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Complete List of Authors:	He, Li-xian; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital, Anesthesiology Shao, Ken; Jingmen No. 1 people's hospital, Anesthesiology Ma, Jie; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital, Pharmacy Zhao, Yuan-yuan; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital, Anesthesiology Yao, Yun-tai; Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital, Anesthesiology
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Dezocine prevents opioids-induced cough during general anesthesia induction: a protocol for systematic review and meta-analysis

Li-xian He[1], Ken Shao[2], Jie Ma[3], Yuan-yuan Zhao[1], Yun-tai Yao[1,*]

[1]Department of Anesthesiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100037, China

[2]Department of Anesthesiology, Jingmen No.1 People's Hospital, Jingmen 448000, China

[3]Department of Pharmacy, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100037, China

*Correspondence: Yun-tai Yao, Department of Anesthesiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing,

China. No. 167, Beilishi Road, Xicheng District, Beijing 100037, China (e-mail: yuntaiyao@126.com).

Abstract

Introduction

Cough is often observed when administrating a bolus of opioids. Opioid-induced cough(OIC) is mostly transient, benign and self-limiting, but could be associated with adverse effects. Numerous pharmacological and non-pharmacological interventions have been used to manage OIC with controversial efficacy and safety. Recent studies suggested that, pretreatment of intravenous dezocine(DZC) could completely suppress OIC during anesthesia induction. To address this knowledge lack, we will performe a systemic review and meta-analysis to evaluate the efficacy of DZC on OIC and possible complications. We provide here a protocol that will outline the methods and analyses planned for the systematic review.

Methods

Electronic databases will be searched to identify all randomized controlled trials(RCTs) comparing DZC with placebo on the incidence and severity of OIC. Two authors will independently extract relevant variables and outcome data. For continuous variables, treatment effects

will be calculated as weighted mean difference(WMD) and 95% confidential interval(CI). For dichotomous data, treatment effects will be calculated as odds ratio(OR) and 95% CI. Each outcome will be tested for heterogeneity, and randomized-effects or fixed-effects model will be used in the presence or absence of significant heterogeneity. Sensitivity analyses will be done by examining the influence of statistical model and individual trial(s) on estimated treatment effects. Publication bias will be explored through visual inspection of funnel plots of the outcomes. Statistical significance will be defined as $P<0.05$.

Ethics and dissemination

This study is a protocol of meta-analysis of previously published literatures, ethical approval was not necessary according to the Ethical Committee of Fuwai Hospital. The study will be submitted to a peer-reviewed journal and disseminated via research presentations.

PROSPERO registration number

CRD42019141255

Keywords: dezocine, opioid, cough, general anesthesia, meta-analysis

Strengths and limitations of this study

- The protocol describes what will be the first systematic review to conduct a comprehensive assessment of the efficacy of DZC on OIC

and possible complications.

- The exclusion of trials absent of OIC incidence or placebo control group might leave relevant studies out of the review.
- The main limitation of this review is that varied quality and heterogeneity of included studies may limit the certainty of the findings of meta-analysis.

Introduction

Cough is often observed when administrating a bolus of opioids(*e.g.* fentanyl[1-4], sufentanil[5-7], remifentanil[8-13], alfentanil[14]), with the reported incidence ranging from 7% to 70%[1-14]. The mechanism of opioid-induced cough(OIC) is complex and remains poorly understood, which may involve pulmonary chemoreflex, enhanced activity of parasympathetic nerve, histamine release, opioid receptor dualism and muscular rigidity[1-3,15-17]. OIC is mostly transient, benign and self-limiting, but could be associated with adverse effects such as hypertension, tachycardia, increased intra-cranial, ocular and abdominal pressures, and airway obstruction[1,2,15-17]. OIC could be spasmodic, explosive[18] and life threatening at times[19]. OIC is especially undesirable during the induction of general anesthesia. Numerous pharmacological interventions including lidocaine, atropine, magnesium sulfate($MgSO_4$),

dexamethasone, propofol, midazolam, muscular relaxant(rocurounium, vencuronium), ketamine, pentazocine, tramadol, α_2-agonists(clonidine, dexmeditomidine), ß2-agonists(terbutaline, ephedrine), sodium chromoglycate, beclomethasone, salbutamol, dextromethorphan, *etc*, and non-pharmacological interventions such as priming, dilution and slow injection of opioids, have been used to manage OIC[1,2,4-9,11-13,15,17,19-22]. Unfortunately, the efficacy and safety of those anti-tussive interventions remains controversial.

Dezocine(DZC), a mixed opioid agonist/antagnost, was synthesized in 1970s and approved by the Food and Drug Administration of US for perioperative pain management but was discontinued with the closure of its parent company[23-27]. Although no longer used clinically in Western countries, DZC has gained popularity in China and been widely used as a peri-operative analgesic for decades[24,28-32]. Recent studies suggested that, pretreatment of intravenous DZC 0.1mg/kg could completely suppress the cough induced by bolus injection of fentanyl or sufentanil during anesthesia induction. For example, Sun *et al*[4] evaluated the suppressive effect of DZC on fentanyl-induced cough(FIC). One hundred and twenty patients were randomized to receive DZC 0.1 mg/kg or placebo 10 min before fentanyl 5 μ g/kg. They demonstrated that, no DZC-pretreated patient had FIC, as compared to 70%(42/60) non-DZC-pretreated patients developing FIC. In another RCT involving 370 patients, Liu and

colleagues[6] evaluated the anti-tussive effect of DZC 0.1 mg/kg on sufentanil-induced cough(SIC) during anesthesia induction. They demonstrated the incidence of SIC in the placebo group was 31%(59/185), while no SIC was observed in the DZC group. It is so encouraging that, DZC might be more effective than those above-mentioned anti-tussive interventions, and that DZC could possibly eliminate OIC without causing OIC itself. Therefore, we will perform a systemic review and meta-analysis to evaluate the efficacy of DZC on OIC during general anesthesia induction, and possible complications.

Objectives

To systematically review the effects of DZC on the incidence and severity of OIC and possible complications during general anesthesia induction.

Methods and analysis

This protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist[33]. The systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[34].

Patient and public involvement statement

There will be no patient or public involved in this systematic review and

meta-analysis.

Inclusion and exclusion criteria

We will include all RCTs comparing DZC with placebo or blank with respect to their effects on OIC. In studies which also included other comparator drugs, only data of DZC and placebo groups will be abstracted. Primary outcomes of interest include the incidence and severity of OIC. Secondary outcomes of interest include possible complications or adverse effects. Exclusion criteria include (1)studies published as review, case report or abstract; (2)animal or cell studies; (3)duplicate publications; (4) studies lacking information about outcomes of interest. The two authors will independently review the titles and abstracts of all identified studies for eligibility, excluding obviously ineligible ones. The eligibility of those remaining studies for final inclusion will be further determined by reading the full text.

Search strategy

We will conducted a systemic review according to the Preferred Reporting Items for Systemic Reviews and Meta-Analysis Quality of Reporting of Meta-analysis(PRIMSA) Guidelines[34]. The protocol of current meta-analysis was published in PROSPERO with the registration number of CRD42019141255. Relevant trials will be identified by computerized searches of MEDLINE, Cochrane Library and EMBASE

till December 31th 2019, using different combination of search words as follows: *(opioid OR fentanyl OR sufentanil OR remifentanil OR alfentanil) AND cough AND dezocine AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR randomly OR trial)*(**Supplement Appendix**). No language restriction will be used. We will also search Chinese BioMedical Literature & Retrieval System(SinoMed), China National Knowledge Infrastructure（CNKI），Wanfang Data and VIP Data(from 1978 to December 31th 2019). Additionally, we will use the bibliography of retrieved articles to further identify relevant studies.

Study quality assessment

Two authors will independently assess the risk of bias, using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions[35]. The modified 7-point *Jadad* score[36] will be used independently by two authors to evaluate the methodological quality of each included trial. Trials with 1-3 points will be deemed to be of low quality, and those with 4-7 points will be deemed to be of high quality.

Data abstraction

The following data will be abstracted from the included studies to a data collection form by two authors independently: (1)author, year of publication and journal of included studies; (2)total number of patients,

number of patients in the DZC and control groups, gender, age; (3)data regarding outcomes of interest in both groups. Disagreements will be resolved by discussion among all authors during the process of data abstraction. The authors of the included RCTs will be contacted if necessary.

Statistical analysis

All data will be analyzed by utilizing RevMan 5.3(Cochrane Collaboration, Oxford, UK). Pooled odds ratio(OR) and 95% confidence interval(CI) will be estimated for dichotomous data, and weighted mean difference(WMD) and 95% CI for continuous data, respectively. Each outcome will be tested for heterogeneity, and randomized-effects or fixed-effects model will be used in the presence or absence of significant heterogeneity(Q-statistical test $P<0.05$). Sensitivity analyses will be done by examining the influence of statistical model on estimated treatment effects, and analyses which adopt the fixed-effects model will be repeated again by using randomized-effects model and *vice versa*. In addition to that, sensitivity analysis will also be performed to evaluate the influence of individual study on the overall effects. The possible effects of opioid type and doses will be evaluated by subgroup analysis. Publication bias will be explored through visual inspection of funnel plots of the outcomes. All *P*-values will be two-sided and statistical significance was defined as

$P<0.05$.

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Supplements

Table 1. Search strategy

PUBMED *(Cardiac Surgical Procedure[Mesh terms] OR Cardiac Surgical Procedure[All field] OR Cardiopulmonary Bypass[Mesh terms] OR Cardiopulmonary Bypass[All field]) AND (Opioid[All field] OR fentanyl[All field] OR sufentanil[All field] OR remifentanil[All field] OR alfentanil[All field]) AND （cough[All field]）AND (Randomized controlled trial[pytp] OR controlled clinical trial[pytp] OR randomized[All field] OR placebo[All field] OR randomly[All field] OR trial[All field]） AND (dezocine[All field])*
EMBASE *(Cardiac Surgical Procedure[Mesh terms] OR Cardiac Surgical Procedure[All field] OR Cardiopulmonary Bypass[Mesh terms] OR Cardiopulmonary Bypass[All field]) AND (Opioid[All field] OR fentanyl[All field] OR sufentanil[All field] OR remifentanil[All field] OR alfentanil[All field]) AND （cough[All field]）AND (Randomized controlled trial[pytp] OR controlled clinical trial[pytp] OR randomized[All field] OR placebo[All field] OR randomly[All field] OR trial[All field]） AND (dezocine[All field])*
SinoMed

(Opioid[All field] OR fentanyl[All field] OR sufentanil[All field] OR remifentanil[All field] OR alfentanil[All field]) AND (cardiac-surgery[All field] OR cardiopulmonary bypass[All field] OR extracorporeal circulation[All field] OR coronary artery bypass[All field] OR valve surgery[All field] OR aorta[All field]) AND （cough[All field]）AND (Randomized controlled trial[pytp] OR controlled clinical trial[pytp] OR randomized[All field] OR placebo[All field] OR randomly[All field] OR trial[All field]） AND (dezocine[All field])
CNKI *(Opioid[All field] OR fentanyl[All field] OR sufentanil[All field] OR remifentanil[All field] OR alfentanil[All field]) AND (cardiac-surgery[All field] OR cardiopulmonary bypass[All field] OR extracorporeal circulation[All field] OR coronary artery bypass[All field] OR valve surgery[All field] OR aorta[All field]) AND （cough[All field]）AND (Randomized controlled trial[pytp] OR controlled clinical trial[pytp] OR randomized[All field] OR placebo[All field] OR randomly[All field] OR trial[All field]） AND (dezocine[All field])*
Wanfang Data *(Opioid[All field] OR fentanyl[All field] OR sufentanil[All field] OR remifentanil[All field] OR alfentanil[All field]) AND (cardiac-surgery[All field] OR cardiopulmonary bypass[All field] OR extracorporeal circulation[All field] OR coronary artery bypass[All field] OR valve surgery[All field] OR aorta[All field]) AND （cough[All field]）AND (Randomized controlled trial[pytp] OR controlled clinical trial[pytp] OR randomized[All field] OR placebo[All field] OR randomly[All field] OR trial[All field]） AND (dezocine[All field])*

VIP Data

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Primary Subject Heading:	Anaesthesia
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Keywords:	Adult anaesthesia < ANAESTHETICS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, ANAESTHETICS

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[1]Department of Anesthesiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100037, China

[2]Department of Anesthesiology, Jingmen No.1 People's Hospital, Jingmen 448000, China

[3]Department of Pharmacy, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100037, China

*Correspondence: Yun-tai Yao, Department of Anesthesiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China. No. 167, Beilishi Road, Xicheng District, Beijing 100037, China (e-mail: yuntaiyao@126.com).

Abstract

Introduction

Cough is often observed when administrating a bolus of opioids. Opioid-induced cough (OIC) is mostly transient, benign and self-limiting, but could be associated with adverse effects. Numerous pharmacological and non-pharmacological interventions have been used to manage OIC with controversial efficacy and safety. Recent studies suggested that, pretreatment of intravenous dezocine (DZC) could completely suppress OIC during anesthesia induction. To address this knowledge lack, we will perform a systemic review and meta-analysis to evaluate the efficacy of DZC on OIC and possible complications. We provide here a protocol that will outline the methods and analyses planned for the systematic review.

Methods

PubMed, Embase, Cochrane Library, Web of Science as well as Chinese BioMedical Literature & Retrieval System(SinoMed), China National Knowledge Infrastructure(CNKI), Wanfang Data and VIP Data will be searched from 1978 to December 31th 2019 to identify all randomized controlled trials(RCTs) comparing DZC with placebo on the incidence and severity of OIC. Primary outcomes of interest include the incidence and severity of OIC. Secondary outcomes of interest include possible complications or adverse effects of DZC. Two authors will independently extract relevant variables and outcome data. For continuous variables,

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Ethics and dissemination

This study is a protocol of meta-analysis of previously published literatures, ethical approval was not necessary according to the Ethical Committee of Fuwai Hospital. The study will be submitted to a peer- reviewed journal and disseminated via research presentations.

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Keywords: dezocine, opioid, cough, general anesthesia, meta-analysis

Strengths and limitations of this study

- The protocol describes what will be the first systematic review to conduct a comprehensive assessment of the efficacy of DZC on OIC and possible complications.

- The exclusion of trials absent of OIC incidence or placebo control group might leave relevant studies out of the review.
- The main limitation of this review is that varied quality and heterogeneity of included studies may limit the certainty of the findings of meta-analysis.

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Cough is often observed when administrating a bolus of opioids (*e.g.* fentanyl[1-4], sufentanil[5-7], remifentanil[8-13], alfentanil[14]), with the reported incidence ranging from 7% to 70%[1-14]. The mechanism of opioid-induced cough (OIC) is complex and remains poorly understood, which may involve pulmonary chemoreflex, enhanced activity of parasympathetic nerve, histamine release, opioid receptor dualism and muscular rigidity[1-3,15-17]. Besides, factors such as age, race, gender and familial inheritance may also play a role in OIC[3,18]. OIC is mostly transient, benign and self-limiting, but could be associated with adverse effects such as hypertension, tachycardia, increased intra-cranial, ocular and abdominal pressures, and airway obstruction[1,2,15-20], which are especially undesirable during the induction of general anesthesia. Numerous pharmacological interventions including lidocaine, atropine, magnesium sulfate($MgSO_4$), dexamethasone, propofol, midazolam, muscular relaxant, ketamine, pentazocine, tramadol, α_2-agonists, ß2-agonists, sodium chromoglycate, beclomethasone, salbutamol, dextromethorphan, *etc*, and non-pharmacological interventions such as priming, dilution and slow injection of opioids, have been used to manage OIC[1,2,4-9,11-13,15,17,18,20-23]. Unfortunately, the efficacy and safety of those anti-tussive interventions remains controversial.

Dezocine(DZC), a mixed opioid agonist/antagnost, was synthesized in

1970s and approved by the Food and Drug Administration of US for perioperative pain management but was discontinued with the closure of its parent company[24-28]. Although no longer used clinically in Western countries, DZC has gained popularity in China and been widely used as a peri-operative analgesic for decades[25,29-33]. Recent studies suggested that, pretreatment of intravenous DZC could completely suppress the cough induced by bolus injection of fentanyl or sufentanil during anesthesia induction. For example, Sun *et al*[4] demonstrated that no fentanyl-induced cough (FIC) was observed in DZC group. In another RCT, Liu and colleagues[6] shared the same suppressive effect of DZC on sufentanil-induced cough (SIC). It is so encouraging that, DZC might be more effective than those above-mentioned anti-tussive interventions, and could possibly eliminate OIC without causing OIC itself. Therefore, we will perform a systemic review and meta-analysis to evaluate the efficacy of DZC on OIC during general anesthesia induction, and possible complications.

Objectives

To systematically review the effects of DZC on the incidence and severity of OIC and possible complications during general anesthesia induction.

Methods and analysis

This protocol follows the Preferred Reporting Items for Systematic

Review and Meta-Analysis Protocols (PRISMA-P) checklist[34]. The systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[35].

Patient and public involvement statement

There will be no patient or public involved in this systematic review and meta-analysis.

Inclusion and exclusion criteria

We will include all RCTs comparing DZC with placebo or blank with respect to their effects on OIC. In studies which also included other comparator drugs, only data of DZC and placebo groups will be abstracted. Primary outcomes of interest include the incidence and severity of OIC. The severity of OIC will be graded as mild (1-2 coughs), moderate (3-4 coughs), or severe (≥5 coughs)[18]. Secondary outcomes of interest include the incidence of possible complications or adverse effects of DZC such as respiratory inhibition, nausea and emesis, truncal rigidity, dizziness, drowsiness and chill. Exclusion criteria include (1)studies published as review, case report or abstract; (2)animal or cell studies; (3)duplicate publications; (4)studies lacking information about outcomes of interest. The two authors will independently review the titles and abstracts of all identified studies for eligibility, excluding obviously ineligible ones. The eligibility of those remaining studies for final inclusion will be further determined by reading the full text.

Search strategy

We will conducted a systemic review according to the Preferred Reporting Items for Systemic Reviews and Meta-Analysis Quality of Reporting of Meta-analysis(PRIMSA) Guidelines[35]. The protocol of current meta-analysis was published in PROSPERO with the registration number of CRD42019141255. Relevant trials will be identified by computerized searches of PubMed, Embase, Cochrane Library, Web of Science till December 31th 2019, using different combination of search words as follows: *(opioid OR fentanyl OR sufentanil OR remifentanil OR alfentanil) AND cough AND dezocine AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR randomly OR trial)*(**Table 1**). No language restriction will be used. We will also search Chinese BioMedical Literature & Retrieval System(SinoMed), China National Knowledge Infrastructure（CNKI）， Wanfang Data and VIP Data(from 1978 to December 31th 2019). Additionally, we will use the bibliography of retrieved articles to further identify relevant studies.

Study quality assessment

Two authors will independently assess the risk of bias, using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions[36]. The Cochrane collaboration's tool for assessing risk of bias will be used independently by two authors to evaluate the methodological quality of each included trial. The domains considered

included (1)random sequence generation(selection bias), (2)allocation concealment(selection bias), (3)blinding of participants and personnel(performance bias), (4)blinding of outcome assessment(detection bias), (5)incomplete outcome data(attrition bias), (6)selective reporting(reporting bias), and (7)other bias. Each domain will be deemed to be low risk of bias, uncertain risk of bias and high risk of bias and showed as risk of bias summary and graph.

Data abstraction

The following data will be abstracted from the included studies to a data collection form by two authors independently: (1)author, year of publication and journal of included studies; (2)total number of patients, number of patients in the DZC and control groups, gender, age; (3)data regarding outcomes of interest in both groups. Disagreements will be resolved by discussion among all authors during the process of data abstraction. The authors of the included RCTs will be contacted if necessary.

Statistical analysis

All data will be analyzed by utilizing RevMan 5.3(Cochrane Collaboration, Oxford, UK). Pooled odds ratio(OR) and 95% confidence interval(CI) will be estimated for dichotomous data, and weighted mean difference(WMD) and 95% CI for continuous data, respectively. Each outcome will be tested for heterogeneity, and randomized-effects or fixed-effects model will be

used in the presence or absence of significant heterogeneity(Q-statistical test $P<0.05$). Sensitivity analyses will be done by examining the influence of statistical model on estimated treatment effects, and analyses which adopt the fixed-effects model will be repeated again by using randomized-effects model and *vice versa*. The influence of statistical model on estimated treatment effects will be showed in a table comparing the two models. In addition to that, sensitivity analyses will also be performed to evaluate the influence of individual study on the overall effects. The possible effects of opioid type and doses will be evaluated by subgroup analysis. Subgroup analysis will also be conducted to detect the potential effects of sex, age and heredity if possible. Publication bias will be explored through visual inspection of funnel plots of the outcomes. All *P*-values will be two-sided and statistical significance was defined as $P<0.05$.

Ethics and dissemination

This study is a protocol of meta-analysis of previously published literatures, ethical approval was not necessary according to the Ethical Committee of Fuwai Hospital. The study will be submitted to a peer-reviewed journal and disseminated via research presentations.

Authors' contributions

Li-xian He: The first author. Substantial contributions to the conception and design of the work; the acquisition, analysis, interpretation of data for the work; And drafting the work or revising it critically for important

intellectual content; And final approval of the version to be published.

Ken Shao, Yuan-yuan Zhao and Jie Ma: Substantial contributions to the acquisition, analysis; Revising the work critically; Final approval of the version to be published.

Yun-tai Yao: Corresponding author. Substantial contributions to the conception and design of the work; Revising the work critically for important intellectual content; Final approval of the version to be published.

All authors are agree to be accountable for all aspects of the work.

Competing interests

The authors declare that they have no competing interests.

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Data sharing statement

No additional unpublished data are available.

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Table 1. Search strategy

PubMed	
No.	**Search items**
#1	"dezocine"[Supplementary Concept] OR dezocine[Title/Abstract]
#2	((((((((((((((Analgesics, Opioid[MeSH Terms]) OR Opioid[Title/Abstract]) OR Fentanyl[MeSH Terms]) OR Fentanyl[Title/Abstract]) OR Phentanyl[Title/Abstract]) OR Fentanyl Citrate[Title/Abstract]) OR Sufentanil[MeSH Terms]) OR Sufentanil[Title/Abstract]) OR Sulfentanyl[Title/Abstract]) OR Sulfentanil[Title/Abstract]) OR Sufentanil Citrate[Title/Abstract]) OR Remifentanil[MeSH Terms]) OR Remifentanil[Title/Abstract]) OR Remifentanil Hydrochloride[Title/Abstract]) OR Alfentanil[MeSH Terms]) OR Alfentanil[Title/Abstract]) OR Alfentanyl[Title/Abstract]) OR Alfentanil Hydrochloride[Title/Abstract]
#3	((((Cough[MeSH Terms]) OR Cough[Title/Abstract]) OR Coughs[Title/Abstract]) OR Antitussive[Title/Abstract]) OR Anti-tussive[Title/Abstract]
#4	((((((Randomized Controlled Trial[Publication Type]) OR Randomized Controlled Trial) OR Controlled Clinical Trial[Publication Type]) OR Controlled Clinical Trial) OR Randomized) OR Placebo) OR randomly
#5	#1 AND #2 AND #3 AND #4

Embase

('dezocine'/exp OR dezocine:ab,ti) AND ('opiate agonist'/exp OR opioid:ab,ti OR 'fentanyl derivative'/exp OR fentanyl:ab,ti OR 'fentanyl citrate':ab,ti OR sufentanil:ab,ti OR 'sufentanil citrate':ab,ti OR remifentanil:ab,ti OR alfentanil:ab,ti) AND ('coughing'/exp OR coughing:ab,ti OR cough:ab,ti OR antitussive:ab,ti OR anti-tussive:ab,ti) AND ('randomized controlled trial'/exp OR 'randomized controlled trial':it OR 'randomized controlled trial':ab,ti OR randomized OR placebo OR randomly)

Cochrane Library

No.	Search items
#1	(dezocine): ti, ab, kw
#2	[Analgesics, Opioid] explode all trees OR (opioid): ti, ab, kw OR [Fentanyl] explode all trees OR (fentanyl): ti, ab, kw OR (fentanyl citrate): ti, ab, kw OR (phentanyl): ti, ab, kw OR [Sufentanil] explode all trees OR (sufentanil): ti, ab, kw OR (sufentanil citrate): ti, ab, kw OR (sulfentanyl): ti, ab, kw OR [Remifentanil] explode all trees OR (remifentanil): ti, ab, kw OR (remifentanil monohydrochloride): ti, ab, kw OR (remifentanil hydrochloride): ti, ab, kw OR [Alfentanil] explode all trees OR (alfentanil): ti, ab, kw OR (alfentanil hydrochloride): ti, ab, kw OR (alfentanyl): ti, ab, kw
#3	[Cough] explode all trees OR (cough): ti, ab, kw OR (coughs): ti, ab, kw OR (antitussive):ti, ab, kw OR (anti-tussive):ti, ab, kw

#4	[Randomized Controlled Trial] explode all trees OR (Randomized Controlled Trial): ti, ab, kw OR [Randomized Controlled Trials as Topic] explode all trees OR [Controlled Clinical Trial] explode all trees OR (Controlled Clinical Trial): ti, ab, kw OR [Controlled Clinical Trial as Topic] explode all trees
#5	#1 AND #2 AND #3 AND #4

Web of Science

TS=dezocine AND TS=(opioid OR opioid OR "Analgesics, Opioid" OR fentanyl OR phentanyl OR "fentanyl citrate" OR sufentanil OR sulfentanyl OR "sufentanil citrate" OR remifentanil OR "remifentanil hydrochloride" OR alfentanil OR alfentanyl OR "alfentanil hydrochloride") AND TS=(cough OR coughs OR coughing OR antitussive OR anti-tussive) AND TS=("randomized controlled trial" OR "controlled clinical trial" OR randomized OR placebo OR randomly)

SinoMed

No.	Search items
#1	"地佐辛"[不加权:扩展] OR "地佐辛"[摘要:智能]
#2	"阿片"[不加权:扩展] OR "阿片"[中文标题:智能] OR "镇痛药,"[不加权:扩展] AND "阿片类"[不加权:扩展] OR "芬太尼"[不加权:扩展] OR "芬太尼"[中文标题:智能] OR "舒芬太尼"[不加权:扩展] OR "舒芬太尼"[中文标题:智能] OR "瑞芬太尼"[中文标题:智能] OR "阿芬太尼"[不加权:扩展] OR "阿芬太尼"[中文标题:智能]

#3 "咳嗽"[不加权:扩展] OR "咳嗽"[中文标题:智能] OR "呛咳"[中文标题:智能] OR "止咳"[不加权:扩展] OR "止咳"[中文标题:智能] OR "镇咳"[不加权:扩展] OR "镇咳"[中文标题:智能]

#4 "随机对照试验"[不加权:扩展] OR "临床对照试验"[不加权:扩展] OR "随机地"[摘要:智能] OR "随机的"[摘要:智能] OR "对照"[摘要:智能] OR "安慰剂"[摘要:智能]

#5 #1 AND #2 AND #3 AND #4

CNKI

(SU='地佐辛' OR AB='地佐辛') AND (SU=('阿片'+'阿片类镇痛药'+'芬太尼'+'舒芬太尼'+'瑞芬太尼'+'阿芬太尼') OR TI=('阿片'+'阿片类镇痛药'+'芬太尼'+'舒芬太尼'+'瑞芬太尼'+'阿芬太尼')) AND (SU=('咳嗽'+'呛咳'+'止咳'+'镇咳') OR TI=('咳嗽'+'呛咳'+'止咳'+'镇咳')) AND (SU=('随机对照试验'+'临床对照试验'+'随机的'+'随机地'+'安慰剂'+'对照') OR AB=('随机对照试验'+'临床对照试验'+'随机的'+'随机地'+'安慰剂'+'对照'))

Wanfang Data

(主题:地佐辛+摘要:地佐辛)*(主题:(阿片+阿片类镇痛药+芬太尼+舒芬太尼+瑞芬太尼+阿芬太尼)+题名:(阿片+阿片类镇痛药+芬太尼+舒芬太尼+瑞芬太尼+阿芬太尼))*(主题:(咳嗽+呛咳+止咳+镇咳)+题名:(咳嗽+呛咳+止咳+镇咳))*(主题:(随机对照试验+临床对照试验+随机的+随机地+安慰剂+对照)+ 摘要:(随机对照试验+临床对照试验+随机的+随机地+安慰剂+对照))

VIP Data

(M=地佐辛 OR R=地佐辛) AND (M=阿片 OR 阿片类镇痛药 OR 芬太尼 OR 舒芬太尼 OR 瑞芬太尼 OR 阿芬太尼 OR R=阿片 OR 阿片类镇痛药 OR 芬太尼 OR 舒芬太尼 OR 瑞芬太尼 OR 阿芬太尼) AND (M=咳嗽 OR 呛咳 OR 止咳 OR 镇咳 OR R=咳嗽 OR 呛咳 OR 止咳 OR 镇咳) AND (M=随机对照试验 OR 临床对照试验 OR 随机的 OR 随机地 OR 安慰剂 OR 对照 OR R=随机对照试验 OR 临床对照试验 OR 随机的 OR 随机地 OR 安慰剂 OR 对照)

PRISMA-P 2015 checklist

Section and topic	Item No	Checklist item	Page No
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title, page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	None
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Abstract, page 3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Authors' contributions, page 10-11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	None
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Funding, page 11
Sponsor	5b	Provide name for the review funder and/or sponsor	Funding, page 11

Section and topic	Item No	Checklist item	Page No
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Funding, page 11
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	Introduction, page 5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Introduction, page 6
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Methods and analysis, page 6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Methods and analysis, page 8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Methods and analysis, page 8 and Table 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Methods and analysis, page 8-9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in	Methods and analysis, page 8-9

Section and topic	Item No	Checklist item	Page No
		meta-analysis)	
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Methods and analysis, page 8-9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Methods and analysis, page 8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Methods and analysis, page 7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Methods and analysis, page 8-10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Methods and analysis, page 9-10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Methods and analysis, page 9-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Methods and analysis, page 9-10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Methods and analysis, page 9-10

Section and topic	Item No	Checklist item	Page No
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Methods and analysis, page 9-10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Methods and analysis, page 8-9