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The effects of concurrent prescription of benzodiazepines for people undergoing opioid maintenance treatment

Systematic review

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Key messages

Opioid maintenance treatment uses long-acting opiates to reduce an opioid dependent person’s urge to take illicit opioid substances. Opioid-dependent persons are likely to experience elevated levels of anxiety and sleep disturbance. Therefore, patients undergoing opioid maintenance treatment often use medications containing benzodiazepines, both prescribed by a doctor and from the illegal market, to alleviate these problems. Concurrent use of benzodiazepines during opioid maintenance treatment raise a concern.

This systematic review aimed to summarize the effects of concurrent prescription of benzodiazepines among people who receive opioid maintenance treatment.

After a systematic literature search we did not find any studies that could answer this question.

Experimental studies with controlled use of benzodiazepines are needed to elucidate the effects and consequences of taking benzodiazepines during opioid maintenance treatment.

Title:
The effects of concurrent prescription of benzodiazepines for people undergoing opioid maintenance treatment: A systematic review

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:
- Excluded studies are not evaluated
- No recommendation
- No cost-effectiveness evaluation

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Executive summary

Background

In Opioid Maintenance Treatment patients receive long-acting opioids as a substitute for heroin and other common illegally used opioids. People with opioid dependence are likely to experience elevated levels of anxiety and sleep disturbance. Therefore, benzodiazepines are often prescribed for these patients to alleviate such problems. Meanwhile, benzodiazepines are readily available on the illicit street market and are in high risk to be misused. Several studies find that concurrent prescription of benzodiazepines during opioid maintenance treatment is associated with more drug abuse and dependence. Prolonged use of benzodiazepines may result in anxiety and mental health problems, and increased risk of personal injury. However, the evidence is mostly descriptive and does not distinguish between prescribed versus illicitly procured benzodiazepines.

Objective

The purpose of this systematic review is to assess the effects of concurrent benzodiazepines prescription among people who receive opioid maintenance treatment (i.e. methadone, buprenorphine or buprenorphine combined with naloxone).

Method

We first searched for systematic reviews that could answer our research question in the following databases: Epistemonikos, Cochrane Library (CDSR, DARE, HTA), MEDLINE (Ovid), PubMed [sb] and Embase (Ovid). Thereafter, we searched for primary studies to conduct a systematic review to summarize the available evidence.

Randomized and non-randomized controlled trials, controlled before-and-after studies and interrupted time series were included as relevant study designs. The target population was people 18 years or older who received substitution treatment with methadone, buprenorphine or buprenorphine combined with naloxone for opioid dependence. Relevant intervention was prescription of benzodiazepines as compared with no prescription of benzodiazepines. The outcomes of interest were retention in treatment, patients' satisfaction, opioid use (self-report or biological test), other substance use (self-report or biological test), extent of anxiety and depression, sleep disorders, mortality, side effects (overdose, injury and use of hospital emergency) and criminal offenses.

We carried out a systematic search for literature, with no limit of publication time or language, in Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid), PubMed [sb], Embase (Ovid), CINAHL (EBSCO) and PsycINFO. Three authors evaluated the references based on the title and abstract, in pairs independently of each other (Kristoffer Yunpeng Ding evaluated all, Annhild Mosdøl and Laila Hov half each). Potentially relevant references were read in full-text (Kristoffer Yunpeng Ding evaluated all, Annhild Mosdøl and Laila Hov half each). We planned to assess the risk of bias, synthesize the data if possible and use the GRADE method (Grading of Recommendation Assessment, Development and Evaluation) to assess our confidence in the estimated effects.

Results

The literature search for systematic reviews identified 998 titles and abstracts. No systematic reviews were relevant for this topic after screening.

The search for primary studies identified 3696 references. We considered eight references as potentially relevant and read them in full-text. However, none of these references met our inclusion criteria.

Discussion

We did not find any relevant systematic reviews, clinical trials or controlled studies meeting our inclusion criteria.

Experimental studies with controlled use of benzodiazepines are needed to evaluate the effects and consequences of benzodiazepines prescription during opioid maintenance treatment. We suggest the following outcomes: drug retention rates and abuse; patient satisfaction; mental health; sleep disorders; side effects and criminal behaviours.

Conclusion

We found no controlled studies focusing on the effects and consequences of concurrent benzodiazepines prescription during opioid maintenance treatment.

Hovedbudskap (norsk)

I legemiddelassistert rehabilitering får personer med opioidavhengighet langtidsvirkende opiatere som kan tas peroralt for at de skal få redusert trang til å ta illegale opioider. Personer med opioidavhengighet har ofte et høyt nivå av angst og søvnforstyrrelser. En del pasienter i legemiddelassistert rehabilitering bruker legemidler med benzodiazepiner for å lette disse plagene, både forskrevet fra lege og fra det ulovlig markedet. Slik bruk, og misbruk, av benzodiazepiner regnes som et problem.

Målet med denne systematiske oversikten er å oppsummere effekten av å forskrive benzodiazepiner til pasienter som mottar legemiddelassistert rehabilitering.

Etter å ha gjennomført et systematisk litteratursøk fant vi ingen relevante studier som kan belyse dette spørsmålet.

Eksperimentelle studier med kontrollert bruk av benzodiazepiner er nødvendig for å klargjøre effekter og konsekvenser av å forskrive benzodiazepiner til personer i legemiddelassistert rehabilitering.

Tittel:

Effekten av samtidig foreskrivning av benzodiazepiner for personer i legemiddelassistert rehabilitering: En systematisk oversikt

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 i Folehelseinstituttet har skrevet rapporten på oppdrag fra Helsedirektoratet.

Når ble litteratursøket utført?

Søk etter studier ble avsluttet Juli 2016.

Eksterne fagfeller:

Britteline Bakstad, Helsedirektoratet
Gabrielle Welle-Strand, Helsedirektoratet

Sammendrag (norsk)

Innledning

I legemiddelassistert rehabilitering får personer med opioidavhengighet langtidsvirkendeopioider som substitusjon for heroin og andre opioider oftest brukt illegalt. Personer med opioidavhengighet har ofte et høyt nivå av angst og søvnforstyrrelser og pasienter i legemiddelassistert rehabilitering får ofte forskrevet benzodiazepiner for disse lidelsene. Benzodiazepiner kan også misbrukes og er lett tilgjengelig på det illegale markedet. Flere studier viser at bruk av benzodiazepiner mens man får legemiddelassistert behandling er assosiert med mer bruk av rusmidler, angst, psykiske helseplager og økt risiko for personskade. Disse funnene stammer imidlertid fra observasjonsstudier og skiller ikke mellom benzodiazepiner som er forskrevet av lege eller skaffet illegalt.

Formål

Målet med denne systematiske oversikten er å oppsummere effekten av å forskrive benzodiazepiner for pasienter som mottar legemiddelassistert rehabilitering (metadon, buprenorfin eller buprenorfin kombinert med nalokson).

Metode

Vi søkte først etter systematiske oversikter som kunne besvare problemstillingen vår i følgende databaser: Epistemonikos, Cochrane Library (CDSR, DARE, HTA), MEDLINE (Ovid), PubMed [sb] og Embase (Ovid). Vi fant ingen relevante systematiske oversikter. Deretter søkte vi etter primærstudier for å få oversikt over tilgjengelig kunnskap.

Randomiserte kontrollerte studier og ikke-randomiserte kontrollerte studier, kontrollerte før-og-etter studier og avbrutte tidsserier ble inkludert som relevante studiedesign. Målgruppen var personer 18 år eller eldre som fikk substitusjonsbehandling for opioidavhengighet med metadon, buprenorfin eller buprenorfin kombinert med nalokson. Relevant intervensjon var forskrivning av benzodiazepiner sammenlignet med ingen forskrivning av benzodiazepiner. Relevante utfall er gjennomført behandling, pasienttilfredsstillelse, bruk av opioider (selvrapportert eller biologiske tester), annen rusmiddelbruk (selvrapportering eller biologisk test), grad av angst og depresjon, søvnforstyrrelser, dødelighet, bivirkninger (overdose, skade- og bruk av sykehusets akuttmtak) og straffbare forhold.

Vi gjennomførte et systematisk litteratursøk uten begrensninger i tid eller språk i Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid), PubMed

[sb], Embase (Ovid), CINAHL (EBSCO) og PsycINFO. Tre forfattere vurderte referansene basert på tittel og abstrakt, i par uavhengig av hverandre (KYD leste alle, AM og LH halvparten hver). Potensielt relevante referanser ble lest i fulltekst (KYD leste alle, AM og LH halvparten hver). Vi hadde planlagt å vurdere risikoen for systematiske skjevheter, syntetisere data hvis mulig og bruke GRADE (Grading of Recommendation Assessment, Development and evaluation) metoden for å vurdere vår tillit til effektestimertene.

Resultat

Det systematiske litteratursøket etter systematiske oversikter identifiserte 998 titler og abstrakter. Ingen systematiske oversikter var relevant for temaet etter screening.

Vårt søk etter primærstudier identifiserte 3696 referanser, og vi leste åtte av dem i fulltekst. Ingen av referansene møtte våre inklusjonskriterier.

Diskusjon

Vi fant ingen relevante kliniske studier eller kontrollerte studier som undersøkte problemstillingen i denne oversikten.

Eksperimentelle studier med kontrollert bruk av benzodiazepiner er nødvendig for å skille effekter og konsekvenser av å foreskrive benzodiazepiner til personer som mottar legemiddelassistert rehabilitering fra det som er knyttet til illegal bruk og kontrollere for den underliggende symptomprofilen. Det vil være relevant å inkludere utfallmålene: narkotika oppbevaring og misbruk, pasient tilfredshet, mental helse, søvnforstyrrelser, bivirkninger og kriminell atferd.

Konklusjon

Vi fant ingen kontrollerte studier om mulige effekter og konsekvenser av samtidig forskrivning av benzodiazepiner til pasienter i legemiddelassistert rehabilitering.

Preface

The Norwegian Directorate of Health is revising the national clinical guideline for the treatment of people with opioid dependence. They have commissioned this systematic review to The Knowledge Centre for the Health Services in the Norwegian Institute of Public Health focusing on the effects and consequences of concurrent prescription of benzodiazepines among people receiving opioid maintenance treatment.

The project group consisted of:

- Kristoffer Y. Ding (KYD), project leader, Norwegian Institute of Public Health
- Annhild Mosdøl (AM), Norwegian Institute of Public Health
- Laila Hov (LH), Norwegian Institute of Public Health
- Gyri H. Staumann (GHS), Norwegian Institute of Public Health
- Gunn E. Vist (GEV), Norwegian Institute of Public Health

We thank Rigmor C. Berg, Atle Fretheim and Liv M. Reinar for being the internal reviewers, Brittelise Bakstad and Gabrielle Welle-Strand as the external reviewers for our research protocol and final report. We also want to thank Hilde Strømme as peer reviewer for our literature search.

All authors have completed the Conflicts of Interest form, and no conflicts of interest was stated.

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Department Director

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Project leader

Introduction

Opioid dependence includes signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or, if another medical condition is present that requires opioid treatment, that are used in doses greatly in excess of the amount needed for that medical condition (ICD-10-F11). Opioid maintenance treatment (Norwegian: Legemiddelassistert rehabilitering, LAR) is based on the administration of medications that work through the same receptors as the addictive substances, but are longer acting, can administered orally and are less likely to produce the harmful behaviors that characterize addiction [1].

The current Norwegian national guideline for LAR recommends buprenorphine combined with naloxone as the first choice for the initial substitution treatment. Other commonly used medications include buprenorphine mono-formulation and methadone. According to a Norwegian nationwide survey in 2015, 7498 people were enrolled in LAR. Of these, 24% received the combined treatment of buprenorphine and naloxone, 36% received buprenorphine mono-formulation and 39% received methadone treatment [2].

People with opioid dependence are more likely to experience elevated levels of anxiety [3]. Benzodiazepines are a class of psychoactive drugs that are used to treat anxiety and sleep disorders. Although prescription of benzodiazepines for these disorders are quite common, they should be used with caution as prolonged use may result in physical [4] and psychological dependence [5], and increased risk of personal injury [6, 7]. Notably, although evidence suggests that long-term benzodiazepines tolerance develops quickly for the sedative and anticonvulsant actions, its tolerance to anxiolytic and amnesic effects may not develop at all [8]. Findings from population-based studies also showed that there is no increase in prescribed dose of benzodiazepines among long-term users [9, 10].

On the other hand, benzodiazepines can be misused as a drug alone in high doses or combined with illicit substances or alcohol. The Norwegian Police recently reported that benzodiazepines are readily available on the illegal street market [11]. An annual report of the Norwegian LAR-program showed that approximately 40% of the LAR population reported taking benzodiazepines within a month before the survey. However, only 25% reported that their benzodiazepines were prescribed from their doctors [2]. Several studies describe that patients who use benzodiazepines during opioid maintenance treatment have lower retention rate in treatment and are more at risk of continued drug abuse [12], higher anxiety sensitivity [13] and more mental health

problems [14]. However, this evidence is mostly descriptive and derived from surveys or observational studies. Furthermore, these findings do not distinguish between prescribed versus illicitly procured benzodiazepines, nor do they sufficiently account for the possible underlying symptomatology of benzodiazepines users.

Concurrent use and misuse of benzodiazepines among patients in the LAR-program have been widely discussed, but there is no comprehensive evidence evaluating the effects and consequences among people in opioid maintenance treatment.

Method

First, we searched for systematic reviews published during the last 5 years (after 1.1.2011) on the effects of concurrent benzodiazepines prescription for people in opioid maintenance treatment in the following databases:

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

Since we did not find any systematic reviews relevant for the topic, we conducted a systematic search for primary studies on the effects of concurrent benzodiazepines prescription for people in opioid maintenance treatment.

Inclusion criteria

Study design:	Randomized controlled trials (RCT, including cluster RCT) Non-randomized controlled trials (NRCTs) Controlled before-and-after studies (CBA) Interrupted time series (ITS)
Population:	People who are 18 years or older who receive buprenorphine with naloxone, buprenorphine or methadone substitution treatment for opioid dependence
Intervention:	Prescription of benzodiazepines
Comparison:	No prescription of benzodiazepines
Outcome:	Retention in treatment Patients' satisfaction Opioid use (self-report or biological test) Other substance use (self-report or biological test) Extent of anxiety Extent of depression Sleep disorders Mortality Side effects (overdose, injury and use of hospital emergency)

Language: Criminal offenses
No language limits applied to the searches. Project members only read English, Norwegian, Danish, Swedish and Chinese. Publications in other languages would not be read but be listed in a table.

Literature search

We searched for primary studies with no limit of publication time or language in the following databases:

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

We also searched for ongoing trials in clinicaltrials.gov, WHO International Clinical Trials Registry Platform, Current Controlled Trials, EU Clinical Trials Register and Trials. Research librarian, Gyri Hval Straumann, conducted the search, which was peer-reviewed by librarian Hilde Strømme.

Article selection and assessment

Three review authors independently screened abstracts identified by the searches in duplicates. Kristoffer Yunpeng Ding screened all the references while Annhild Mosdøl and Laila Hov screened half each.

Articles were excluded if the title and/or abstract did not meet the inclusion criteria. For potentially relevant studies, the full-text articles were obtained and screened with discrepancies resolved by consensus of reviewers. Studies that are relevant to the review topic but do not meet all the inclusion criteria for the review are listed in the 'Characteristics of excluded studies' table, with the reason for their exclusion described. We recorded the selection process in sufficient detail to complete a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Assessment of risk of bias in included studies

We had planned to assess the included studies for risk of bias for RCTs, NRCTs and CBAs independently with the EPOC risk of bias tool [13]. Potential conflicts would have

been solved by consensus or referral to a third review author if disagreement persisted.

We would have assessed the risk of bias for each of the following domains:

- Adequate sequence generation
- Allocation concealment
- Blinding of outcome assessors
- Incomplete outcome data
- Selective outcome reporting
- Comparability of baseline outcome measurements across groups
- Comparability of baseline characteristics across groups
- Free of contamination between groups
- Free of other bias

For cluster RCT, we would have considered particular biases [14] including:

- Recruitment bias
- Baseline imbalance
- Loss of clusters
- Incorrect analysis
- Comparability with individually randomized trials

A separate risk of bias checklist would have been used for ITS studies, which includes seven criteria [13] as follows:

- Independent intervention
- Pre-specified intervention effect shape
- Data collection being affected by intervention
- Outcomes assessed blindly
- Missing data
- Publication bias
- Free of other bias

Data extraction

Kristoffer Yunpeng Ding would have been responsible for extracting the relevant data from the included studies, while Annhild Mosdøl validated the extraction. The following information was planned to be extracted: authors, year, country, title, population, intervention (drug type and dosage) as well as the outcomes as follows: Retention in treatment; patients' satisfaction, opioid use (self-report or biological test), other substance use (self-report or biological test), extent of anxiety, sleep disorders, side effects (overdose, injury, hospital emergency use or mortality) and criminal offenses.

Analyses

We anticipate that outcome data would be presented as dichotomous, continuous or ordinal. In cases of dichotomous data, risk ratios (RR) would be calculated. In cases of continuous data, we would use mean difference (MD) or calculate the standardized mean difference (SMD) if more than one study measured the same outcome using different tools.

The ordinal data would have been analyzed as a continuous outcome, or been dichotomized based upon the scale used and existence of well-defined cut-off values. For all effect measures, effect estimates would have been presented with 95% confidence intervals (CIs).

We would have performed meta-analysis using RevMan software (RevMan 5.3). Notably, meta-analysis would only have been performed when there were two or more studies with sufficiently similar inclusion criteria. If the included studies reported the same or similar outcome, and there were no apparent unit of analysis errors (or ICC data were available for cluster RCT), we would have calculated summary measures of intervention effects. In addition, data synthesis would have been stratified and presented separately for different study designs. We had planned to conduct meta-analysis with random effects model, using standard methods to account for cluster RCT as relevant. If substantial heterogeneity ($I^2 > 75\%$) was found, or we were unable to adjust for unit of analysis errors in two or more studies with same or similar outcomes, we would have presented the results descriptively as the median effect and interquartile range.

Assessment of quality of evidence

The review team planned to assess the certainty of the evidence together (high, moderate, low or very low) for each outcome using the GRADE approach [15]. Disagreements on certainty ratings would have been resolved by discussion and providing justification for decisions to down- or up-grade the ratings using footnotes in the table.

Results

We initially searched for systematic reviews to address the question of the effects of concurrent prescription of benzodiazepines among people in opioid maintenance treatment. After the literature search, we found 998 systematic reviews but none of them were relevant for the topic.

Description of studies

Results of literature search

We searched for primary studies to conduct a systematic review and identified 3696 references. We considered eight references as potentially relevant and read them in full-text. However, we found no reference that met our inclusion criteria (Figure 1). Those excluded references are presented in Appendix 2 with an explanation for exclusion.

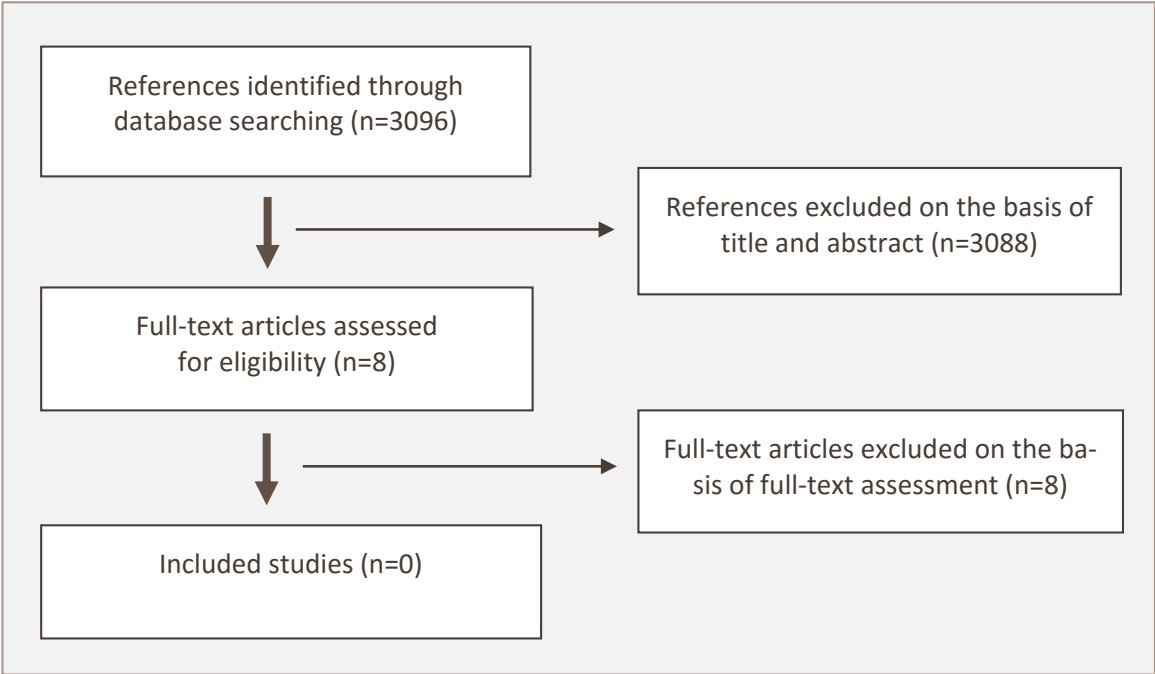


Figure 1
Flow chart of literature selection

Excluded studies

We evaluated the full-text of the eight studies, and found that none of them met our inclusion criteria. The detailed reasons for exclusion are provided in Appendix 2. Specifically, one study had an observational design with no intervention group; one study compared the effect of two drugs with no control group; two studies targeted on different populations; two studies focused on pharmacodynamics of benzodiazepines and physiological responses of subjects; two studies were published in the form of long abstract but not full-text articles.

Discussion

Key findings summary

We have conducted a systematic review on the effects and consequences of concurrent prescription of benzodiazepines among people in opioid maintenance treatment. After conducting a systematic literature search, we did not find any relevant systematic review or primary study that meet the research question.

Strengths and weaknesses

A strength of this systematic review is the systematic and explicit methods used. Although we did not find any relevant study in our systematic literature search, we have to bear in mind the possibility that relevant studies may have been published after the search was conducted, which is a limitation of all systematic reviews. This systematic review is considered up-to-date as of July 2016.

Consistency with other literature

The background for this review is the concern that patients who are receiving the prescription of benzodiazepines during opioid maintenance treatment may have lower retention in treatment or at higher risk of continued drug abuse [12], elevated anxiety sensitivity [13] and more mental health problems [14].

However, we found no controlled studies of benzodiazepines use, as separated from illicit substances, which can take into account the underlying symptomatology of benzodiazepines users. One of the excluded studies, an observational study of patients in a trial with different opioid maintenance treatments [16], indicates different risk profiles for patients with baseline benzodiazepines use and ongoing benzodiazepines use, but with no prescription information.

Identified research gaps

Experimental studies are needed to evaluate the effects and consequences of controlled use of benzodiazepines during opioid maintenance treatment. We suggest the following

outcomes: drug retention and abuse; patient satisfaction; mental health; sleep disorders; side effects and criminal behaviours.

Conclusion

There is a lack of controlled studies on the effects and consequences of concurrent benzodiazepines prescription among people in opioid maintenance treatment.

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Appendices

Appendix 1. Search strategy

Part I. Search strategy for systematic reviews.

Database: Cochrane Database of Systematic Reviews (Reviews only)

Date on search: 01.07.16

	Searches	Results
#1	MeSH descriptor: [Opiate Substitution Treatment] explode all trees	204
#2	MeSH descriptor: [Methadone] explode all trees	997
#3	MeSH descriptor: [Buprenorphine] explode all trees	733
#4	MeSH descriptor: [Naloxone] explode all trees	1688
#5	((((opiate or opioid) next (replacement or substitution or agonist or maintenance) next (therap* or treatment* or program*)) or (Adadon* or Algidon* or Algolysin* or Algoxale* or Amidon* or Anorfin* or Antioplaz* or Biodon* or Bunavail* or Buprenex* or Buprenorpin* or Buprex* or Buprine* or Butalgin* or Butrans* or Dolophin* or Evzio* or Finibron* or Lepetan* or Maloxon* or Mapin* or Metado* or Metasedin* or Methaddict* or Methado* or Methaforte* or Methex* or Miadon* or Nalaxon* or Nalone* or Naloxon* or Narcan* or Narcon* or Narvcam* or Norphin* or Pentorel* or Phenadon* or Phymet* or Physepton* or Pinadon* or Prefin* or Probuphin* or Suboxon* or Subutex* or Symoron* or Temgesic* or Transtec* or Zubsolv* or Zynox*)):ti,ab,kw	3878
#6	#1 or #2 or #3 or #4 or #5	4970
#7	MeSH descriptor: [Benzodiazepines] explode all trees	8125
#8	(benzodiazepine* or alprazolam or bromazepam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flunitrazepam or flurazepam or halazepam or ketazolam or loprazolam or lorazepam or lormetazepam or medazepam or nordazepam or oxazepam or prazepam or quazepam or temazepam or triazolam):ti,ab,kw	11772
#9	#7 or #8	17025
#10	#6 and #9 Publication Year from 2011 to 2016, in Cochrane Reviews (Reviews only)	4

Database: DARE, HTA, Cochrane Database of Systematic Reviews (Protocols only)**Date on search: 01.07.16**

	Searches	Results
#1	MeSH descriptor: [Opiate Substitution Treatment] explode all trees	204
#2	MeSH descriptor: [Methadone] explode all trees	997
#3	MeSH descriptor: [Buprenorphine] explode all trees	733
#4	MeSH descriptor: [Naloxone] explode all trees	1688
#5	(((opiate or opioid) next (replacement or substitution or agonist or maintenance) next (therap* or treatment* or program*)) or (Adadon* or Algidon* or Algolysin* or Algoxale* or Amidon* or Anorfin* or Antioplaz* or Biodon* or Bunavail* or Buprenex* or Buprenorpin* or Buprex* or Buprine* or Butalgin* or Butrans* or Dolophin* or Evzio* or Finibron* or Lepetan* or Maloxon* or Mapin* or Metado* or Metasedin* or Methaddict* or Methado* or Methaforte* or Methex* or Miadon* or Nalaxon* or Nalone* or Naloxon* or Narcan* or Narcon* or Narvcam* or Norphin* or Pentorel* or Phenadon* or Phymet* or Physepton* or Pinadon* or Prefin* or Probuphin* or Suboxon* or Subutex* or Symoron* or Temgesic* or Transtec* or Zubsolv* or Zynox*)):ti,ab,kw	4130
#6	#1 or #2 or #3 or #4 or #5	5210
#7	MeSH descriptor: [Benzodiazepines] explode all trees	8125
#8	(benzodiazepine* or alprazolam or bromazepam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flunitrazepam or flurazepam or halazepam or ketazolam or loprazepam or lorazepam or lormetazepam or medazepam or nordazepam or oxazepam or prazepam or quazepam or temazepam or triazolam):ti,ab,kw	12526
#9	#7 or #8	14514
#10	#6 and #9 Publication Year from 2011 to 2016, in Other Reviews, Technology Assesments, Cochrane Reviews (Protocols only)	7

Database: Epistemonikos**Date on search: 01.07.16**

benzodiazepines (last 5 years) : 1 broad synthesis, 11 structured summaries, 37 systematic reviews

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Date on search: 01.07.16

	Searches	Results
1	"Opiate substitution treatment"/ or exp "Methadone"/ or exp "Buprenorphine"/ or exp "Naloxone"/ or (((opiate or opioid) adj (replacement or substitution or agonist or maintenance) adj (therap* or treatment* or program*)) or (Adadon* or Algidon* or Algolysin* or Algoxale* or Amidon* or Anorfin* or Antioplaz* or Biodon* or Bunavail* or Buprenex* or Buprenorpin* or Buprex* or Buprine* or Butalgin* or Butrans* or Dolophin* or Evzio* or Finibron* or Lepetan* or Maloxon* or Mapin* or Metado* or Metasedin* or Methaddict* or Methado* or Methaforte* or Methex* or Miadon* or Nalaxon* or Nalone* or Naloxon* or Narcan* or Narcon* or Narvcam* or Norphin* or Pentorel* or Phenadon* or Phymet* or Physepton* or Pinadon* or Prefin* or Probuphin* or Suboxon* or Subutex* or Symoron* or Temgesic* or Transtec* or Zubsolv* or Zynox*)).ab,ti,kw,kf.	47409
2	exp Benzodiazepines/ or (benzodiazepine* or alprazolam or bromazepam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flunitrazepam or flurazepam or halazepam or ketazolam or loprazolam or lorazepam or lormetazepam or medazepam or nordazepam or oxazepam or prazepam or quazepam or temazepam or triazolam).ti,ab.	80651
3	1 and 2	2131
4	limit 3 to (yr="2011 -Current" and "reviews (maximizes sensitivity)")	183

Database: Embase 1974 to 2016 June 29

Date on search: 01.07.16

	Searches	Results
1	exp benzodiazepine derivative/	163314
2	(benzodiazepine* or adinazolam or alprazolam or anthramycin or bentazepam or bromazepam or chlordiazepoxide or cinolazepam or clobazam or clonazepam or "clorazepam clorazepate" or clotiazepam or cloxazolam or cyprazepam or diazepam or doxefazepam or estazolam or etizolam or flunitrazepam or flurazepam or flutazoram or fosazepam or girisopam or halazepam or haloxazepam or ketazolam or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or midazepam or nerisopam or nitrazepam or nordazepam or oxazepam or oxazolam or pinasepam or pinazepam or prazepam or temazepam or tetrazepam or tofiso-pam or triazolam or triflubazam).ti,ab.	85631
3	1 or 2	189205

4	"Opiate substitution treatment"/ or "Methadone treatment"/ or "Methadone"/ or "Buprenorphine"/ or "Buprenorphine plus naloxone"/ or "Naloxone"/ or (((opiate or opioid) adj (replacement or substitution or agonist or maintenance) adj (therap* or treatment* or program*)) or (Adadon* or Algidon* or Algolysin* or Algoxale* or Amidon* or Anorfin* or Antioplaz* or Biodon* or Bunavail* or Buprenex* or Buprenorpin* or Buprex* or Buprine* or Butalgin* or Butrans* or Dolophin* or Evzio* or Finibron* or Lepetan* or Maloxon* or Mapin* or Metado* or Metasedin* or Methaddict* or Methado* or Methaforte* or Methex* or Miadon* or Nalaxon* or Nalone* or Naloxon* or Narcan* or Narcon* or Narvcam* or Norphin* or Pentorel* or Phenadon* or Phymet* or Physepton* or Pinadon* or Prefin* or Probuphin* or Suboxon* or Subutex* or Symoron* or Temgesic* or Transtec* or Zubsolv* or Zynox*)).ab,ti,kw.	72658
5	3 and 4	9341
6	limit 5 to ("reviews (maximizes sensitivity)" and yr="2011 -Current")	846

Database: PROSPERO

Date on search: 01.07.16

benzodiazepines : 5

Part II. Searching strategy for primary studies.

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date on search: 01.07.16

	Searches	Results
1	"Opiate substitution treatment"/ or exp "Methadone"/ or exp "Buprenorphine"/ or exp "Naloxone"/ or (((opiate or opioid) adj (replacement or substitution or agonist or maintenance) adj (therap* or treatment* or program*)) or (Adadon* or Algidon* or Algolysin* or Algoxale* or Amidon* or Anorfin* or Antioplaz* or Biodon* or Bunavail* or Buprenex* or Buprenorpin* or Buprex* or Buprine* or Butalgin* or Butrans* or Dolophin* or Evzio* or Finibron* or Lepetan* or Maloxon* or Mapin* or Metado* or Metasedin* or Methaddict* or Methado* or Methaforte* or Methex* or Miadon* or Nalaxon* or Nalone* or Naloxon* or Narcan* or Narcon* or Narvcam* or Norphin* or Pentorel* or Phenadon* or Phymet* or Physepton* or Pinadon* or Prefin* or Probuphin*	47409

	or Suboxon* or Subutex* or Symoron* or Temgesic* or Transtec* or Zubsolv* or Zynox*)).ab,ti,kw,kf.	
2	exp Benzodiazepines/ or (benzodiazepine* or alprazolam or bromazepam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flunitrazepam or flurazepam or halazepam or ketazolam or loperazolam or lorazepam or lormetazepam or medazepam or nordazepam or oxazepam or prazepam or quazepam or temazepam or triazolam).ti,ab.	80651
3	dt.fs.	1877700
4	randomized controlled trial.pt.	422232
5	controlled clinical trial.pt.	91094
6	multicenter study.pt.	205482
7	(randomis* or randomiz* or randomly or groups).ti,ab.	2054110
8	(trial or multicenter or multi center or multicentre or multi centre).ti.	184649
9	(intervention* or controlled or control group or compare or compared or quasiexperiment* or quasi experiment* or evaluat* or effect* or impact*).ti,ab.	9428146
10	or/3-9	10916460
11	1 and 2 and 10	1577
12	limit 11 to yr="1990 -Current"	1189

Database: Embase 1974 to 2016 June 29

Date on search: 01.07.16

	Searches	Results
1	exp benzodiazepine derivative/	163314
2	(benzodiazepine* or alprazolam or bromazepam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flunitrazepam or flurazepam or halazepam or ketazolam or loperazolam or lorazepam or lormetazepam or medazepam or nordazepam or oxazepam or prazepam or quazepam or temazepam or triazolam).ti,ab.	72658
3	1 or 2	177416
4	"Opiate substitution treatment"/ or "Methadone treatment"/ or "Methadone"/ or "Buprenorphine"/ or "Burprenophine plus naloxone"/ or "Naloxone"/ or (((opiate or opioid) adj (replacement or substitution or agonist or maintenance) adj (therap* or treatment* or program*)) or (Adadon* or Algidon* or Algolysin* or Allogoxale* or Amidon* or Anorfin* or Antioplaz* or Biodon* or Buprenex* or Buprenorphine* or Buprex* or Buprine* or Butalgin* or Butrans* or Dolophin* or Evzio* or Finibron* or Lepetan* or Maloxon* or Mapin* or Metado* or Metasedin* or Methaddict* or Methado* or Methaforte* or Methex* or Miadon*	76474

	or Nalaxon* or Nalone* or Naloxon* or Narcan* or Narcon* or Narvcam* or Norphin* or Pentorel* or Phenadon* or Phymet* or Physepton* or Pinadon* or Prefin* or Probuphin* or Suboxon* or Subutex* or Symoron* or Temgesic* or Transtec* or Zubsolv* or Zynox*)).ab,ti,kw.	
5	exp crossover procedure/	47729
6	exp double blind procedure/	131975
7	exp single blind procedure/	22380
8	exp clinical trial/	1100072
9	exp randomized controlled trial/	410685
10	(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.	7844788
11	or/5-10	8215393
12	3 and 4 and 11	3901
13	limit 12 to yr="1990 -Current"	3132

Database: Central

Date on search: 01.07.16

	Searches	Results
#1	MeSH descriptor: [Opiate Substitution Treatment] explode all trees	204
#2	MeSH descriptor: [Methadone] explode all trees	998
#3	MeSH descriptor: [Buprenorphine] explode all trees	734
#4	MeSH descriptor: [Naloxone] explode all trees	1690
#5	((((opiate or opioid) next (replacement or substitution or agonist or maintenance) next (therap* or treatment* or program*)) or (Adadon* or Algidon* or Algolysin* or Algoxale* or Amidon* or Anorfin* or Antioplaz* or Biodon* or Bunavail* or Buprenex* or Buprenorpin* or Buprex* or Buprine* or Butalgin* or Butrans* or Dolophin* or Evzio* or Finibron* or Lepetan* or Maloxon* or Mapin* or Metado* or Metasedin* or Methaddict* or Methado* or Methaforte* or Methex* or Miadon* or Nalaxon* or Nalone* or Naloxon* or Narcan* or Narcon* or Narvcam* or Norphin* or Pentorel* or Phenadon* or Phymet* or Physepton* or Pinadon* or Prefin* or Probuphin* or Suboxon* or Subutex* or Symoron* or Temgesic* or Transtec* or Zubsolv* or Zynox*))	4140
#6	#1 or #2 or #3 or #4 or #5	5222
#7	MeSH descriptor: [Benzodiazepines] explode all trees	8128
#8	(benzodiazepine* or alprazolam or bromazepam or chlordiaze-poxide or clobazam or clonazepam or clorazepate or diazepam or	12525

	estazolam or flunitrazepam or flurazepam or halazepam or ketazolam or loprazolam or lorazepam or lormetazepam or medazepam or nordazepam or oxazepam or prazepam or quazepam or temazepam or triazolam)	
#9	#7 or #8	14513
#10	#6 and #9 Publication Year from 1990 to 2016, in Trials	154

Database: ClinicalTrials.gov (www.clinicaltrials.gov)

Date on search: 30.06.16

benzodiazepine AND opioid : 69

Database: World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)

Date on search: 30.06.16 (apps.who.int/trialsearch/)

benzodiazepine AND opioid : 7

benzodiazepines AND opioids : 14

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

Date on search: 30.06.16

benzodiazepine AND opioid : 3

benzodiazepines AND opioids : 10

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

Date on search: 30.06.16

benzodiazepine AND opioid : 1

benzodiazepines AND opioids : 5

Database: Trials (www.trialsjournal.com)

Date on search: 30.06.16

benzodiazepine AND opioid : 211

benzodiazepines AND opioids : 313

Appendix 2. Excluded studies

Studies evaluated in full-text	Reason for exclusion
Eiroa-Orosa, Francisco José, et al. Benzodiazepine use among patients in heroin-assisted vs. methadone maintenance treatment: findings of the German randomized controlled trial. <i>Drug and alcohol dependence</i> 112.3 (2010): 226-233.	The study has no intervention on benzodiazepines (an observational study derived from a clinical trial).
Jariani, Mojghan, et al. The effect of Olanzapine and Sertraline on personality disorder in patients with methadone maintenance therapy. <i>Psychiatria Danubina</i> 22.4. (2010): 544-547.	The study compared the effect of olanzapine with another intervention (Sertraline) in treating depression and anxiety among patients with methadone maintenance therapy. The study design does not meet our inclusion criteria, because they compared the effects of two interventions and there was no control group.
Lintzeris, Nicholas, et al. Interactions on mixing diazepam with methadone or buprenorphine in maintenance patients. <i>Journal of clinical psychopharmacology</i> 26.3 (2006): 274-283.	The outcomes of this study were physiological responses and subjective drug effects, which were only measured 6 hours after dosing. There were no long-term outcomes in this study.
Lintzeris, Nicholas, et al. Pharmacodynamics of diazepam co-administered with methadone or buprenorphine under high dose conditions in opioid dependent patients. <i>Drug and alcohol dependence</i> 91.2 (2007): 187-194.	The outcomes of this study were about pharmacodynamics of diazepam, which was not considered relevant for the current systematic review.
Lopatko, et al. Reducing benzodiazepine consumption in opioid maintenance therapy patients: A controlled clinical trial. <i>Proceedings of the 68th Annual Scientific Meeting of the College on Problems of Drug Dependence</i> ; 2006 June 17-22; Scottsdale, Arizona, USA.	This is a conference paper which is published in the form of long abstract, a full-text article is not available.
Mijatović, V. et al. PP042-Safety assessment of low doses of methadone in combination with benzodiazepines in real occasions during methadone	This is a conference paper which is published in the form of long abstract, a full-text article is not available.

maintenance treatment-A pilot study.
Clinical Therapeutics , Volume 35, Issue 8,
e30.

Stella, Luigi, et al. Naltrexone plus benzodiazepine aids abstinence in opioid-dependent patients. Life sciences 77.21 (2005): 2717-2722.	The population in this study used naltrexone alone for treating opioid dependence, which is not the standard treatment in Norway. The population is therefore irrelevant for the current study.
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Zarghami, M., et al. A comparative study of beneficial effects of Olanzapine and sodium valproate on aggressive behavior of patients who are on methadone maintenance therapy: a randomized triple blind clinical trial. Eur Rev Med Pharmacol Sci 17.8 (2013): 1073-1081.	The study compares the effect of olanzapine and sodium valproate on patients behaviors. There is no control group in this study.
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