condition (observational data).</i>	
Funding	Mundipharma Medical Company, Basel, and Mundipharma Gesellschaft m.b.H.	
Trial registration	EudraCT no.: 2008-002185-60. Svissmedic no.: 2007DR3124. NOH Study code: nct01079117.	
Risk of bias	Judgement	Support for judgement
Random sequence generation	Low risk (phase 1) Unclear risk (phase 2)	Computer-generated randomisation list with a 1: ratio and permuted blocks of six without stratification factors. In the second phase of the study (crossover), the treatment allocation is not random nor concealed. We consider that the magnitude and direction of bias on results are unclear.
Allocation concealment	Low risk (phase 1) Unclear risk (phase 2)	Concealment procedures described. Otherwise as above for second phase of study.
Blinding of participants and personnel	Unclear risk	Non-blinded study. Justification given by authors: "Intrinsic pharmacological differences of morphine and methadone mean that patients are experienced in perceiving specific drug effects, either from prior illicit consumption or from previous maintenance treatment [...]". We consider that the magnitude and direction of bias of non-binding on results are unclear overall, but high risk for self-reported outcomes.
Blinding of outcome assessment	Low risk Unclear risk	We consider low risk of bias for urine analyses and registered adverse events. Unclear magnitude and direction of bias for self-reports.
Incomplete outcome data	Low risk	Both ITT and PP population analyses of results presented and discussed for some findings. Unclear risk for some outcomes.
Selective reporting	Low risk	
Other bias	Unclear risk	Risk of bias domains specific to crossover trials considered. Some of the statistical analyses were not sufficiently corrected for the effect of paired data for participants in both phases of the crossover.
Overall risk of bias	Unclear risk	

Slow-release oral morphine: Eder 2005 (19)

Study design	Randomised controlled trial, 2x2 crossover. <i>Study objective:</i> "to test the hypothesis that slow-release oral morphine is at least as effective as methadone in preventing withdrawal, reducing craving and use of heroin with a similar duration in action."
Country	Austria.
Participants	<i>Inclusion criteria:</i> Patients defined as opioid dependent according to DSM-IV criteria and aged 19-60 years. <i>Exclusion criteria:</i> Persons already receiving maintenance therapy; Serious psychiatric or somatic illnesses (excluding hepatitis); Co-dependence on alcohol or cocaine. Misuse of benzodiazepines was not an exclusion criterion, but patients were gradually withdrawn the first two weeks using meprobamate. Women were screened for pregnancies, provided contraception and monthly pregnancy tests throughout the study. <i>Included sample:</i> 64 patients recruited; 8 women and 56 men. Mean age 29.5 and 27.9 years in two groups respectively. Mean age when heroin injection started 21.8 years and 21.4 years in two groups respectively.
Intervention and comparison (crossover)	Patients were randomised to receive slow-release morphine for 7 weeks, followed by methadone for 7 weeks, or vice versa. No washout phase between drugs. Daily observed oral intake in clinic. When starting with slow-release morphine (Substitol® retard capsules, Mundipharma GesmbH, Vienna, Austria, 120 mg or 200 mg dosages), all patients received 200 mg the first day and 320 mg the second day. Subsequent days the dose titration was standardised according to withdrawal scores with possible increments to 440 mg, 600 mg or 800 mg. After the titration phase (first week), patients remained fixed on this dose for 6 weeks. When starting with oral morphine (EBEWE Arzneimittel GESMBH and Gatt/Koller GesmbH and CoKG, Unterach, Austria, prepared as oral solution), all patients started with dose of 40 mg the first day and 55 mg the second day. Subsequent days the dose titration was standardised according to withdrawal scores with possible increments to 70 mg, 85 mg or 100 mg. After the titration phase (first week), patients remained fixed on this dose for 6 weeks. Mean dose of OMT drug used during the study: 85 mg methadone and 680 mg slow-release oral morphine.
Outcomes	<i>Retention in treatment:</i> Registered participant flow. <i>Patient satisfaction:</i> Not reported. <i>Use of opioids:</i> Not reported. <i>Use of illicit drugs:</i> Urine samples (twice weekly). <i>Adverse effects:</i> Recording of all adverse events as registered through vital signs, haematology, biochemistry, physical examination, electrocardiogram and self-reported complaints. <i>Crime:</i> Not reported. This study also present results for craving (heroin, cocaine and alcohol), withdrawal symptoms, registration of new injection sites, depression and anxiety scores and questionnaires for physical and psychological health.
Follow up	Repeat measurements throughout the trial. Last follow up towards end of trial (week 12).

Funding	Internal funds at Universitätsklinik Innsbruck-Ambulanz für Abhängigkeits-erkrankungen, Austria.	
Trial registration	Not stated.	
Risk of bias	Judgement	Support for judgement
Random sequence generation	Low risk (phase 1) Unclear risk (phase 2)	Computer randomised. In the second phase of the study (crossover), the treatment allocation is not random nor concealed. We consider that the magnitude and direction of bias on results are unclear.
Allocation concealment	Low risk (phase 1) Unclear risk (phase 2)	Concealment procedures described. Otherwise as above.
Blinding of participants and personnel	Unclear risk	The authors describe that drugs were administered blind and taste modification of drugs used to match the alternative treatment. Unclear how capsules versus oral solution were concealed. Also likely that patients have experienced specific drug effects. We consider risk of bias to be unclear overall, but high risk for self-reported outcomes.
Blinding of outcome assessment	Low risk Unclear risk	We consider low risk of bias for urine analyses and registered adverse events. Unclear magnitude and direction of bias for self-reports.
Incomplete outcome data	Low risk	86 % completed the study, analysed as balanced in both study arms.
Free off selective reporting	Low risk	
Free of other bias	Unclear risk	Risk of bias domains specific to crossover trials considered. Statistical analyses were not sufficiently corrected for the effect of paired data for participants in both phases of the crossover.
Overall risk of bias	Unclear risk	

Slow-release oral morphine: Giacomuzzi 2009 (20)

Study design	Randomised controlled trial with three treatment arms. Comparison with measurements from 120 patients at admission is not presented in this systematic review. <i>Study objective:</i> "to compare quality of life ratings, physical symptoms, and urine analyses of opioid addicts at admission with slow-release oral morphine, methadone, and buprenorphine maintenance program participants."
Country	Austria.
Participants	<i>Inclusion criteria:</i> Patients diagnosed as opioid dependent according to DSM-IV criteria at admission or were in a methadone, sublingual buprenorphine or, slow-release oral morphine maintenance program for 6 months, aged ≥ 17 years, lived within commuting distance of hospital, and mentally competent to give informed content. <i>Exclusion criteria:</i> Acute medical condition last 6 months, currently using antipsychotic medication, or in another trial. Forced discharge criteria were drug trafficking in clinical centre or aggressive behaviour.

	<i>Included sample:</i> 120 patients recruited, 57% men. Mean age from 26.3 to 27.8 years in the three treatment groups and length of addiction from 8.2 to 9.0 years (not significantly different between groups). Most participants had a history of morphine dependency rather than heroin.	
Intervention	Open-label, flexible dosing regimen of slow-release oral morphine. 60-180 mg low-release oral morphine given during 5-6 days induction. Increasing doses depending on the severity of withdrawal symptoms and patient's opinion. Stable dose thereafter for 6 months. Observed intake in clinic and take-home doses at weekends.	
Comparison	<p><i>Alternative treatment 1:</i> Open-label, flexible dosing regimen of methadone. 10-30 mg methadone given during induction. Induction dose adjustments and trial procedures otherwise as for slow-release morphine.</p> <p><i>Alternative treatment 2:</i> Open-label, flexible dosing regimen of sublingual buprenorphine. 2-8 mg sublingual buprenorphine given during induction. Induction dose adjustments and trial procedures otherwise as for slow-release morphine.</p>	
Outcomes	<p><i>Retention in treatment:</i> Not reported.</p> <p><i>Patient satisfaction:</i> Not reported.</p> <p><i>Use of opioids:</i> Not reported.</p> <p><i>Patient satisfaction:</i> Quality of life measured with "Berlin Quality of Life Questionnaire".</p> <p>Use of illicit drugs: Urine samples (three times over 8 weeks, random time intervals)</p> <p><i>Adverse effects:</i> Recording of all adverse events (unspecified procedure)</p> <p><i>Crime:</i> Not reported.</p> <p>This study also present results depression and anxiety, and satisfaction scores for different domains.</p>	
Follow up	Repeat measurements throughout the trial. Last follow up towards end of trial (6 months).	
Funding	Mundipharma GesmbH, Vienna.	
Trial registration	Not stated.	
Risk of bias	Judgement	Support for judgement
Random sequence generation	Unclear risk	Only described as randomized.
Allocation concealment	Unclear risk	Allocation concealment not described.
Blinding of participants and personnel	Unclear risk	Open label study. We consider that the magnitude and direction of bias of non-blinding on results are unclear overall, but high risk for self-reported outcomes.
Blinding of outcome assessment	Low risk Unclear risk	We consider low risk of bias for urine analyses. Unclear magnitude and direction of bias for self-reports.
Incomplete outcome data	Unclear risk	No information on drop-outs or patient flow given or discussed. No drop-outs is considered unlikely.
Free off selective reporting	Low risk	
Free of other bias	Low risk	
Overall risk of bias	Unclear risk	

Levomethadone: Scherbaum 1998 (21)		
Study design	Randomised controlled trial. <i>Study objective:</i> "to compare the clinical effects of the two drugs [racemic methadone and levomethadone] in a double-blind design".	
Country	Germany.	
Participants	<i>Inclusion criteria:</i> Opiate addicts in levomethadone treatment. <i>Exclusion criteria:</i> Unstable methadone dose (daily dose fluctuation > 5 mg last 4 weeks), current serious psychological problems. <i>Included sample:</i> 19 men and 7 women. Mean age 32.9 years. Mean duration of treatment 1.9 year. Mean dose levomethadone at baseline 55.6 mg/day.	
Intervention	Baseline week: Fixed individual levomethadone as pre-trial dose. Trial, 2 weeks: Continued fixed individual dose of levomethadone (L-Polamdion, Hoechst). After trial: Double dose (relative to pre-trial levomethadone) methadone.	
Comparison	Baseline week: Fixed individual levomethadone as pre-trial dose. Trial, 2 weeks 2-3: Double dose (relative to pre-trial levomethadone) of racemic methadone (Methandonhydrochloric, Synopharm). After trial: Continued treatment with methadone.	
Outcomes	<i>Retention in treatment:</i> Not reported. <i>Patient satisfaction:</i> Self-rated patient satisfaction with clinical effects of drug. <i>Use of opioids:</i> Urine samples (weekly). <i>Use of illicit drugs:</i> Urine samples (weekly). <i>Adverse effects:</i> Recording of all adverse events through several questionnaires on withdrawal symptoms, somatic and psychic state, detoxification symptoms, self-related somatic and psychological complaints. <i>Crime:</i> Not reported.	
Follow up	Repeat measurements throughout the trial. Last follow up end of trial (week 3). After third week of trial, all patients in this study were offered methadone. We do not present these data as this phase has no control condition (observational data).	
Risk of bias	Judgement	Support for judgement
Random sequence generation	Unclear risk	Only described as randomized.
Allocation concealment	Unclear risk	Allocation concealment not described.
Blinding of participants and personnel	Low risk	Double blind drugs administration.
Blinding of outcome assessment	Low risk Unclear risk	We consider low risk of bias for urine analyses and registered adverse events. Unclear magnitude and direction of bias for self-reports.
Incomplete outcome data	Unclear risk	No description of patient flow or compliance.
Free off selective reporting	Low risk	
Free of other bias	Low risk	
Overall risk of bias	Unclear risk	

Levomethadone: Verthein 2005 (22, 23)

Study design	Randomised controlled trial, 2x2 crossover. <i>Study objective:</i> "it was hypothesized that switching from l-methadone to racemic d,l-methadone is associated with more withdrawal symptoms and opioid side-effects when compared to switching from d,l-methadone to l-methadone."	
Country	Germany.	
Participants	<p><i>Inclusion criteria:</i> Opioid dependent with minimum one year of stable substitution with either racemic methadone or levomethadone, contact with clinic physician at least once per week, ≥ 18 years of age. Patients on racemic methadone or levomethadone were recruited and randomised separately.</p> <p><i>Exclusion criteria:</i> Change of methadone maintenance treatment (substance or clinic) preceding year, antiretroviral or interferon treatment, pregnancy, illicit opioid use or alcohol abuse last 4 weeks.</p> <p><i>Included sample:</i> 75 patients recruited; 87% men. 68 completed trial. Baseline characteristics presented separately for completers and dropouts. Among completers: 90% men. 22% on levomethadone at baseline, otherwise racemic methadone. Mean age 38.7 years. Mean 3.5 years in treatment. Mean dose analogue to racemic methadone 105.6 mg/day. Dropouts were younger, had been longer in methadone maintenance treatment and higher frequency in concomitant psychosocial care.</p>	
Intervention and comparison (crossover)	Patients on racemic methadone or levomethadone at baseline were recruited and randomised separately. Patients were randomised to receive either racemic methadone or levomethadone (product names not specified) for 4 weeks, i.e. 50% in each group of previous racemic methadone or levomethadone user would switch drug. After the fourth week, participants switched to the opposite drug for another 4 weeks of trial.	
Outcomes	<p><i>Retention in treatment:</i> Not reported.</p> <p><i>Patient satisfaction:</i> Self-rated patient satisfaction with clinical effects of drug (22).</p> <p><i>Use of opioids:</i> Urine samples (unspecified) (22).</p> <p><i>Use of illicit drugs:</i> Urine samples (unspecified) (22).</p> <p><i>Adverse effects:</i> Recording of all adverse events through several questionnaires on self-reported withdrawal symptoms, registration of tiredness, sweating, uneasiness, disturbance of virility/sexual arousal, constipation and difficulty with urination (22).</p> <p><i>Crime:</i> Not reported.</p> <p>This study also present results depression and anxiety (23).</p>	
Follow up	Outcomes measured three times per week for all 8 weeks of trial.	
Risk of bias	Judgement	Support for judgement
Random sequence generation	Unclear risk	Only described as randomized. In the second phase of the study (crossover), the treatment allocation is not random nor concealed. We consider that the magnitude and direction of bias on results are unclear.
Allocation concealment	Unclear risk	Allocation concealment not described. Otherwise as above for second phase of study.
Blinding of participants and personnel	Low risk	Double blind drugs administration. Study medication also blinded by blending with a flavour neutralizing substance and volume adjustment.
Blinding of outcome assessment	Low risk Unclear risk	We consider low risk of bias for urine analyses. Unclear magnitude and direction of bias for self-reports.

Incomplete outcome data	Low risk	
Free off selective reporting	Low risk	
Free of other bias	Low risk	Risk of bias domains specific to crossover trials considered. Some of the statistical analyses were not sufficiently corrected for the effect of paired data for participants in both phases of the crossover.
Overall risk of bias	Unclear risk	

Levomethadone: de Vos 1998 (24)

Study design	Randomised controlled trial. <i>Study objective:</i> "(a) to compare the frequency of requested dose adjustments and the magnitude of the dose difference of l-methadone and d,l-methadone; (b) to determine illicit use of opiates, cocaine and benzodiazepines; (c) to assess the level of opiate craving; (d) to measure plasma concentrations of methadone enantiomers and their main metabolite EDDP (1,5-dimethyl-3,3-diphenyl-2-ethylene-pyrrolidine), during l-methadone treatment and after the replacement of l-methadone by d,l-methadone."	
Country	The Netherlands.	
Participants	<p><i>Inclusion criteria:</i> Males or females older than 18 years who had been receiving methadone maintenance treatment for at least 1 month, currently as outpatients.</p> <p><i>Exclusion criteria:</i> Confirmed AIDS disease (HIV-positive subjects were included) and pregnancy. Subjects were dropped from the study in the event of: serious adverse reactions, non-compliance, personal or medical reasons and withdrawal of consent.</p> <p><i>Included sample:</i> 40 participants were recruited. 2 were dropouts and 8 did not fulfil protocol conditions (missing blood or urine samples) and were excluded (not specified from which group or reasons). The remaining sample were 18 men and 12 women, mean age 30 years (range 20-44).</p>	
Intervention	Previous daily levomethadone dose (L-Polamidon®, Hoechst, Germany) maintained for all 22 days of trial. Optional individual dose adjustments as needed.	
Comparison	Previous daily levomethadone dose maintained for 8 days, and changed then to racemic methadone (Symoron®, Yamanouchy Pharma, The Netherlands) at double the dose of levomethadone. Optional individual dose adjustments as needed.	
Outcomes	<p><i>Retention in treatment:</i> Not reported.</p> <p><i>Patient satisfaction:</i> Not reported.</p> <p><i>Use of opioids:</i> Urine samples (weekly).</p> <p><i>Use of illicit drugs:</i> Urine samples (weekly).</p> <p><i>Adverse effects:</i> Subjectively experience of opiate craving based on six questions.</p> <p><i>Crime:</i> Not reported.</p>	
Follow up	Urine samples collected once per week (random day of week), three times. Adverse effects measured at day 8, 15 and 22.	
Risk of bias	Judgement	Support for judgement
Random sequence generation	Unclear risk	Only described as randomized.
Allocation concealment	Unclear risk	Allocation concealment not described.

Blinding of participants and personnel	Low risk	Double blind drugs administration.
Blinding of outcome assessment	Low risk	We consider low risk of bias for urine analyses. Unclear magnitude and direction of bias for self-reports.
Incomplete outcome data	Unclear risk	25 % drop-outs. Not specified from which treatment group or reasons.
Free off selective reporting	Low risk	
Free of other bias	Low risk	
Overall risk of bias	Unclear risk	

Appendix 3: Excluded studies

References assessed in full-text	Reason for exclusion
Cimander, K.F. and T. Poehlke, Replacement of racemic methadone by levomethadone in patients with inadequate substitution efficiency. [German]. Suchtmedizin in Forschung und Praxis, 2010. 12(4): p. 187-196.	Non-randomised controlled study with only post-measurements.
Clark, N., et al., A randomised trial of once-daily low-release morphine versus methadone for heroin dependence. Drug and Alcohol Dependence, 2002. 66(Suppl 1): p. S33.	Study included in the systematic review of Ferri 2013, but only presented in a conference abstract. Excluded in this systematic review. Crossover study (slow-release oral morphine and methadone) with 11 participants.
Falcato, L.M., et al., Self-reported cravings for heroin and cocaine during maintenance treatment with slow-release oral morphine compared to methadone: A randomized crossover clinical trial. Sucht, 2014. 60: p. 113.	Conference abstract. Results presented in Falcato 2015 (study included).
Soyka, M. and C. Zingg, Feasibility and safety of transfer from racemic methadone to (R)-methadone in primary care: Clinical results from an open study. World Journal of Biological Psychiatry, 2009. 10(3): p. 217-224.	Prospective study without control group.

Appendix 4: GRADE assessment profiles

GRADE assessment profile for treatment with slow-release oral morphine compared to methadone or buprenorphine for people in OMT treatment.

Quality assessment							No of patients		Effect		Quality
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Slow-release oral morphine	methadone	Relative (95% CI)	Absolute (95% CI)	
Retention in treatment - First period of crossover trial											
2	randomised trials	not serious	not serious	not serious	serious ¹	none	152/173 (87.9%)	152/167 (91.0%)	RR 0.97 (0.90 to 1.04)	27 fewer per 1 000 (from 36 more to 91 fewer)	⊕⊕⊕○ MODERATE
Retention in treatment - Second period of crossover trial											
2	randomised trials ²	not serious	not serious	not serious	serious ¹	none	130/152 (85.5%)	136/152 (89.5%)	RR 0.99 (0.89 to 1.10)	9 fewer per 1 000 (from 89 more to 98 fewer)	⊕⊕○○ LOW
Patient satisfaction – Treatment satisfaction score											
1	randomised trials	serious ^{3,4}	not serious	not serious	serious ^{1,5}	none	See narrative summary in table 3			⊕○○○ VERY LOW	
Patient satisfaction – Quality of life score											
1	randomised trials	serious ^{3,4}	not serious	not serious	serious ^{1,5,6}	none	See narrative summary in table 3			⊕○○○ VERY LOW	
Use of illicit opioids – Urine samples											
1	randomised trials	serious ³	not serious	not serious	serious ^{1,5}	none	See narrative summary in table 3			⊕⊕○○ LOW	
Use of illicit opioids – Self-reported use											
1	randomised trials	very serious ^{3,4}	not serious	not serious	serious ^{1,5}	none	See narrative summary in table 3			⊕○○○ VERY LOW	

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Slow-release oral morphine	methadone	Relative (95% CI)	Absolute (95% CI)	
Adverse effects – all adverse effects/events											
3	randomised trials	serious ³	not serious	not serious	serious ^{1,5,6}	none	See narrative summary in table 3				⊕⊕○○ LOW
Adverse effects – Serious adverse events											
2	randomised trials	very serious ^{3,4}	not serious	not serious	serious ^{1,5,6}	none	See narrative summary in table 3				⊕⊕○○ LOW
Mortality											
1	randomised trials	serious ¹	not serious	not serious	very serious ⁶	none	See narrative summary in table 3				⊕○○○ VERY LOW
Crime											
0	-	-	-	-	-	-	-	-	-	-	

CI: Confidence interval; **RR:** Risk ratio

1. One to three studies with relatively few participants.
2. Allocation to treatment is not random in second part of crossover trial, i.e. bears resemblance to a non-randomised controlled trial. Downgraded one point.
3. Unclear risk of bias.
4. Self-reported outcome in non-blinded study.
5. Not sufficiently adjusted for paired data, arising when participants undergo both treatments in a sequence.
6. Insufficient data to analyse effect.

GRADE assessment profile for treatment with levomethadone compared to methadone for people in OMT treatment.

Quality assessment							No of patients		Effect		Quality
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Slow-release oral morphine	methadone	Relative (95% CI)	Absolute (95% CI)	
Retention in treatment - First period of crossover trial											
0	-	-	-	-	-	-	-	-	-	-	-
Patient satisfaction – Different treatment satisfaction measures											
2	randomised trials	serious ¹	not serious	not serious	very serious ^{2,3}	none	See narrative summary in table 5				⊕○○○ VERY LOW
Use of illicit opioids – Urine samples											
3	randomised trials	serious ¹	not serious	not serious	very serious ^{2,3}	none	See narrative summary in table 5				⊕○○○ VERY LOW
Use of illicit drugs – Urine samples											
3	randomised trials	serious ¹	not serious	not serious	very serious ^{2,3}	none	See narrative summary in table 5				⊕○○○ VERY LOW
Adverse effects – all adverse effects/events											
3	randomised trials	serious ¹	not serious	not serious	very serious ^{2,3}	none	See narrative summary in table 5				⊕○○○ VERY LOW
Crime											
0	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio

1. Unclear risk of bias.
2. Small studies and few events. Short trial duration.
3. No or insufficient data to estimate effect.

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