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Efficacy of dezocine on preventing opioid-induced cough during general anaesthesia induction: a PRISMA-compliant systematic review and meta-analysis

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ABSTRACT

Objectives To systematically review the effects of dezocine (DZC) on the occurrence rate and severity of opioid-induced cough (OIC).

Design Systematic review and meta-analysis

Data sources PubMed, Embase, Cochrane Library, Ovid, Web of Science as well as Chinese BioMedical Literature & Retrieval System, China National Knowledge Infrastructure, Wanfang and VIP Data were searched from 1978 to 31 December 2020.

Inclusion criteria All randomised controlled trials (RCTs) comparing DZC with placebo on the occurrence rate and severity of OIC.

Data analysis All data were analysed by using RevMan V.5.3. Each outcome was tested for heterogeneity, and randomised-effects or fixed-effects model was used in the presence or absence of significant heterogeneity.

Results Our search yielded 33 RCTs including 4442 patients, and 2521 patients were allocated into the DZC group and 1921 into the control group. Fentanyl was administrated in 1880 patients and sufentanil in 2562 patients during the induction of general anaesthesia. The meta-analysis demonstrated that DZC significantly reduced the occurrence rate of OIC induced by either fentanyl (8.8% vs 49.7%, OR=0.07, 95% CI 0.04 to 0.12, $p<0.00001$) or sufentanil (5.0% vs 41.5%, OR=0.07, 95% CI 0.04 to 0.12, $p<0.00001$). The meta-analysis also indicated that the occurrence rate of mild, moderate and severe OIC in the DZC group was remarkably lower than that of the control group (mild: 3.6% vs 13.6%, OR=0.19, 95% CI 0.14 to 0.25, $p<0.00001$; moderate: 2.0% vs 13.6%, OR=0.12, 95% CI 0.09 to 0.18, $p<0.00001$; severe: 1.0% vs 13.9%, OR=0.08, 95% CI 0.05 to 0.12, $p<0.00001$). Additionally, the current meta-analysis indicated that DZC pretreatment was not associated with increased occurrence rate of adverse effects (7.0% vs 4.2%, OR=2.34, 95% CI 0.60 to 9.14, $p=0.22$) except for dizziness (11.8% vs 0%, OR=8.06, 95% CI 1.40 to 46.35, $p=0.02$).

Conclusion This meta-analysis demonstrated that DZC significantly inhibited OIC and may be used to manage OIC. More high-quality RCTs are needed to complement the safety of DZC.

PROSPERO registration number CRD42019141255.

Strengths and limitations of this study

- ► This is the first systematic review to investigate the occurrence rate of opioid-induced cough induced by either fentanyl or sufentanil.
- ► Subgroup analyses were performed on dose-effect of dezocine (DZC) and various kinds of opioids to investigate the optimal dosage of DZC.
- ► 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 (eg, fentanyl,[1–4] sufentanil,[5–7] remifentanil,[8–13] alfentanil,[14] with the reported occurrence rate 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 intracranial, 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 anaesthesia. 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

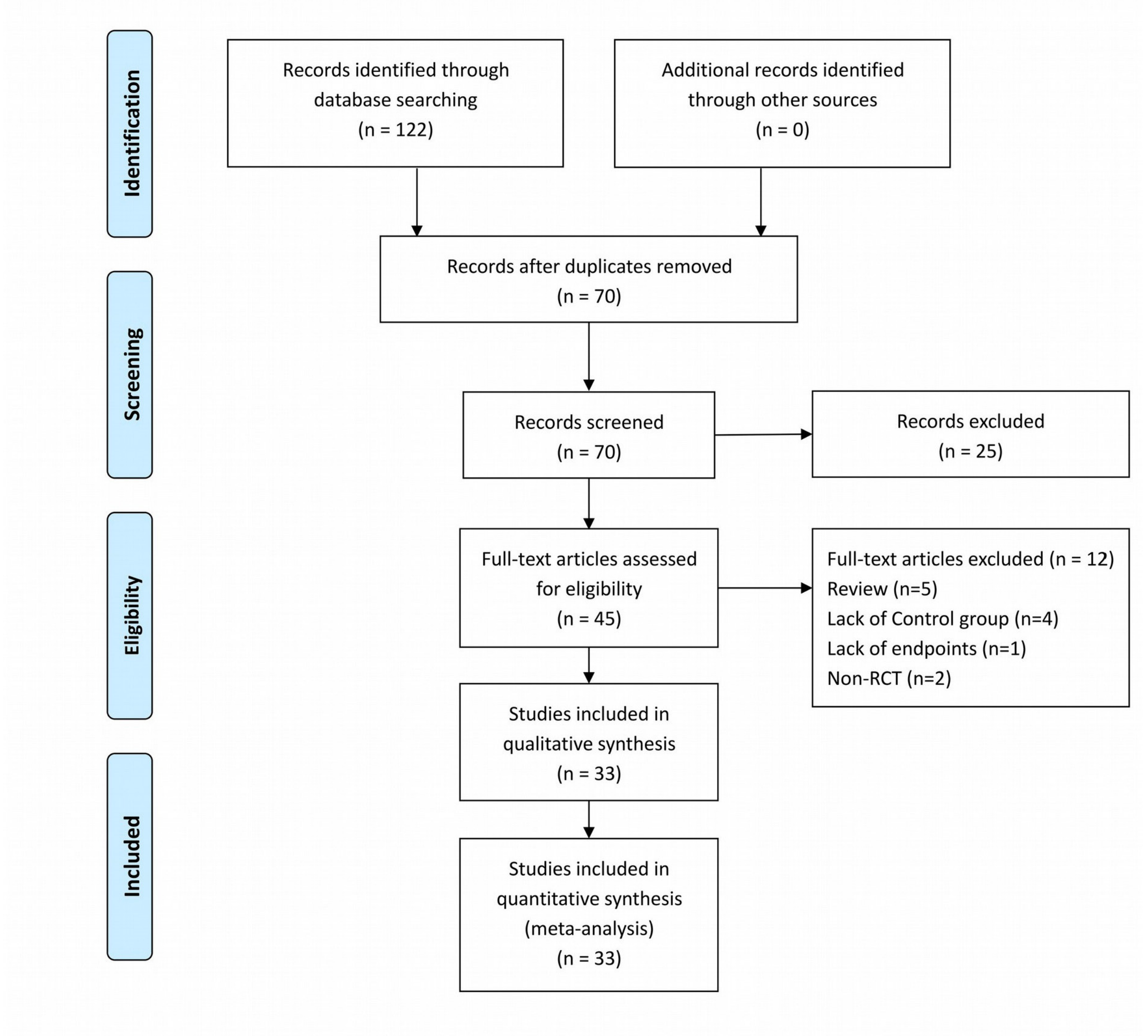

Figure 1 Flowchart.

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 antitussive interventions remain controversial.

Dezocine (DZC), a mixed opioid agonist/antagnost, was synthesised in 1970s and approved by the FDA 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 perioperative analgesic for decades.[24 28–32] Recent studies suggested that pretreatment of intravenous DZC 0.1 mg/kg could completely suppress the cough induced by bolus injection of fentanyl or sufentanil during anaesthesia induction. For example, Sun and colleagues[4] evaluated the suppressive effect of DZC on fentanyl-induced cough (FIC). One hundred and twenty patients were randomised to receive DZC 0.1 mg/kg or placebo 10 min before fentanyl 5 µg/kg. They demonstrated that no DZC-pretreated patient had FIC, as compared with 70% (42/60) non-DZC-pretreated patients developing FIC. In another randomised controlled trials (RCT) involving 370 patients, Liu and colleagues[6] evaluated the antitussive effect of DZC 0.1 mg/kg on sufentanil-induced cough (SIC) during anaesthesia induction. They demonstrated the occurrence rate of SIC in the placebo group, which 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 antitussive interventions, and that DZC could possibly eliminate OIC without causing OIC itself. Therefore, we performed this systemic review and meta-analysis to evaluate the efficacy of DZC on OIC during general anaesthesia induction and possible adverse effects.

METHODS

Patient and public involvement

No patient involved.

Table 1 Characteristics of the included RCTs and administration protocols of dezocine

Study	Language	Patient characteristics: Age (years)	Patient characteristics: Sex (M/F)	Opioids: Type	Opioids: Dose (μg/kg)	Opioids: Duration (s)	Opioids: Timing (min)	Group dezocine: n	Group dezocine: Dose (mg/kg)	Group control: n	Group control: Dose	Outcomes reported: CID	Outcomes reported: CIC	Outcomes reported: SCID	Outcomes reported: SCIC	Outcomes reported: Adverse effect
Qing-Ming *et al*[36]	Chinese	23–64	48/53	S	3.0	≤5 s	5	50	5 mg	50	Equal volume NS	2.00%	30.00%	0	6.00%	NR
Xiao-Ming and Guang-Hong[37]	Chinese	20–60	39/41	S	2.0	≤2 s	NR	40	5 mg	40	2 mL NS	5.00%	45.00%	0	25.00%	NR
Liang[38]	Chinese	20–60	66/58	F	5.0	≤3 s	10	62	0.1	62	Equal volume NS	9.68%	62.90%	NR	NR	NR
Ya-Ping *et al*[39]	Chinese	20–50	0/120	F	3.0 3.0 3.0	NR	10	40 40 40	0.05 0.1 0.15	14 13 13	5 mL NS	57.50% 17.50% 15.00%	64.29% 53.85% 53.85%	17.5% 2.5% 2.5%	20.00%	NR
Li Yan-Juan[40]	Chinese	23–72	134/106	S	0.3 0.3	≤10 s	10	80 80	0.05 0.1	40 40	Equal volume NS	2.50% 1.25%	32.50% 35.00%	0	7.50%	NR
Liu *et al*[6]	English	18–70	189/181	S	0.5	> 3 s	2	185	0.1	185	NS	0.00%	31.89%	0	13.51%	NR
Zhen-zhen *et al*[41]	Chinese	28–55	39/41	S	0.4	≤2 s	2	40	0.1	40	Equal volume NS	0.00%	72.50%	NR	NR	NR
Ming-fang *et al*[42]	Chinese	22–65	51/49	F	4.0	≤3 s	10	50	0.1	50	Equal volume NS	12.00%	68.00%	NR	NR	NR
Jian-Bin[43]	Chinese	20–65	119/81	S	0.5	NR	NR	100	5 mg	100	2 mL NS	5.00%	45.00%	0	39.00%	NR
Liang-Cheng *et al*[44]	Chinese	18–45	0/120	F	3.0	≤5 s	2	60	0.1	60	5 mL NS	1.67%	25.00%	0	3.33%	NR
Hui *et al*[45]	Chinese	18–65	40/80	F	4.0	≤5 s	2	60	0.05	60	Equal volume NS	0.00%	26.67%	0	11.67%	NR
Tian-yi *et al*[46]	Chinese	24–55	NR	S	0.4	NR	10	35	0.1	35	Equal volume NS	5.71%	57.14%	0	28.57%	NR
Jie *et al*[47]	Chinese	20–65	0/120	S	0.3	< 5 s	5	60	0.05	60	5 mL NS	8.33%	28.33%	3.33%	10.00%	NR
Da-Wei *et al*[48]	Chinese	19–70	44/52	S	0.3	≤10 s	8	48	0.1	48	5 mL NS	0.00%	64.58%	NR	NR	CH, RI, NE
Sun *et al*[4]	Chinese	20–60	68/52	F	5.0	≤2 s	10	60	0.1	60	NS	0.00%	70.00%	NR	NR	NR
Li *et al*[49]	Chinese	15–60	78/62	F	5.0	≤5 s	10	70	0.1	70	10 mL NS	1.43%	75.71%	NR	NR	NR
Jun-Liang and Rong[50]	Chinese	18–70	190/180	S	0.5	NR	Immediately	185	0.1	185	Equal volume NS	0.00%	31.89%	0	29.41%	TR, RI, NE
Zhi-Yong[51]	Chinese	22–61	67/53	S	NR	NR	NR	60	0.05	60	NS	16.67%	55.00%	0	6.67%	NR
Hui and En-Ming[52]	Chinese	25–65	42/58	S	0.3	< 5 s	10	50	0.1	50	2 mL NS	2.00%	32.00%	0	8.00%	NR
Li-Ping[53]	Chinese	60–85	59/41	S	0.3 0.3 0.3	≤5 s	5	25 25 25	0.04 0.08 0.12	9 8 8	5 mL NS	28.00% 12.00% 8.00%	44.44% 37.50% 37.50%	NR	NR	DI, DR

Continued

Table 1 Continued

Study	Language	Patient characteristics		Opioids				Group dezocine		Group control		Outcomes reported				
		Age (years)	Sex (M/F)	Type	Dose (µg/kg)	Duration (s)	Timing (min)	n	Dose (mg/kg)	n	Dose	CID	CIC	SCID	SCIC	Adverse effect
Zhi and Feng[54]	Chinese	18–55	31–29	F	4	≤3 s	1	30	0.1	30	2 mL NS	13.33%	53.33%	0	23.33%	NR
Wen-Feng and Yong-Hua[55]	Chinese	18–55	33–27	F	4	≤3 s	1	30	0.1	30	2 mL NS	16.67%	50.00%	0	16.67%	NR
Wu 2014[56]	Chinese	18–60	105/55	F	3 3 3	< 3 s	10	40 40 40	0.1 0.2 0.3	14 13 13	Equal volume NS	7.50% 2.50% 0.00%	71.43% 61.54% 61.54%	0	15.00%	NR
Qing *et al*[57]	Chinese	20–65	102/98	S	0.5 0.5	< 3 s < 30 s	5 5	50 50	0.1 0.1	50 50	5 mL NS	6.00% 2.00%	80.00% 8.00%	0 0	7.50% 0	NR
Xu *et al*[35]	English	20–70	243/157	F	3 3 3	< 5 s	Immediately	100 100 100	0.025 0.05 0.1	34 33 33	NS	12.00% 4.00% 0.00%	41.18% 39.39% 39.39%	0	5.00%	NR
Ming-Feng and Yu[58]	Chinese	25–55	NR	F	3 3 3	NR	10	30 30 30	0.05 0.1 0.2	10 10 10	NS	56.67% 13.33% 6.67%	60.00% 60.00% 60.00%	26.67% 0 0	33.33%	DI, DR
Jian-Feng and Han-Zhong[59]	Chinese	25–56	41/39	F	3	< 3 s	12	40	0.1	40	2 mL NS	2.50%	45.00%	0	6.67%	NR
Ji-Hong[60]	Chinese	23–56	72/48	F	4	≤3 s	5	30	5 mg	30	10 mL NS	3.33%	46.67%	0	22.50%	NR
Lu-Hong[61]	Chinese	20–61	19/33	S	5	NR	5–8	26	0.1	26	NS	7.69%	65.38%	0	19.23%	NR
Qin-Shu[62]	Chinese	39±5	61/39	S	0.4 0.4 0.4	≤3 s	1 3 8	25 25 25	2 mg 2 mg 2 mg	9 8 8	Equal volume NS	28.00% 4.00% 4.00%	66.67% 50.00% 50.00%	0	8.00%	NR
Xiao-Zhen *et al*[63]	Chinese	18–56	92/108	S	0.4	≤6 s	3	50	5 mg	50	Equal volume NS	16.00%	44.00%	0	8.00%	NR
Tao-Yu *et al*[64]	Chinese	18–65	23/37	S	0.3	< 10 s	10	30	0.1	30	5 mL NS	0.00%	26.67%	0	3.33%	DI, DR
Fang[65]	Chinese	22–75	31/29	S	0.4	NR	2	30	0.1	30	Equal volume NS	3.33%	13.33%	NR	NR	NE

CH, chill; CIC, cough occurrence rate of control; CID, cough occurrence rate of dezocine; DI, dizziness; DR, drowsiness; NE, nausea and emesis; NR, not reported; RCT, randomised controlled trial; RI, respiratory inhibition; SCIC, severe cough occurrence rate of control; SCID, severe cough occurrence rate of dezocine; TR, truncal rigidity.

Registration

The protocol of current meta-analysis was published in PROSPERO on 11 November 2019.

Search strategy

We conducted a systemic review according to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses Quality of Reporting of Meta-analysis (PRIMSA) Guidelines (online supplemental table 1).[33] Relevant trials were identified by computerised searches of PubMed, Embase, Cochrane Library, Ovid, Web of Science as well as Chinese BioMedical Literature & Retrieval System (SinoMed), China National Knowledge Infrastructure (CNKI), Wanfang Data and VIP Data till 31 December 2019, with an updated database search on 31 December 2020 prior to submission, 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*) (online supplemental table 2). No language restriction was used. Additionally, we used the bibliography of retrieved articles to further identify relevant studies.

Criteria for considering studies for this review

We included all RCTs comparing DZC with placebo or blank with respect to their effects on OIC. In studies that also included other comparator drugs, only data of DZC and placebo groups were abstracted. Primary outcomes of interest included the occurrence rate and severity of OIC. The severity of OIC was graded as mild (1–2 coughs), moderate (3–5 coughs) or severe (> 5 coughs).[6] Secondary outcomes of interest include possible adverse effects. Exclusion criteria included (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 (L-XH and KS) independently reviewed the titles and abstracts of all identified studies for eligibility, excluding obviously ineligible ones. The eligibility of those remaining studies for final inclusion was further determined by reading the full text.

Study quality assessment

Two authors (JM and Y-YZ) independently assessed the risk of bias, using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions[34] and GRADE scoring. Each potential source of bias was graded as low, uncertain or high risk of bias and showed as risk of bias summary and graph. The quality of each outcome was assigned a score of high quality, moderate quality, low quality and very low Quality.

Data abstraction

The following data were abstracted from the included studies to a data collection form by two authors (L-XH and KS) 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 were resolved by discussion among all authors during the process of data abstraction. The authors of the included RCTs were contacted if necessary.

Statistical analysis

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

RESULTS

Characteristics of the included trials

As shown in figure 1, initial literature search generated 70 results. Finally, 33 RCTs[4 6 35–65] involving 4442 patients were included in the meta-analysis. Of the 33 RCTs, 30[36–65] were written in Chinese, and the other 3[4 6 35] in English (table 1). The 33 RCTs were performed, respectively, in 2 provincial hospitals,[36 44] 13 affiliated hospitals,[4 6 35 38 41 46 48 49 52 54–56 63] 16 urban hospitals[37 39 40 42 43 45 47 50 51 53 57 59 61 62 64 65] and 2 county hospitals[58 60] from 15 provinces and municipalities in China. All enrolled patients were of American society of Anesthesiologists physical status classification I–II, whose ages ranged from 18 to 85 year (table 1). No included RCT reported the OIC induced by remifentanil or alfentanil. As shown in table 1, fentanyl was administrated in 1880 patients during the induction of general anaesthesia with dosages of 2.0 µg/kg to 5.0 µg/kg and sufentanil in 2562 patients with dosages of 0.3 µg/kg to 5.0 µg/kg. The injection duration of fentanyl and sufentanil varied from 2 s to 30 s. Out of the 4442 patients, 2521 were allocated into the DZC group and 1921 into the control (placebo) group. DZC administration protocols differed among the 33 included trials. DZC was administered intravenously with dosages of 0.025 mg/kg to 0.3 mg/kg (or 2 mg to 5 mg), 1 to 10 min prior to fentanyl or sufentanil injection (table 1).

Methodological quality

The risk of bias analysis is shown in figures 2 and 3. There were no patient withdrawal or dropout, neither selectiveness nor bias in all 33 RCTs.

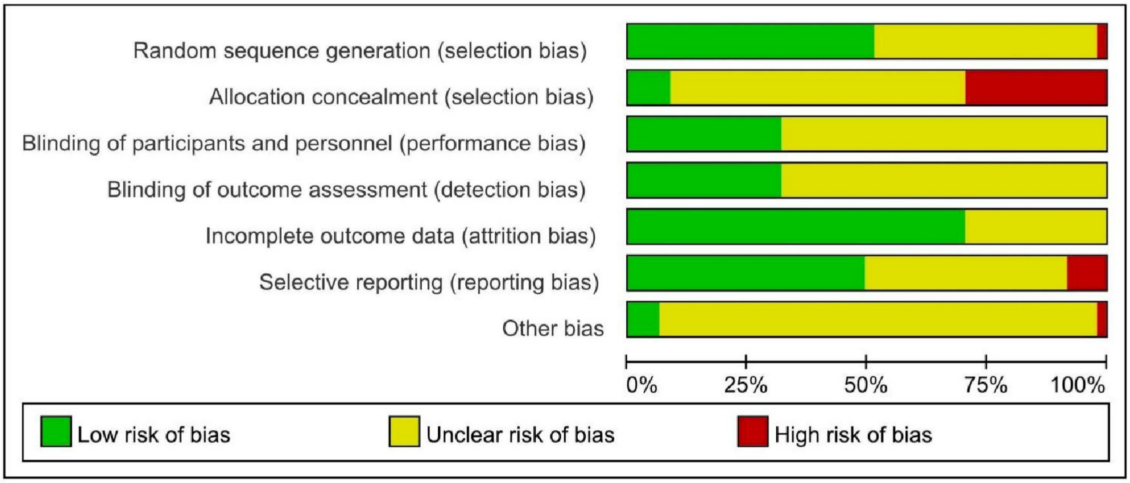

Figure 2 Risk of bias graph.

Quality of evidence

For primary outcome, GRADE scoring shows high quality of evidence on DZC preventing OIC(table 2). While for secondary outcomes, high quality of evidence appeared in drowsiness, moderate quality of evidence in dizziness and nausea, very low quality of evidence in truncal rigidity, chill and respiratory inhibition (table 3).

Effects of interventions

Occurrence rate of OIC

All the 33 included studies reported the occurrence rate of OIC. As shown in figure 4, meta-analysis demonstrated that the occurrence rate of OIC in the DZC group was statistically lower than that of the control group (6.7% vs 44.5%, OR=0.07, 95% CI 0.05 to 0.11, p<0.00001, I^2=56%). To analyse the type effects of opioids (fentanyl and sufentanil), subgroup analysis was performed, which indicated that DZC significantly reduced the occurrence rate of FIC (8.8% vs 49.7%, OR=0.07, 95% CI 0.04 to 0.12, p<0.00001, I^2=61%) and SIC (5.0% vs 41.5%, OR=0.07, 95% CI 0.04 to 0.12, p<0.00001, I^2=53%). As shown in online supplemental figure 1, subgroup analysis demonstrated that the FIC occurrence rate increased from 45.0%, 43.1%, 47.5% to 73.1% in the control group when fentanyl dosage increased from 2, 3, 4 to 5 µg/kg, respectively. Dose effect of sufentanil dosage on the occurrence rate of SIC is shown in online supplemental figure 2.

Twenty-two RCTs[6 35–37 39 40 43 45–47 50–52 56–64] reported the occurrence rate of mild and moderate OIC. As shown in online supplemental figures 3; 4, meta-analysis demonstrated that DZC group showed significantly lower occurrence rate of OIC than control group both on mild and moderate grades (mild OIC: 3.6% vs 13.6%, OR=0.19, 95% CI 0.14 to 0.25, p<0.00001, I^2=22; moderate OIC: 2.0% vs 13.6%, OR=0.12, 95% CI 0.09 to 0.18, p<0.00001, I^2=0). Subgroup analysis demonstrated that DZC significantly reduced the occurrence of either FIC (mild FIC: 5.2% vs 15.3%, OR=0.25, 95% CI 0.16 to 0.38, p<0.00001, I^2=28; moderate FIC: 3.1% vs 14.2%, OR=0.17, 95% CI 0.10 to 0.28, p<0.00001, I^2=0) or SIC (mild SIC: 2.4% vs 12.9%, OR=0.14, 95% CI 0.09 to 0.22, p<0.00001, I^2=11; moderate SIC: 1.1% vs 13.4%, OR=0.10, 95% CI 0.06 to 0.17, p<0.00001, I^2=0) when compared with placebo.

Twenty-five enrolled RCTs[6 35–37 39 40 43–47 50–52 54–64] reported the occurrence rate of severe OIC. As shown in online supplemental figure 5, meta-analysis demonstrated that the occurrence rate of severe OIC in the DZC group was remarkably lower than that of the control group (0.9% vs 13.7%, OR=0.08, 95% CI 0.05 to 0.12, p<0.00001, I^2=0). Subgroup analysis demonstrated that DZC significantly reduced the occurrence of either severe FIC (1.8% vs 13.5%, OR=0.12, 95% CI 0.07 to 0.20, p<0.00001, I^2=0) or severe SIC (0.3% vs 13.9%, OR=0.05, 95% CI 0.03 to 0.10, p<0.00001, I^2=0) when compared with placebo.

Subgroup analyses were also performed to investigate the dose effects of DZC on FIC and SIC occurrence rates. As shown in online supplemental figures 6; 7, DZC could effectively suppress OIC by fentanyl or sufentanil when administered at dosages ranging from less than 0.1 mg/kg to 0.3 mg/kg (or 5 mg). The dose of 0.1 mg/kg is mostly investigated and suggested as the optimal dose. Whether the prophylactic effect of DZC on OIC is dose dependent remains further verification.

Adverse effects

Six RCTs[48 50 53 58 64 65] reported possible side effects of DZC administration. As shown in figure 5, meta-analysis suggested that the occurrence rates of drowsiness, truncal rigidity, chill, respiratory inhibition, nausea and emesis of the DZC group were all comparable to those of the control group, with exception that the DZC-treated patients had higher occurrence rate of dizziness as compared with placebo (11.8% vs 0%, OR=8.06, 95% CI 1.40 to 46.35, p=0.02, I^2=0%).

Sensitivity analyses and publication bias

Sensitivity analysis showed that treatment effects on all the outcomes were not affected by the choice of statistical model (table 4). Sensitivity tests were also performed by exclusion of some studies to analyse the influence of the

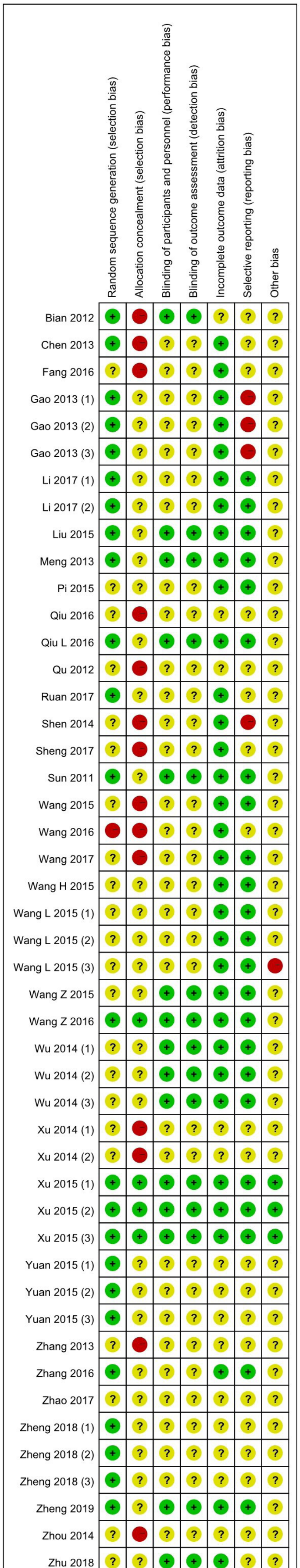

Figure 3 Risk of bias summary.

overall treatment effect on high heterogeneity outcomes (table 4), and no contradictory results were found in pooled OR and 95% CI. For occurrence rate of OIC, heterogeneity changed from 61% to 35% for FIC by exclusion of three studies conducted from Ya-Ping *et al* (female patients only),[39] Li *et al*[49] and Ming-Feng and Yu[58] (preoperative medication with phenobarbital) and 53% to 36% for SIC by exclusion of four studies conducted from Jie *et al* (female patients only),[47] Qing *et al* (duration of sufentanil injection more than 10 s),[57] Li-Ping[53] and Xiao-Zhen *et al*[63] (preoperative medication with phenobarbital). For occurrence rate of adverse effects, heterogeneity changed from 73% to 0% by exclusion of one study from Sheng *et al* (preoperative medication with phenobarbital).[48] No significant publication bias was detected by funnels plot examination for the occurrence rate of OIC (online supplemental figure 8A) and the occurrence rate of mild, moderate and severe OIC (online supplemental figure 8B, online supplemental figure 8C and online supplemental figure 8D).

DISCUSSION

Cough suppression is one useful side effect of opioids, which is the basis of their use in cough suppressants. Opioids depress the cough reflex by directly acting on the medullary cough centre.[16] Fentanyl and its derivatives sufentanil are commonly used opioid analgesics in the induction and maintenance of general anaesthesia. Intravenous bolus injection of fentanyl or sufentanil often cause cough. The present meta-analysis demonstrated that the occurrence rates of FIC and SIC were 49.7% and 41.5%, respectively, the occurrence rates of severe FIC and severe SIC were 13.5% and 13.9%, respectively, which is consistent with previous reports.[2 4 6 7 15] However, significant heterogeneity was found in the results, which may have affected the rigour of those findings. The heterogeneity may be explained by study design. For example, sex of the patients in excluded study in sensitivity analysis was obviously different from others. It was reported by Solanki *et al*[66] that occurrence rate of FIC was low when studied in female cancer patients (12.7%). However, contradictory results of 57.5% and 28.3% were observed in the two excluded study enrolling women only.[39 47] This may suggest that sex to some extent contributes to heterogeneity. In addition to that, study from Qing *et al*[57] with significant low SIC occurrence rate (3% in DZC group and 8% in Control group) was excluded owing to prolonged injection time (>30 s) in sensitivity analysis, which though made no influence on pooled effect, may improve the credibility of current meta-analysis.

Till now, the mechanism of OIC remains poorly understood. Various hypotheses have been proposed, which may involve opioid receptors, C-fibre receptors, rapid adapting pulmonary stretch receptors, histamine release and citrate in fentanyl and sufentanil injection.[1–3 15–17] Additionally, many factors can contribute to the occurrence of OIC, which can be divided into two categories.

Table 2 Quality assessment for primary outcomes

Quality assessment							Number of patients		Effect			Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DZC**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	
Effect of DZC on OIC occurrence rate												
47	Randomised trials	Serious	Serious	No serious indirectness	Serious	Strong association reduced effect for RR>>1 or RR<<1 dose response gradient	169/2521 (6.7%)	857/1921 (44.6%)	OR 0.07 (0.05 to 0.1)	393 fewer per 1000 (from 372 fewer to 407 fewer)	ÅÅÅÅ HIGH	CRITICAL
								50%		435 fewer per 1000 (from 409 fewer to 452 fewer)		
Effect of DZC on FIC occurrence rate												
23	Randomised trials	Serious	Serious	No serious indirectness	Serious	Strong association reduced effect for RR>>1 or RR<<1 dose response gradient	101/1150 (8.8%)	363/730 (49.7%)	OR 0.07 (0.04 to 0.12)	433 fewer per 1000 (from 391 fewer to 459 fewer)	ÅÅÅÅ HIGH	CRITICAL
								53.9%		463 fewer per 1000 (from 416 fewer to 494 fewer)		
Effect of DZC on SIC occurrence rate												
24	Randomised trials	Serious	Serious	No serious indirectness	Serious	Strong association reduced effect for RR>>1 or RR<<1 dose response gradient	68/1371 (5%)	494/1191 (41.5%)	OR 0.07 (0.04 to 0.12)	368 fewer per 1000 (from 336 fewer to 387 fewer)	ÅÅÅÅ HIGH	CRITICAL
								44.2%		389 fewer per 1000 (from 355 fewer to 411 fewer)		

DZC, dezocine; FIC, fentanyl-induced cough; OIC, opioid-induced cough; SIC, sufentanil-induced cough.

Table 3 Quality assessment for secondary outcomes

Quality assessment							Number of patients		Effect			
Numbero of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DZC	Control	Relative (95% CI)	Absolute	Quality	Importance
Dizziness												
3	Randomised trials	Serious	Serious	No serious indirectness	Serious	Strong association reduced effect for RR>>1 or RR<<1	10/85 (11.8%)	0/85 (0%) 0%	OR 8.06 (1.40 to 46.35)	– –	ÅÅÅO MODERATE	IMPORTANT
Drowsiness												
3	Randomised trials	Serious	No serious inconsistency	No serious indirectness	Serious	Strong association reduced effect for RR>>1 or RR<<1	6/85 (7.1%)	0/85 (0%) 0%	OR 4.91 (0.80 to 30.19)	– –	ÅÅÅÅ HIGH	IMPORTANT
Truncal rigidity												
1	Randomised trials	Very serious	No serious inconsistency	No serious indirectness	Serious	None	4/185 (2.2%)	0/185 (0%) 0%	OR 9.2 (0.49 to 172.07)	– –	ÅOOO VERY LOW	CRITICAL
Chill												
1	Randomised trials	Serious	Serious	No serious indirectness	Very serious	None	2/48 (4.2%)	11/48 (22.9%) 22.9%	not pooled	not pooled not pooled	ÅOOO VERY LOW	IMPORTANT
Respiratory inhibition												
2	Randomised trials	Serious	Very serious	No serious indirectness	Serious	None	17/233 (7.3%)	9/233 (3.9%) 9.4%	OR 1.7 (0.00 to 766.69)	25 more per 1000 (from 39 fewer to 930 more) 56 more per 1000 (from 94 fewer to 894 more)	ÅOOO VERY LOW	CRITICAL
Nausea and emesis												
3	Randomised trials	Serious	Serious	No serious indirectness	No serious imprecision	Reduced effect for RR>>1 or RR<<1	24/263 (9.1%)	18/263 (6.8%) 6.7%	OR 1.32 (0.03 to 53.18)	20 more per 1000 (from 66 fewer to 728 more) 20 more per 1000 (from 65 fewer to 725 more)	ÅÅÅO MODERATE	IMPORTANT

DZC, dezocine.

Study or Subgroup	Dezocine Events	Dezocine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
2.1.1 Fentayl						
Bian 2012	1	50	15	50	1.8%	0.05 [0.01, 0.38]
Chen 2013	2	40	18	40	2.4%	0.06 [0.01, 0.30]
Gao 2013 (1)	23	40	9	14	2.8%	0.75 [0.21, 2.65]
Gao 2013 (2)	7	40	7	13	2.7%	0.18 [0.05, 0.71]
Gao 2013 (3)	6	40	7	13	2.6%	0.15 [0.04, 0.61]
Pi 2015	6	50	34	50	3.2%	0.06 [0.02, 0.18]
Qiu L 2016	1	60	15	60	1.8%	0.05 [0.01, 0.40]
Qu 2012	0	60	16	60	1.2%	0.02 [0.00, 0.38]
Sun 2011	0	60	42	60	1.2%	0.00 [0.00, 0.06]
Wang 2015	1	70	53	70	1.8%	0.00 [0.00, 0.04]
Wang Z 2015	4	30	16	30	2.8%	0.13 [0.04, 0.48]
Wang Z 2016	5	30	15	30	2.9%	0.20 [0.06, 0.66]
Wu 2014 (1)	3	40	10	14	2.3%	0.03 [0.01, 0.17]
Wu 2014 (2)	1	40	8	13	1.6%	0.02 [0.00, 0.16]
Wu 2014 (3)	0	40	8	13	1.1%	0.01 [0.00, 0.16]
Xu 2015 (1)	12	100	14	34	3.4%	0.19 [0.08, 0.48]
Xu 2015 (2)	4	100	13	33	2.9%	0.06 [0.02, 0.22]
Xu 2015 (3)	0	100	13	33	1.2%	0.01 [0.00, 0.13]
Yuan 2015 (1)	17	30	6	10	2.5%	0.87 [0.20, 3.74]
Yuan 2015 (2)	4	30	6	10	2.3%	0.10 [0.02, 0.53]
Yuan 2015 (3)	2	30	6	10	2.0%	0.05 [0.01, 0.32]
Zhang 2013	1	40	18	40	1.8%	0.03 [0.00, 0.25]
Zhang 2016	1	30	14	30	1.7%	0.04 [0.00, 0.33]
Subtotal (95% CI)		**1150**		**730**	**49.8%**	**0.07 [0.04, 0.12]**
Total events	101		363			
Heterogeneity: Tau² = 0.99; Chi² = 55.82, df = 22 (P < 0.0001); I² = 61%						
Test for overall effect: Z = 9.45 (P < 0.00001)						
2.1.2 Sufentanil						
Fang 2016	6	62	39	62	3.2%	0.06 [0.02, 0.17]
Li 2017 (1)	2	80	13	40	2.4%	0.05 [0.01, 0.25]
Li 2017 (2)	1	80	14	40	1.8%	0.02 [0.00, 0.19]
Liu 2015	0	185	59	185	1.2%	0.01 [0.00, 0.09]
Meng 2013	0	40	29	40	1.2%	0.00 [0.00, 0.08]
Qiu 2016	5	100	45	100	3.3%	0.06 [0.02, 0.17]
Ruan 2017	2	35	20	35	2.4%	0.05 [0.01, 0.22]
Shen 2014	5	60	17	60	3.1%	0.23 [0.08, 0.67]
Sheng 2017	0	48	31	48	1.2%	0.01 [0.00, 0.10]
Wang 2016	0	185	59	185	1.2%	0.01 [0.00, 0.09]
Wang 2017	10	60	33	60	3.5%	0.16 [0.07, 0.38]
Wang H 2015	1	50	16	50	1.8%	0.04 [0.01, 0.34]
Wang L 2015 (1)	7	25	4	9	2.4%	0.49 [0.10, 2.36]
Wang L 2015 (2)	3	25	3	8	2.0%	0.23 [0.03, 1.48]
Wang L 2015 (3)	2	25	3	8	1.8%	0.14 [0.02, 1.11]
Xu 2014 (1)	3	50	40	50	2.7%	0.02 [0.00, 0.06]
Xu 2014 (2)	1	50	4	50	1.6%	0.23 [0.03, 2.18]
Zhao 2017	2	26	17	26	2.3%	0.04 [0.01, 0.23]
Zheng 2018 (1)	7	25	6	9	2.3%	0.19 [0.04, 1.00]
Zheng 2018 (2)	1	25	4	8	1.5%	0.04 [0.00, 0.47]
Zheng 2018 (3)	1	25	4	8	1.5%	0.04 [0.00, 0.47]
Zheng 2019	8	50	22	50	3.3%	0.24 [0.09, 0.62]
Zhou 2014	0	30	8	30	1.1%	0.04 [0.00, 0.79]
Zhu 2018	1	30	4	30	1.6%	0.22 [0.02, 2.14]
Subtotal (95% CI)		**1371**		**1191**	**50.2%**	**0.07 [0.04, 0.12]**
Total events	68		494			
Heterogeneity: Tau² = 0.71; Chi² = 49.24, df = 23 (P = 0.001); I² = 53%						
Test for overall effect: Z = 10.38 (P < 0.00001)						
Total (95% CI)		**2521**		**1921**	**100.0%**	**0.07 [0.05, 0.10]**
Total events	169		857			
Heterogeneity: Tau² = 0.80; Chi² = 105.24, df = 46 (P < 0.00001); I² = 56%						
Test for overall effect: Z = 14.15 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%						

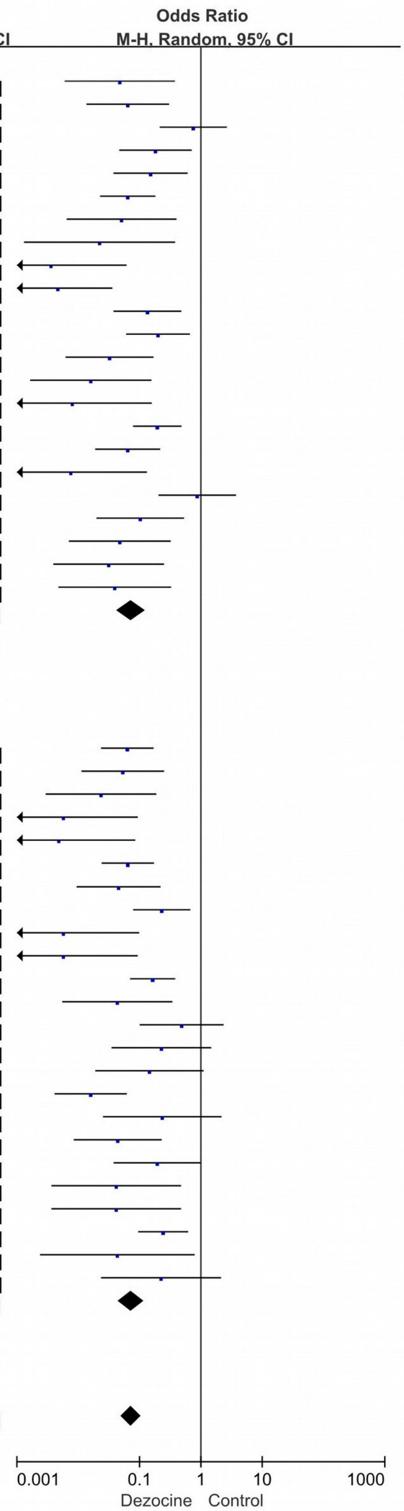

Figure 4 Forest plot of OIC occurrence rate. OIC, opioid-induced cough.

One is patients' individual physical conditions (age, sex, smoking status, disease history, etc). Another is usage of opioids (drug category, dosage, concentration, injection site, injection concentration, injection rate, etc).[15] Subgroup analysis suggested possible dose–effects of fentanyl and sufentanil on the occurrence rates of OIC.

OIC is associated with adverse effects and should be avoided. The antitussive efficacy of numerous

Study or Subgroup	Dezocine Events	Dezocine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
9.1.1 Dizziness						
Wang L 2015 (3)	6	25	0	25	7.2%	17.00 [0.90, 320.37]
Yuan 2015 (3)	2	30	0	30	7.0%	5.35 [0.25, 116.31]
Zhou 2014	2	30	0	30	7.0%	5.35 [0.25, 116.31]
Subtotal (95% CI)		**85**		**85**	**21.3%**	**8.06 [1.40, 46.35]**
Total events	10		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 2 (P = 0.82); I² = 0%						
Test for overall effect: Z = 2.34 (P = 0.02)						
9.1.2 Drowsiness						
Wang L 2015 (3)	4	25	0	25	7.2%	10.67 [0.54, 209.64]
Yuan 2015 (3)	1	30	0	30	6.7%	3.10 [0.12, 79.23]
Zhou 2014	1	30	0	30	6.7%	3.10 [0.12, 79.23]
Subtotal (95% CI)		**85**		**85**	**20.7%**	**4.91 [0.80, 30.19]**
Total events	6		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 2 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.72 (P = 0.09)						
9.1.3 Truncal rigidity						
Wang 2016	4	185	0	185	7.3%	9.20 [0.49, 172.07]
Subtotal (95% CI)		**185**		**185**	**7.3%**	**9.20 [0.49, 172.07]**
Total events	4		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
9.1.4 Chill						
Sheng 2017	2	48	11	48	9.5%	0.15 [0.03, 0.70]
Subtotal (95% CI)		**48**		**48**	**9.5%**	**0.15 [0.03, 0.70]**
Total events	2		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.40 (P = 0.02)						
9.1.7 Respiratory inhibition						
Sheng 2017	1	48	9	48	8.6%	0.09 [0.01, 0.76]
Wang 2016	16	185	0	185	7.4%	36.12 [2.15, 606.62]
Subtotal (95% CI)		**233**		**233**	**16.1%**	**1.70 [0.00, 766.69]**
Total events	17		9			
Heterogeneity: Tau² = 17.84; Chi² = 12.04, df = 1 (P = 0.0005); I² = 92%						
Test for overall effect: Z = 0.17 (P = 0.86)						
9.1.8 Nausea and emesis						
Sheng 2017	1	48	16	48	8.7%	0.04 [0.01, 0.34]
Wang 2016	20	185	0	185	7.4%	45.95 [2.76, 765.77]
Zhu 2018	3	30	2	30	9.1%	1.56 [0.24, 10.05]
Subtotal (95% CI)		**263**		**263**	**25.2%**	**1.32 [0.03, 53.18]**
Total events	24		18			
Heterogeneity: Tau² = 9.35; Chi² = 16.75, df = 2 (P = 0.0002); I² = 88%						
Test for overall effect: Z = 0.15 (P = 0.88)						
Total (95% CI)		**899**		**899**	**100.0%**	**2.34 [0.60, 9.14]**
Total events	63		38			
Heterogeneity: Tau² = 4.43; Chi² = 44.89, df = 12 (P < 0.0001); I² = 73%						
Test for overall effect: Z = 1.22 (P = 0.22)						
Test for subgroup differences: Chi² = 15.06, df = 5 (P = 0.01), I² = 66.8%						

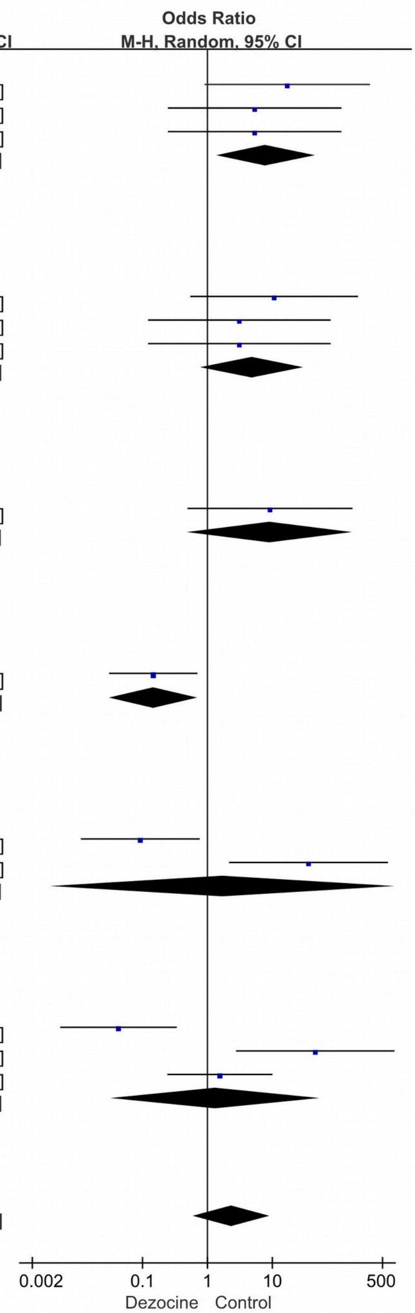

Figure 5 Possible adverse effects.

pharmaceutical and non-pharmaceutical interventions has been tested, some proved to be effective, some ineffective and some have side effects.[15] DZC, a mixed κ and μ opioid receptor agonist-antagonist, is not a well-known drug in Western countries.[24–27] However, DZC is widely applied as perioperative pain analgesic agent in China for decades.[24–26 28–32] The present meta-analysis demonstrated that DZC could significantly suppress both FIC and SIC, with several trials[4 6 35 41 45 48 50 56 64] reporting that DZC could completely prevent OIC. Furthermore, the subgroup analysis of the present meta-analysis suggested that the antitussive effect of DZC on FIC and SIC may be dose dependent. The mechanism responsible for the antitussive effect of DZC remains unknown. Possible explanation for this phenomenon is that DZC suppresses OIC by μ-receptor antagonism or norepinephrine/serotonine reuptake inhibition and reduce cough.[15] Whether a central gating mechanisms via

Table 4 Reliability of results

Influence of statistical model on estimated treatment effects of primary outcomes			
Statistical model	Cough occurrence rate OR (95% CI)	Severe cough occurrence rate OR (95% CI)	Adverse effects occurrence rate OR (95% CI)
Fixed effects	0.07 (0.05 to 0.08)	0.08 (0.05 to 0.12)	1.61 (1.09 to 2.39)
Random effects	0.07 (0.05 to 0.10)	0.11 (0.07 to 0.18)	2.34 (0.60 to 9.14)

Sensitivity analyses of high heterogeneity outcome									
Heterogeneity outcome	Excluded trials	Group DZC (n)	Group C (n)	Heterogeneity		Analysis model	OR	95% CI	Overall effect *P*
				I^2 (%)	*P*				
FIC (%)	39, 49, 58	280	140	35	0.08	M-H, fixed	0.06	(0.04 to 0.08)	<0.00001
SIC (%)	47, 53, 57, 63	285	235	36	0.07	M-H, fixed	0.04	(0.03 to 0.06)	<0.00001
Adverse effects (%)	48	48	48	0	0.59	M-H, fixed	10.75	(4.75 to 24.33)	<0.00001

DZC, dezocine; FIC, fentanyl-induced cough; SIC, sufentanil-induced cough.

C-fibre receptors or inhibition of histamine release play a role in the cough suppression elicited by DZC needs to be investigated.[4]

Because of its partial μ agonism, DZC exhibits a ceiling effect for common opioids-related adverse effects such as respiratory depression.[24–26] The meta-analysis suggested that DZC did not increase the occurrence rates of drowsiness, truncal rigidity, chill, respiratory inhibition, nausea and emesis but was associated with higher occurrence rate of dizziness. Whether DZC pretreatment interferes with opioid analgesia remains to be verified. Initial evidence indicated that DZC can enhance the analgesic effect of opioids and reduced OIC and opioid-related side effects.[67 68]

This study has some limitations. First, meta-analysis can increase the power of analysis by pooling many small low-quality studies, but different clinical practices, varied quality and heterogeneity of included studies may limit the certainty of the findings of meta-analysis. For example, there were no differences in DZC and control group on OIC occurrence rate when using preoperative medication of phenobarbital 30 min before anaesthesia induction.[53 58] One possible explanation is that sedatives exhibit similar effect on suppressing OIC as well according to previous study.[2] Second, all the 33 included RCTs were performed in China. The antitussive effectiveness of DZC may not be generalised to the whole world and remains to be investigated in other ethnicities. Third, the doses, injection rates or injection order of fentanyl or sufentanil varied among these included trials. For example, Sun and colleagues[4] reported DZC administered 10 min before anaesthesia induction could prevent FIC, which may be not a convenient practice in clinical settings. To determine the proper administration protocol of DZC for OIC prevention, a prospective randomised, placebo-controlled, triple-blinded trial is ongoing in our centre.

CONCLUSIONS

This meta-analysis has demonstrated that, DZC significantly inhibited OIC and may be used to manage OIC induced by fentanyl or sufentanil. More high-quality RCTs are needed to complement the safety of DZC.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Ethics approval This study was a meta-analysis of previously published literatures, ethical approval was not necessary according to the Ethical Committee of Fuwai Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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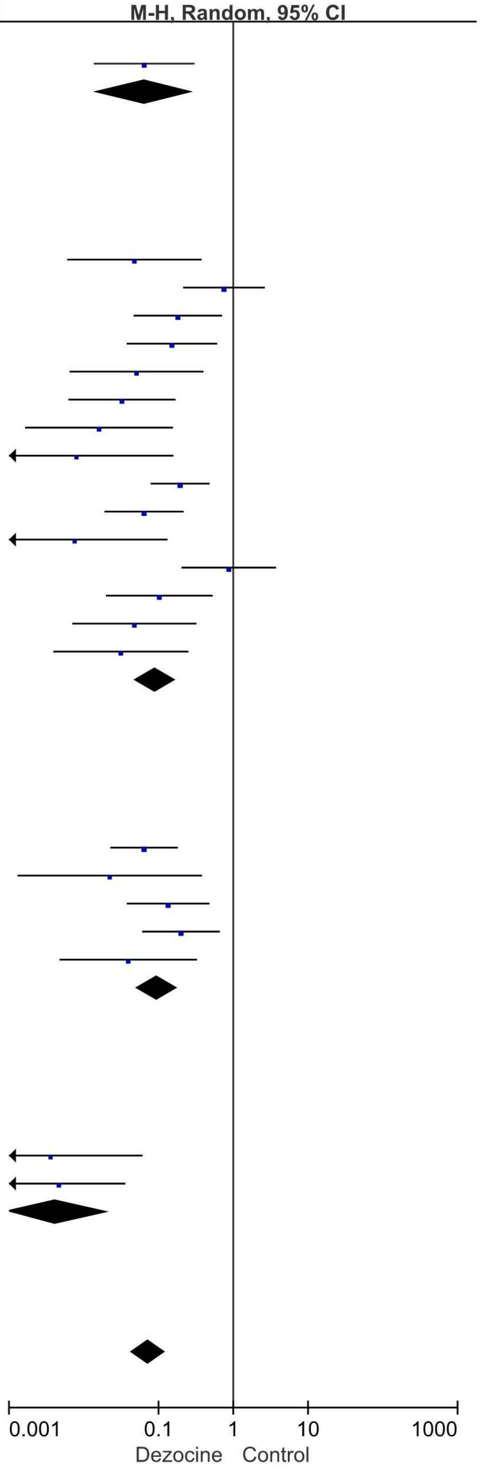
REFERENCES

1 El Baissari MCT, Taha SK, Siddik-Sayyid SM. Fentanyl-induced cough--pathophysiology and prevention. *Middle East J Anaesthesiol* 2014;22:449–56.
2 Kim JE, Min SK, Chae YJ, *et al*. Pharmacological and nonpharmacological prevention of fentanyl-induced cough: a meta-analysis. *J Anesth* 2014;28:257–66.
3 Oshima T, Kasuya Y, Okumura Y, *et al*. Identification of independent risk factors for fentanyl-induced cough. *Can J Anaesth* 2006;53:753–8.
4 Sun Z-T, Yang C-Y, Cui Z, *et al*. Effect of intravenous dezocine on fentanyl-induced cough during general anesthesia induction: a double-blinded, prospective, randomized, controlled trial. *J Anesth* 2011;25:860–3.
5 Sun S, Huang S-qiang. Effects of pretreatment with a small dose of dexmedetomidine on sufentanil-induced cough during anesthetic induction. *J Anesth* 2013;27:25–8.
6 Liu X-S, Xu G-H, Shen Q-Y, *et al*. Dezocine prevents sufentanil-induced cough during general anesthesia induction: a randomized controlled trial. *Pharmacol Rep* 2015;67:52–5.
7 An L-J, Gui B, Su Z, *et al*. Magnesium sulfate inhibits sufentanil-induced cough during anesthetic induction. *Int J Clin Exp Med* 2015;8:13864–8.
8 Bang S-R, Ahn HJ, Kim HJ, *et al*. Comparison of the effectiveness of lidocaine and salbutamol on coughing provoked by intravenous remifentanil during anesthesia induction. *Korean J Anesthesiol* 2010;59:319–22.
9 Kim JY, Park KS, Kim JS, *et al*. The effect of lidocaine on remifentanil-induced cough. *Anaesthesia* 2008;63:495–8.
10 Park KS, Park SY, Kim JY, *et al*. Effect of remifentanil on tracheal intubation conditions and haemodynamics in children anaesthetised with sevoflurane and nitrous oxide. *Anaesth Intensive Care* 2009;37:577–83.
11 Honarmand A, Safavi M, Khalighinejad F. A comparison of the effect of pretreatment with intravenous dexamethasone, intravenous ketamine, and their combination, for suppression of remifentanil-induced cough: a randomized, double-blind, placebo-controlled clinical trial. *Adv Biomed Res* 2013;2:60.
12 Kim JY, Lee SY, Kim DH, *et al*. Effect-site concentration of propofol for reduction of remifentanil-induced cough. *Anaesthesia* 2010;65:697–703.
13 Yu M-S, Kim JY, Kim HY. Intravenous dexamethasone pretreatment reduces remifentanil induced cough. *Korean J Anesthesiol* 2011;60:403–7.
14 Cho HB, Kwak HJ, Park SY, *et al*. Comparison of the incidence and severity of cough after alfentanil and remifentanil injection. *Acta Anaesthesiol Scand* 2010;54:717–20.
15 Shuying L, Ping L, Juan N, *et al*. Different interventions in preventing opioid-induced cough: a meta-analysis. *J Clin Anesth* 2016;34:440–7.
16 Phua WT, Teh BT, Jong W, *et al*. Tussive effect of a fentanyl bolus. *Can J Anaesth* 1991;38:330–4.
17 Sun Q, Zhou W, Wu B, *et al*. Dezocine: a novel drug to prevent fentanyl-induced cough during general anesthesia induction? *J Anesth* 2012;26:470.
18 Tweed WA, Dakin D. Explosive coughing after bolus fentanyl injection. *Anesth Analg* 2001;92:1442–3.
19 Ambesh SP, Singh N, Gupta D, *et al*. A huffing manoeuvre, immediately before induction of anaesthesia, prevents fentanyl-induced coughing: a prospective, randomized, and controlled study. *Br J Anaesth* 2010;104:40–3.
20 Uvelin A, Rakic G. Guidelines for prevention of fentanyl-induced cough. *Acta Anaesthesiol Scand* 2009;53:1228–9.
21 Liu M-Q, Li F-X, Han Y-K, *et al*. Administration of fentanyl via a slow intravenous fluid line compared with rapid bolus alleviates fentanyl-induced cough during general anesthesia induction. *J Zhejiang Univ Sci B* 2017;18:955–62.
22 Gu C, Zhou M, Wu H, *et al*. Effects of different priming doses of fentanyl on fentanyl-induced cough: a double-blind, randomized, controlled study. *Pharmacol Rep* 2012;64:321–5.
23 Fragen RJ, Caldwell N, dezocine C. (WY 16, 225) and meperidine as postoperative analgesics. *Anesth Analg* 1978;57:563–6.
24 Liu R, Huang X-P, Yeliseev A, *et al*. Novel molecular targets of dezocine and their clinical implications. *Anesthesiology* 2014;120:714–23.
25 Wang Y-H, Chai J-R, Xu X-J, *et al*. Pharmacological characterization of dezocine, a potent analgesic acting as a κ partial agonist and μ partial agonist. *Sci Rep* 2018;8:14087.
26 Wu F-X, Babazada H, Gao H, *et al*. Dezocine alleviates morphine-induced dependence in rats. *Anesth Analg* 2019;128:1328–35.
27 O'Brien JJ, Benfield P, Dezocine BP. Dezocine. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1989;38:226–48.
28 Zhu Y, Yang Y, Zhou C, *et al*. Using dezocine to prevent etomidate-induced myoclonus: a meta-analysis of randomized trials. *Drug Des Devel Ther* 2017;11:2163–70.
29 Zhou C, Yang Y, Zhu Y, *et al*. Effects of dezocine on prevention of propofol injection pain: a meta-analysis. *J Pain Res* 2017;10:1369–75.
30 Zhou X, Zhang C, Wang M, *et al*. Dezocine for preventing postoperative pain: a meta-analysis of randomized controlled trials. *PLoS One* 2015;10:e0136091.
31 Wang L, Liu X, Wang J, *et al*. Comparison of the efficacy and safety between dezocine injection and morphine injection for persistence of pain in Chinese cancer patients: a meta-analysis. *Biosci Rep* 2017;37:BSR20170243.
32 Zhang G-F, Guo J, Qiu L-L, *et al*. Effects of dezocine for the prevention of postoperative catheter-related bladder discomfort: a prospective randomized trial. *Drug Des Devel Ther* 2019;13:1281–8.
33 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
34 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
35 Xu Y, Zhu Y, Wang S, *et al*. Dezocine attenuates fentanyl-induced cough in a dose-dependent manner-a randomized controlled trial. *Int J Clin Exp Med* 2015;8:6091–6.
36 Qing-Ming B, Lian-Bing G, Rong G. Effect of intravenous dezocine premedication on fentanyl induced cough. *J Clin Anesthesiol* 2012;28:770–1.
37 Xiao-Ming C, Guang-Hong X. The effect inhibition of dezocine on irritating cough caused by fentanyl in general anesthesia induction: a randomized controlled trial. *J Med Theo Pract* 2013;26:1278–9.
38 Liang F. Inhibition of dezocine on sufentanil-induced cough during induction of general anesthesia. *Electron J Clin Med Literature* 2016;3:5457–60.
39 Ya-Ping G, Xaio NL, Jian-Hong S. The effectiveness of different doses of dezocine in preventing fentanyl cough. *J Clin Med Pract* 2013;17:155–6.
40 Li Yan-Juan LY-J. Comparative study of intravenous different dose of dezocine premedication on sufentanil-induced cough. *J Clin Pulm Med* 2017;22:2219–22.
41 Zhen-zhen M, Lin Z, Shi-rui W. Feasibility of dezocine required to prevent sufentanil-induced cough during anesthesia induction. *Prog Modern Biomed* 2013;13:1911–3.
42 Ming-fang P, Chun C, Jun H. Effect of dezocine premedication on inhibition of fentanyl induced irritating cough. *Jilin Med J* 2015;36:1971–2.
43 Jian-Bin Q. Experience of preventing cough during induction of general anesthesia with dezocine. *J Qiqihar Univ Med* 2016;37:888–9.
44 Liang-Cheng Q, Yu-Sheng Y, Xiao-Dan W. Comparison of oxycodone hydrochloride versus Dizocine for suppression of Fentanyl-induced coughing during induction of general anesthesia. *J Trauma Emerg* 2016;488:89–91.
45 Hui Q, Gang LU, Xiao-Feng P. Clinical observation on the inhibition of fentanyl induced cough by dezocine at low dose. *J Clin Anesthesiol* 2012;28:1232–3.
46 Tian-yi R, Chen Z, Jian-chun C. Effect of Dizocine on preventing sufentanil-induced cough. *Med Pharm Yunnan* 2017;38:577–9.
47 Jie S, Li-li H, Xiao-feng S. Effect of intravenous dezocine premedication on sufentanil-induced cough. *J China Prescription Drug* 2014;12:10–11.
48 Da-Wei S, Yan-Ping G, Jun W. Clinical observation of during the induction of general anesthesia using dezocine prevention and inhibition of sufentanil cough. *J Clin Pulm Med* 2017;22:1773–5.
49 Li W, Yan G, Hui L. Effect of dezocine suppressing Fentanyl-induced cough during general anesthesia induction. *Med J Air Force* 2015;31:243–5.
50 Jun-Liang W, Rong B. Analysis of the effect of dezocine in inhibiting sufentanil-induced cough during the induction of general anesthesia. *Shanxi Med J* 2016;45:1005–6.
51 Zhi-Yong W. Inhibition of dezocine on sufentanil-induced cough during general anesthesia. *World Latest Med Inf* 2017;17:95.
52 Hui W, En-Ming Q. Effect of intravenous dezocine premedication on sufentanil-induced cough. *J Chin Pract Diagn Ther* 2015;29:825–6.

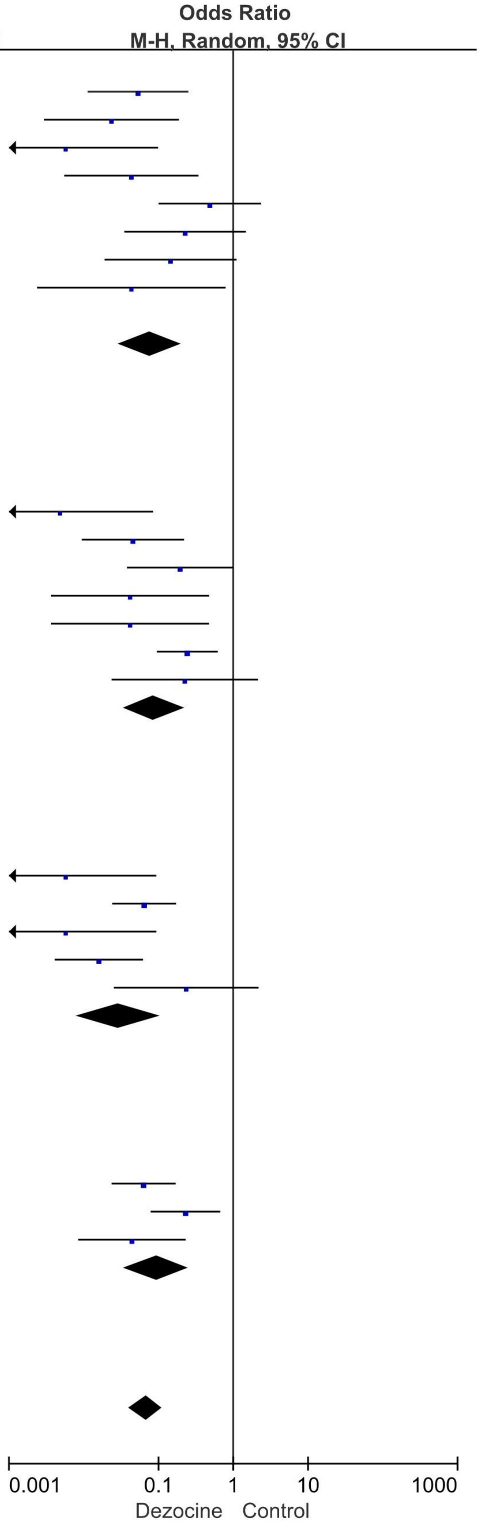
53 Li-Ping W. Comparison of different doses of dezocine in the prevention and treatment of sufentanil-induced cough. *Contemp Med Forum* 2015;13:222–3.
54 Zhi W, Feng L. Dezocine and dexamethasone inhibition of choking cough reflex fentanyl. *J Clin Med Literature* 2015;2:1198–9.
55 Zhi W, Yuan-Hong D, Zhen-yi C. Comparison of the suppressive effect of dezocine, lidocaine and ephedrine on Fentanyl-induced cough. *J Pharm Pract* 2016;34:463–5.
56 Wen-Feng W, Yong-Hua Y. Effect of intravenous dezocine on Fentanyl-induced cough during general anesthesia induction. *Jilin Med J* 2014;35:1374–6.
57 Qing X, De-Xiang Z, Shuang-Bao X. The clinical observation of Preinjection dezocine during induction of general anesthesia with sufentanil on different injection speed on induced cough reflex. *J Clin Med Pract* 2014;18:137–9.
58 Ming-Feng Y, Yu C. Effect of dezocine on preventing Fentanyl-induced cough. *Jiangsu Med J* 2015;41:2176–7.
59 Jian-Feng Z, Han-Zhong C. Observation on the effect of dezocine on preventing Fentanyl-induced cough in 40 cases. *Med J Commun* 2013;27:680–1.
60 Ji-Hong Z. Effects of different anesthetic agents on prevention and inhibition of Fentanyl-induced cough during induction of general anesthesia. *World Latest Med Inf* 2016;16:77–82.
61 Lu-Hong Z. Preventive effect of dezocine on sufentanil-induced cough during the induction of general anesthesia. *J China Prescription Drug* 2017;15:80–1.
62 Qin-Shu Z. Clinical observation on preventing sufentanil-induced cough at different time after small dose of Dezocin injection. *Strait Pharm J* 2018;30:128–9.
63 Xiao-Zhen Z, Yi-Feng R, Xiao-Di H. Effect of intravenous injection of dezocine and midazolam on sufentanil induced cough. *J Henan Univ* 2019;38:44–6.
64 Tao-Yu Z, Chang-Wei Y, Jin-Bao C. Clinical observation on inhibition of sufentanil induced cough reflex by dezocine Preinjection. *Anhui Med Pharm J* 2014;18:1772–3.
65 Fang Z. Effect of intravenous injection of Dizocine on sufentanil-induced cough response during induction of general anesthesia. *Chin Foreign Med Res* 2018;16:118–9.
66 Solanki SL, Doctor JR, Kapila SJ, *et al*. Acupressure versus dilution of fentanyl to reduce incidence of fentanyl-induced cough in female cancer patients: a prospective randomized controlled study. *Korean J Anesthesiol* 2016;69:234–8.
67 Wu L, Dong YP, Sun L, *et al*. Low concentration of dezocine in combination with morphine enhance the postoperative analgesia for thoracotomy. *J Cardiothorac Vasc Anesth* 2015;29:950–4.
68 Yu F, Zhou J, Xia S, *et al*. Dezocine prevents postoperative hyperalgesia in patients undergoing open abdominal surgery. *Evid Based Complement Alternat Med* 2015;2015:1–8.

Study or Subgroup	Dezocine Events	Dezocine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
4.1.1 Fentanyl 2μg/kg						
Chen 2013	2	40	18	40	4.8%	0.06 [0.01, 0.30]
Subtotal (95% CI)		**40**		**40**	**4.8%**	**0.06 [0.01, 0.30]**
Total events	2		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.46 (P = 0.0005)						
4.1.2 Fentanyl 3μg/kg						
Bian 2012	1	50	15	50	3.7%	0.05 [0.01, 0.38]
Gao 2013 (1)	23	40	9	14	5.5%	0.75 [0.21, 2.65]
Gao 2013 (2)	7	40	7	13	5.3%	0.18 [0.05, 0.71]
Gao 2013 (3)	6	40	7	13	5.2%	0.15 [0.04, 0.61]
Qiu L 2016	1	60	15	60	3.7%	0.05 [0.01, 0.40]
Wu 2014 (1)	3	40	10	14	4.6%	0.03 [0.01, 0.17]
Wu 2014 (2)	1	40	8	13	3.3%	0.02 [0.00, 0.16]
Wu 2014 (3)	0	40	8	13	2.3%	0.01 [0.00, 0.16]
Xu 2015 (1)	12	100	14	34	6.4%	0.19 [0.08, 0.48]
Xu 2015 (2)	4	100	13	33	5.6%	0.06 [0.02, 0.22]
Xu 2015 (3)	0	100	13	33	2.5%	0.01 [0.00, 0.13]
Yuan 2015 (1)	17	30	6	10	5.0%	0.87 [0.20, 3.74]
Yuan 2015 (2)	4	30	6	10	4.6%	0.10 [0.02, 0.53]
Yuan 2015 (3)	2	30	6	10	4.0%	0.05 [0.01, 0.32]
Zhang 2013	1	40	18	40	3.7%	0.03 [0.00, 0.25]
Subtotal (95% CI)		**780**		**360**	**65.5%**	**0.09 [0.05, 0.18]**
Total events	82		155			
Heterogeneity: Tau² = 0.95; Chi² = 34.43, df = 14 (P = 0.002); I² = 59%						
Test for overall effect: Z = 7.05 (P < 0.00001)						
4.1.3 Fentanyl 4μg/kg						
Pi 2015	6	50	34	50	6.1%	0.06 [0.02, 0.18]
Qu 2012	0	60	16	60	2.5%	0.02 [0.00, 0.38]
Wang Z 2015	4	30	16	30	5.5%	0.13 [0.04, 0.48]
Wang Z 2016	5	30	15	30	5.7%	0.20 [0.06, 0.66]
Zhang 2016	1	30	14	30	3.6%	0.04 [0.00, 0.33]
Subtotal (95% CI)		**200**		**200**	**23.4%**	**0.09 [0.05, 0.18]**
Total events	16		95			
Heterogeneity: Tau² = 0.02; Chi² = 4.15, df = 4 (P = 0.39); I² = 4%						
Test for overall effect: Z = 7.24 (P < 0.00001)						
4.1.4 Fentanyl 5μg/kg						
Sun 2011	0	60	42	60	2.5%	0.00 [0.00, 0.06]
Wang 2015	1	70	53	70	3.7%	0.00 [0.00, 0.04]
Subtotal (95% CI)		**130**		**130**	**6.2%**	**0.00 [0.00, 0.02]**
Total events	1		95			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 6.44 (P < 0.00001)						
Total (95% CI)		**1150**		**730**	**100.0%**	**0.07 [0.04, 0.12]**
Total events	101		363			
Heterogeneity: Tau² = 0.99; Chi² = 55.82, df = 22 (P < 0.0001); I² = 61%						
Test for overall effect: Z = 9.45 (P < 0.00001)						
Test for subgroup differences: Chi² = 12.31, df = 3 (P = 0.006), I² = 75.6%						

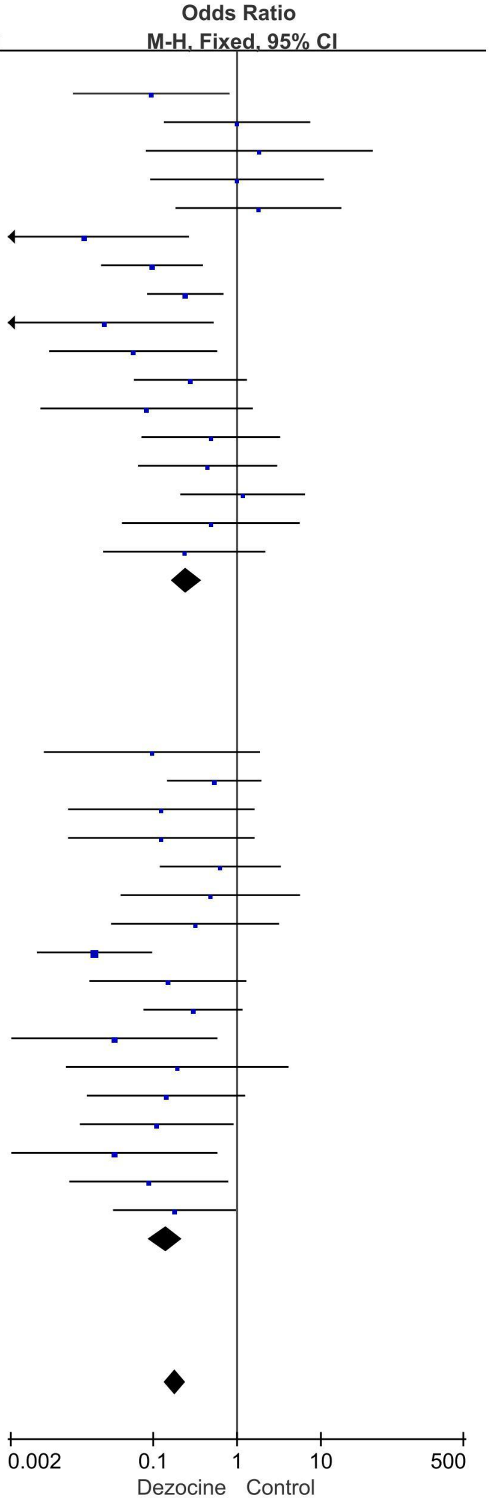
Odds Ratio
M-H, Random, 95% CI



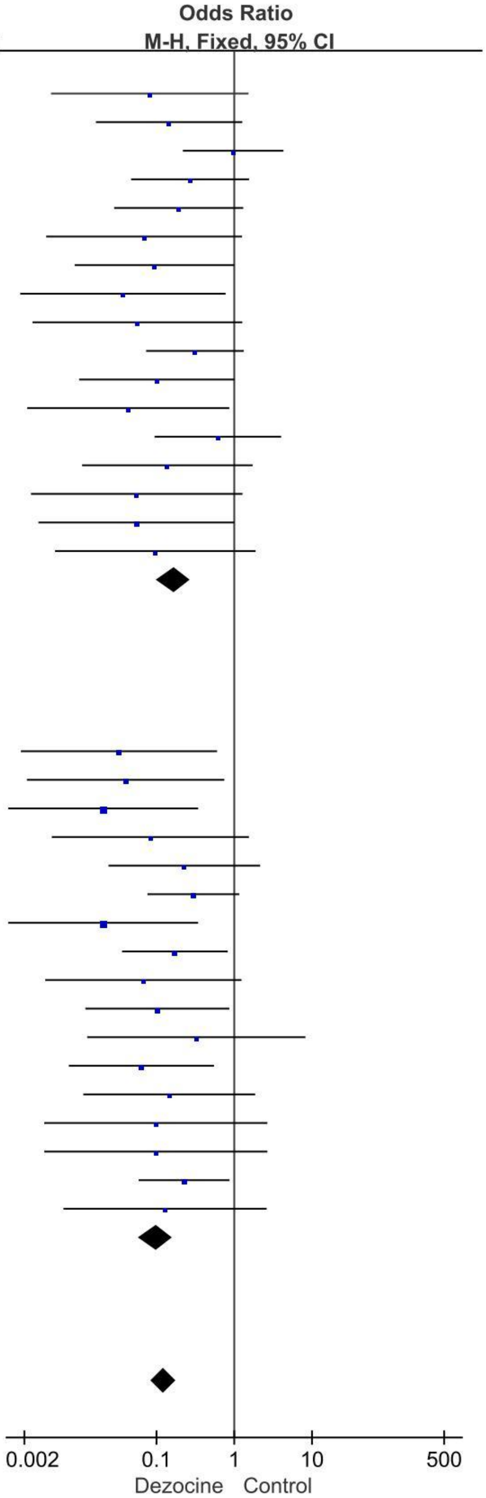
	Dezocine		Control			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
3.1.1 Sufentanil 0.3 μg/kg						
Li 2017 (1)	2	80	13	40	5.1%	0.05 [0.01, 0.25]
Li 2017 (2)	1	80	14	40	3.8%	0.02 [0.00, 0.19]
Sheng 2017	0	48	31	48	2.5%	0.01 [0.00, 0.10]
Wang 2017	1	50	16	50	3.8%	0.04 [0.01, 0.34]
Wang H 2015	7	25	4	9	5.1%	0.49 [0.10, 2.36]
Wang L 2015 (1)	3	25	3	8	4.3%	0.23 [0.03, 1.48]
Wang L 2015 (2)	2	25	3	8	3.9%	0.14 [0.02, 1.11]
Wang L 2015 (3)	0	30	8	30	2.4%	0.04 [0.00, 0.79]
Zhou 2014	0	0	0	0		Not estimable
Subtotal (95% CI)		**363**		**233**	**30.9%**	**0.08 [0.03, 0.20]**
Total events	16		92			
Heterogeneity: Tau² = 0.89; Chi² = 13.03, df = 7 (P = 0.07); I² = 46%						
Test for overall effect: Z = 5.17 (P < 0.00001)						
3.1.2 Sufentanil 0.4 μg/kg						
Meng 2013	0	40	29	40	2.5%	0.00 [0.00, 0.08]
Ruan 2017	2	35	20	35	5.1%	0.05 [0.01, 0.22]
Zheng 2018 (1)	7	25	6	9	4.9%	0.19 [0.04, 1.00]
Zheng 2018 (2)	1	25	4	8	3.1%	0.04 [0.00, 0.47]
Zheng 2018 (3)	1	25	4	8	3.1%	0.04 [0.00, 0.47]
Zheng 2019	8	50	22	50	7.2%	0.24 [0.09, 0.62]
Zhu 2018	1	30	4	30	3.4%	0.22 [0.02, 2.14]
Subtotal (95% CI)		**230**		**180**	**29.2%**	**0.09 [0.03, 0.22]**
Total events	20		89			
Heterogeneity: Tau² = 0.71; Chi² = 11.16, df = 6 (P = 0.08); I² = 46%						
Test for overall effect: Z = 5.04 (P < 0.00001)						
3.1.3 Sufentanil 0.5 μg/kg						
Liu 2015	0	185	59	185	2.6%	0.01 [0.00, 0.09]
Qiu 2016	5	100	45	100	7.0%	0.06 [0.02, 0.17]
Wang 2016	0	185	59	185	2.6%	0.01 [0.00, 0.09]
Xu 2014 (1)	3	50	40	50	5.7%	0.02 [0.00, 0.06]
Xu 2014 (2)	1	50	4	50	3.5%	0.23 [0.03, 2.18]
Subtotal (95% CI)		**570**		**570**	**21.4%**	**0.03 [0.01, 0.11]**
Total events	9		207			
Heterogeneity: Tau² = 1.21; Chi² = 10.16, df = 4 (P = 0.04); I² = 61%						
Test for overall effect: Z = 5.35 (P < 0.00001)						
3.1.4 Sufentanil 3-5 μg/kg						
Fang 2016	6	62	39	62	7.0%	0.06 [0.02, 0.17]
Shen 2014	5	60	17	60	6.7%	0.23 [0.08, 0.67]
Zhao 2017	2	26	17	26	4.8%	0.04 [0.01, 0.23]
Subtotal (95% CI)		**148**		**148**	**18.6%**	**0.09 [0.03, 0.25]**
Total events	13		73			
Heterogeneity: Tau² = 0.39; Chi² = 4.08, df = 2 (P = 0.13); I² = 51%						
Test for overall effect: Z = 4.69 (P < 0.00001)						
Total (95% CI)		**1311**		**1131**	**100.0%**	**0.07 [0.04, 0.11]**
Total events	58		461			
Heterogeneity: Tau² = 0.77; Chi² = 46.43, df = 22 (P = 0.002); I² = 53%						
Test for overall effect: Z = 10.08 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.28, df = 3 (P = 0.52), I² = 0%						



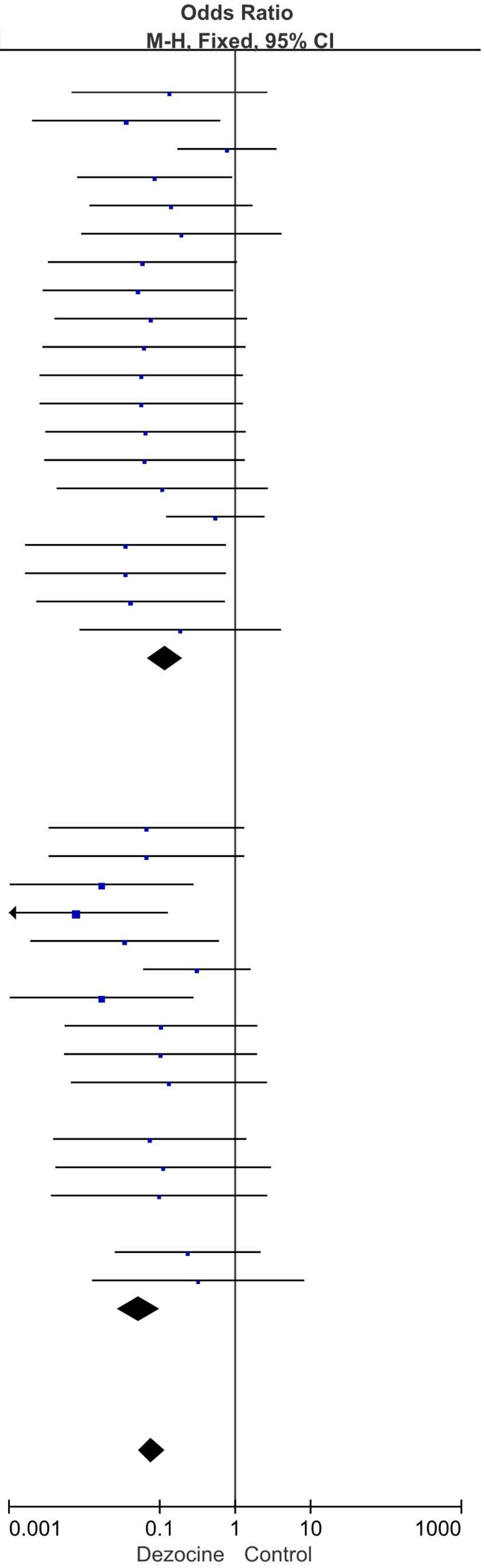
Study or Subgroup	Dezocine Events	Dezocine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
8.3.1 Incidence of mild FIC						
Bian 2012	1	30	8	30	3.7%	0.09 [0.01, 0.82]
Chen 2013	2	40	2	40	0.9%	1.00 [0.13, 7.47]
Gao 2013 (1)	2	30	0	10	0.3%	1.84 [0.08, 41.62]
Gao 2013 (2)	3	30	1	10	0.6%	1.00 [0.09, 10.87]
Gao 2013 (3)	5	30	1	10	0.6%	1.80 [0.18, 17.57]
Qu 2012	0	100	8	33	6.0%	0.01 [0.00, 0.27]
Wu 2014 (1)	3	100	8	33	5.6%	0.10 [0.02, 0.39]
Wu 2014 (2)	8	100	9	34	5.9%	0.24 [0.08, 0.69]
Wu 2014 (3)	0	40	4	13	3.2%	0.03 [0.00, 0.53]
Xu 2015 (1)	1	40	4	13	2.8%	0.06 [0.01, 0.58]
Xu 2015 (2)	4	40	4	14	2.5%	0.28 [0.06, 1.31]
Xu 2015 (3)	0	60	5	60	2.6%	0.08 [0.00, 1.54]
Yuan 2015 (1)	3	40	2	14	1.3%	0.49 [0.07, 3.27]
Yuan 2015 (2)	3	40	2	13	1.3%	0.45 [0.07, 3.02]
Yuan 2015 (3)	7	40	2	13	1.2%	1.17 [0.21, 6.47]
Zhang 2013	1	40	2	40	0.9%	0.49 [0.04, 5.60]
Zhang 2016	1	50	4	50	1.9%	0.23 [0.03, 2.18]
Subtotal (95% CI)		**850**		**430**	**41.4%**	**0.25 [0.16, 0.38]**
Total events	44		66			
Heterogeneity: Chi² = 22.33, df = 16 (P = 0.13); I² = 28%						
Test for overall effect: Z = 6.62 (P < 0.00001)						
8.3.2 Incidence of mild SIC						
Li 2017 (1)	0	30	4	30	2.1%	0.10 [0.00, 1.88]
Li 2017 (2)	4	50	7	50	3.1%	0.53 [0.15, 1.95]
Liu 2015	1	25	2	8	1.4%	0.13 [0.01, 1.62]
Qiu 2016	1	25	2	8	1.4%	0.13 [0.01, 1.62]
Ruan 2017	6	25	3	9	1.6%	0.63 [0.12, 3.33]
Shen 2014	1	26	2	26	0.9%	0.48 [0.04, 5.65]
Wang 2016	1	40	3	40	1.4%	0.32 [0.03, 3.18]
Wang 2017	2	40	29	40	13.1%	0.02 [0.00, 0.10]
Wang H 2015	1	50	6	50	2.8%	0.15 [0.02, 1.29]
Xu 2014 (1)	3	60	9	60	4.1%	0.30 [0.08, 1.16]
Xu 2014 (2)	0	185	13	185	6.4%	0.03 [0.00, 0.58]
Zhao 2017	0	60	2	60	1.2%	0.19 [0.01, 4.11]
Zheng 2018 (1)	1	35	6	35	2.8%	0.14 [0.02, 1.25]
Zheng 2018 (2)	1	60	8	60	3.7%	0.11 [0.01, 0.91]
Zheng 2018 (3)	0	185	13	185	6.4%	0.03 [0.00, 0.58]
Zheng 2019	1	80	5	40	3.1%	0.09 [0.01, 0.79]
Zhou 2014	2	80	5	40	3.1%	0.18 [0.03, 0.97]
Subtotal (95% CI)		**1056**		**926**	**58.6%**	**0.14 [0.09, 0.22]**
Total events	25		119			
Heterogeneity: Chi² = 17.94, df = 16 (P = 0.33); I² = 11%						
Test for overall effect: Z = 8.39 (P < 0.00001)						
Total (95% CI)		**1906**		**1356**	**100.0%**	**0.19 [0.14, 0.25]**
Total events	69		185			
Heterogeneity: Chi² = 42.29, df = 33 (P = 0.13); I² = 22%						
Test for overall effect: Z = 10.87 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.24, df = 1 (P = 0.07), I² = 69.2%						



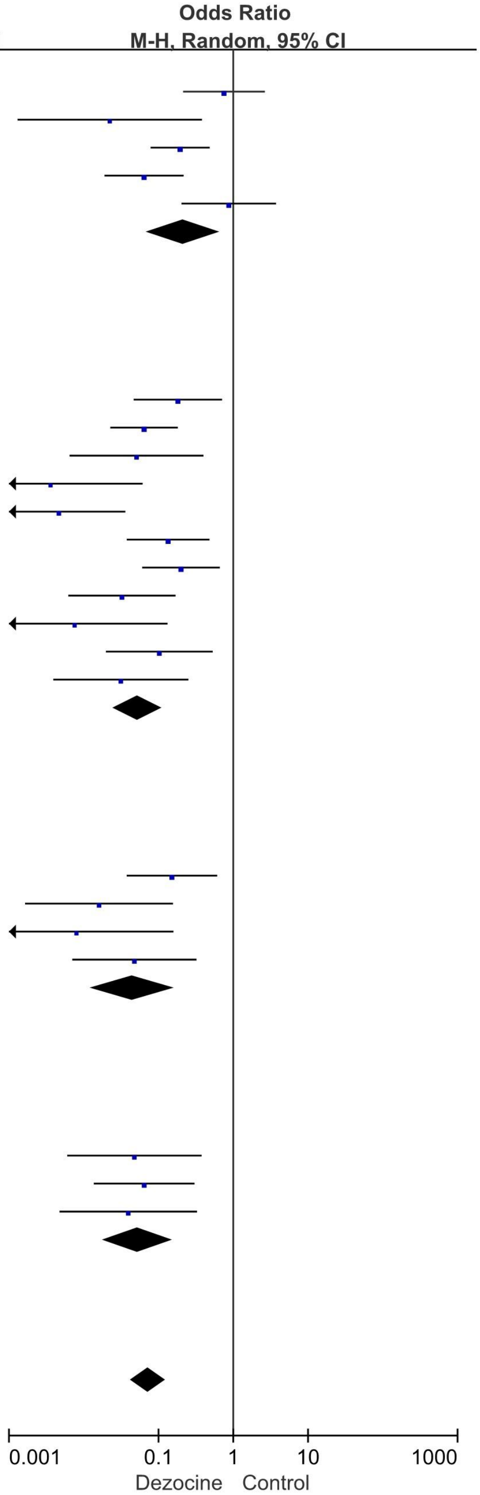
	Dezocine		Control			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
8.2.1 Incidence of moderate FIC						
Bian 2012	0	50	5	50	2.6%	0.08 [0.00, 1.52]
Chen 2013	1	40	6	40	2.8%	0.15 [0.02, 1.27]
Gao 2013 (1)	9	40	3	13	1.7%	0.97 [0.22, 4.29]
Gao 2013 (2)	3	40	3	13	2.0%	0.27 [0.05, 1.55]
Gao 2013 (3)	2	40	3	14	2.0%	0.19 [0.03, 1.30]
Qu 2012	0	60	6	60	3.0%	0.07 [0.00, 1.26]
Wu 2014 (1)	1	40	3	14	2.0%	0.09 [0.01, 1.00]
Wu 2014 (2)	0	40	3	13	2.4%	0.04 [0.00, 0.77]
Wu 2014 (3)	0	40	2	13	1.7%	0.06 [0.00, 1.27]
Xu 2015 (1)	4	100	4	34	2.7%	0.31 [0.07, 1.33]
Xu 2015 (2)	1	100	3	33	2.1%	0.10 [0.01, 1.01]
Xu 2015 (3)	0	100	3	33	2.5%	0.04 [0.00, 0.86]
Yuan 2015 (1)	4	30	2	10	1.2%	0.62 [0.09, 4.01]
Yuan 2015 (2)	1	30	2	10	1.4%	0.14 [0.01, 1.72]
Yuan 2015 (3)	0	30	2	10	1.7%	0.06 [0.00, 1.28]
Zhang 2013	0	40	7	40	3.5%	0.06 [0.00, 1.00]
Zhang 2016	0	30	4	30	2.1%	0.10 [0.00, 1.88]
Subtotal (95% CI)		**850**		**430**	**37.4%**	**0.17 [0.10, 0.28]**
Total events	26		61			
Heterogeneity: Chi² = 12.59, df = 16 (P = 0.70); I² = 0%						
Test for overall effect: Z = 7.01 (P < 0.00001)						
8.2.2 Incidence of moderate SIC						
Li 2017 (1)	0	80	6	40	4.1%	0.03 [0.00, 0.60]
Li 2017 (2)	0	80	5	40	3.4%	0.04 [0.00, 0.74]
Liu 2015	0	185	21	185	10.1%	0.02 [0.00, 0.34]
Qiu 2016	0	60	5	60	2.6%	0.08 [0.00, 1.54]
Ruan 2017	1	35	4	35	1.8%	0.23 [0.02, 2.15]
Shen 2014	3	60	9	60	4.0%	0.30 [0.08, 1.16]
Wang 2016	0	185	21	185	10.1%	0.02 [0.00, 0.34]
Wang 2017	2	60	10	60	4.6%	0.17 [0.04, 0.82]
Wang H 2015	0	50	6	50	3.0%	0.07 [0.00, 1.24]
Xu 2014 (1)	1	40	8	40	3.7%	0.10 [0.01, 0.86]
Xu 2014 (2)	0	40	1	40	0.7%	0.33 [0.01, 8.22]
Zhao 2017	1	26	10	26	4.5%	0.06 [0.01, 0.55]
Zheng 2018 (1)	1	25	2	9	1.3%	0.15 [0.01, 1.86]
Zheng 2018 (2)	0	25	1	8	1.0%	0.10 [0.00, 2.66]
Zheng 2018 (3)	0	25	1	8	1.0%	0.10 [0.00, 2.66]
Zheng 2019	3	50	11	50	4.9%	0.23 [0.06, 0.87]
Zhou 2014	0	30	3	30	1.6%	0.13 [0.01, 2.61]
Subtotal (95% CI)		**1056**		**926**	**62.6%**	**0.10 [0.06, 0.17]**
Total events	12		124			
Heterogeneity: Chi² = 9.26, df = 16 (P = 0.90); I² = 0%						
Test for overall effect: Z = 8.67 (P < 0.00001)						
Total (95% CI)		**1906**		**1356**	**100.0%**	**0.12 [0.09, 0.18]**
Total events	38		185			
Heterogeneity: Chi² = 23.22, df = 33 (P = 0.90); I² = 0%						
Test for overall effect: Z = 11.33 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.20, df = 1 (P = 0.14), I² = 54.6%						



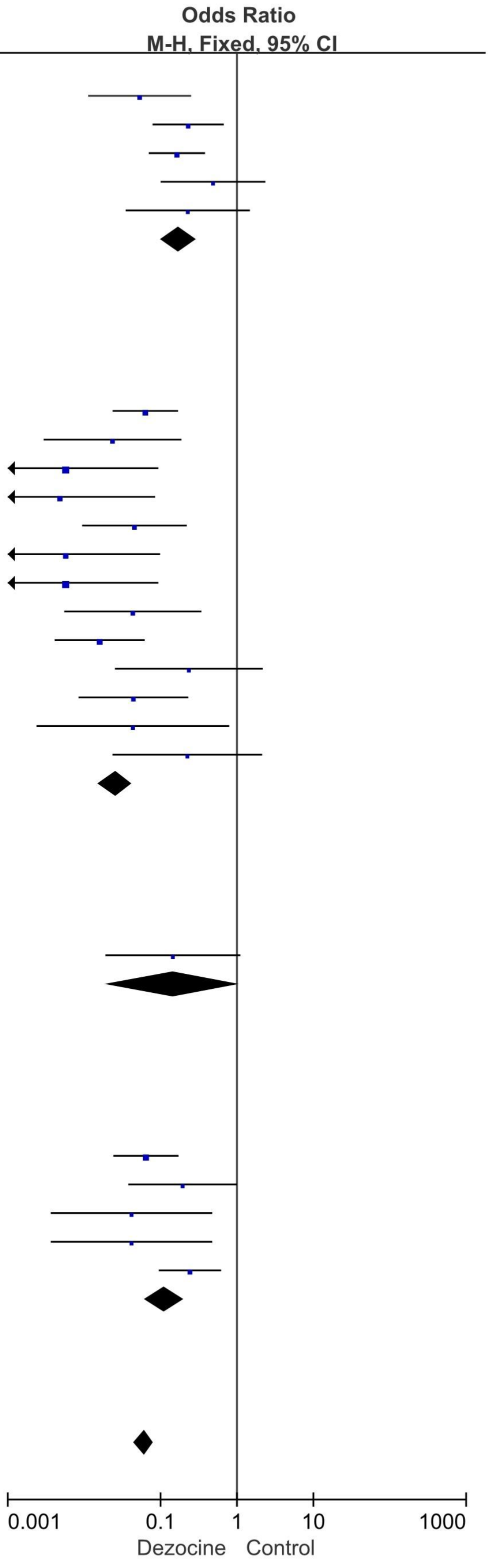
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
8.1.1 Incidence of severe FIC						
Bian 2012	0	50	3	50	1.5%	0.13 [0.01, 2.67]
Chen 2013	0	40	10	40	4.4%	0.04 [0.00, 0.64]
Gao 2013 (1)	7	40	3	14	1.5%	0.78 [0.17, 3.54]
Gao 2013 (2)	1	40	3	13	1.9%	0.09 [0.01, 0.91]
Gao 2013 (3)	1	40	2	13	1.2%	0.14 [0.01, 1.70]
Qiu L 2016	0	60	2	60	1.0%	0.19 [0.01, 4.11]
Qu 2012	0	60	7	60	3.1%	0.06 [0.00, 1.06]
Wang Z 2015	0	30	7	30	3.1%	0.05 [0.00, 0.95]
Wang Z 2016	0	30	5	30	2.3%	0.08 [0.00, 1.44]
Wu 2014 (1)	0	40	2	14	1.5%	0.06 [0.00, 1.37]
Wu 2014 (2)	0	40	2	13	1.5%	0.06 [0.00, 1.27]
Wu 2014 (3)	0	40	2	13	1.5%	0.06 [0.00, 1.27]
Xu 2015 (1)	0	100	2	34	1.6%	0.06 [0.00, 1.38]
Xu 2015 (2)	0	100	2	33	1.6%	0.06 [0.00, 1.34]
Xu 2015 (3)	0	100	1	33	0.9%	0.11 [0.00, 2.71]
Yuan 2015 (1)	8	30	4	10	1.9%	0.55 [0.12, 2.45]
Yuan 2015 (2)	0	30	3	10	2.1%	0.04 [0.00, 0.76]
Yuan 2015 (3)	0	30	3	10	2.1%	0.04 [0.00, 0.76]
Zhang 2013	0	40	9	40	3.9%	0.04 [0.00, 0.73]
Zhang 2016	0	30	2	30	1.0%	0.19 [0.01, 4.06]
Subtotal (95% CI)		**970**		**550**	**39.8%**	**0.12 [0.07, 0.20]**
Total events	17		74			
Heterogeneity: Chi² = 14.14, df = 19 (P = 0.78); I² = 0%						
Test for overall effect: Z = 7.85 (P < 0.00001)						
8.1.2 Incidence of severe SIC						
Li 2017 (1)	0	80	3	40	1.9%	0.07 [0.00, 1.32]
Li 2017 (2)	0	80	3	40	1.9%	0.07 [0.00, 1.32]
Liu 2015	0	185	25	185	10.7%	0.02 [0.00, 0.28]
Qiu 2016	0	100	39	100	16.5%	0.01 [0.00, 0.13]
Ruan 2017	0	35	10	35	4.4%	0.03 [0.00, 0.61]
Shen 2014	2	60	6	60	2.4%	0.31 [0.06, 1.60]
Wang 2016	0	185	25	185	10.7%	0.02 [0.00, 0.28]
Wang 2017	0	60	4	60	1.9%	0.10 [0.01, 1.97]
Wang H 2015	0	50	4	50	1.9%	0.10 [0.01, 1.95]
Xu 2014 (1)	0	40	3	40	1.5%	0.13 [0.01, 2.65]
Xu 2014 (2)	0	40	0	40		Not estimable
Zhao 2017	0	26	5	26	2.3%	0.07 [0.00, 1.41]
Zheng 2018 (1)	0	25	1	9	0.9%	0.11 [0.00, 2.99]
Zheng 2018 (2)	0	25	1	8	0.9%	0.10 [0.00, 2.66]
Zheng 2018 (3)	0	25	0	8		Not estimable
Zheng 2019	1	50	4	50	1.6%	0.23 [0.03, 2.18]
Zhou 2014	0	30	1	30	0.6%	0.32 [0.01, 8.24]
Subtotal (95% CI)		**1096**		**966**	**60.2%**	**0.05 [0.03, 0.10]**
Total events	3		134			
Heterogeneity: Chi² = 11.70, df = 14 (P = 0.63); I² = 0%						
Test for overall effect: Z = 8.67 (P < 0.00001)						
Total (95% CI)		**2066**		**1516**	**100.0%**	**0.08 [0.05, 0.12]**
Total events	20		208			
Heterogeneity: Chi² = 27.29, df = 34 (P = 0.79); I² = 0%						
Test for overall effect: Z = 12.02 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.40, df = 1 (P = 0.07), I² = 70.6%						

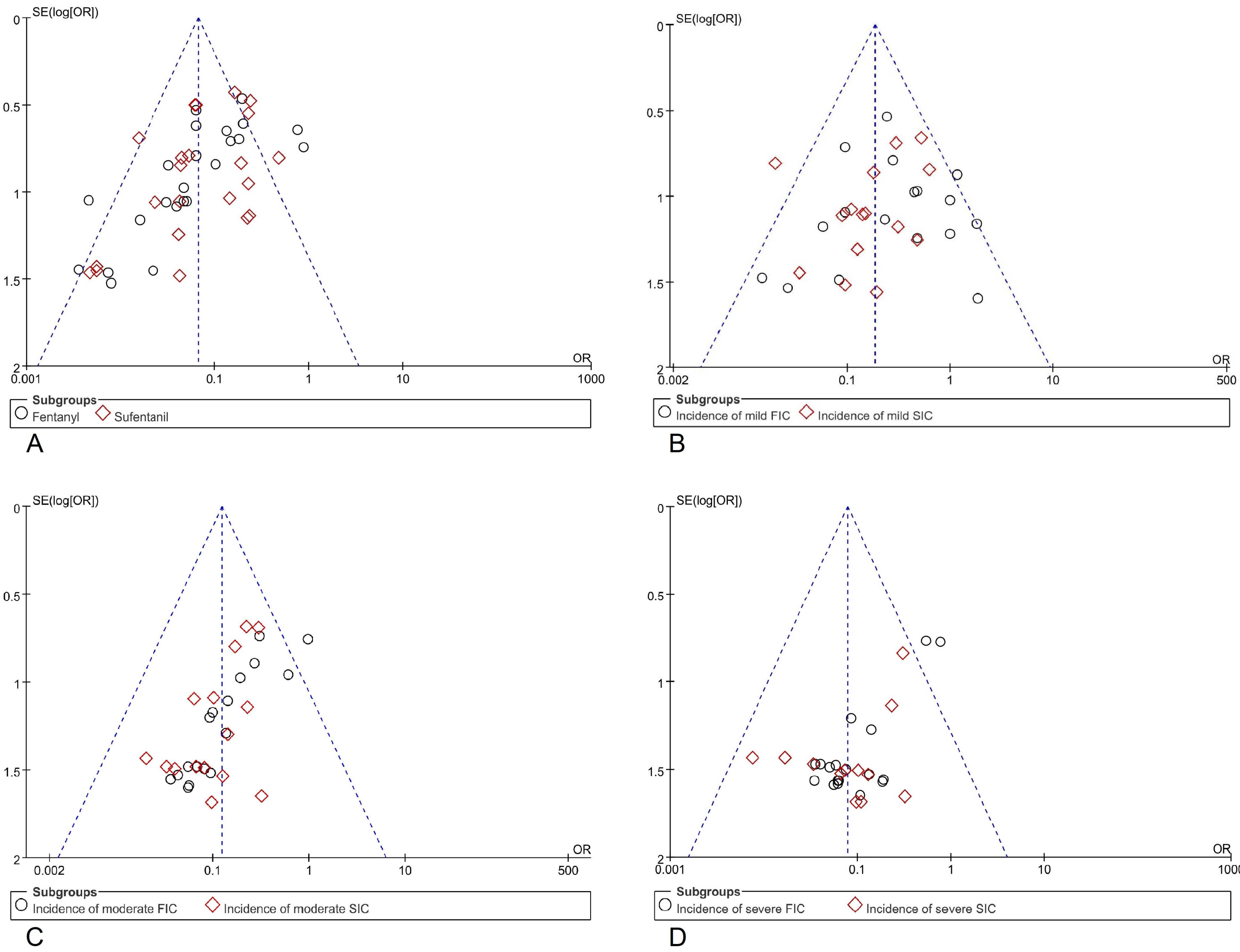


Study or Subgroup	Dezocine Events	Dezocine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
6.1.1 Dezocine 0.025-0.05 mg/kg						
Gao 2013 (1)	23	40	9	14	5.5%	0.75 [0.21, 2.65]
Qu 2012	0	60	16	60	2.5%	0.02 [0.00, 0.38]
Xu 2015 (1)	12	100	14	34	6.4%	0.19 [0.08, 0.48]
Xu 2015 (2)	4	100	13	33	5.6%	0.06 [0.02, 0.22]
Yuan 2015 (1)	17	30	6	10	5.0%	0.87 [0.20, 3.74]
Subtotal (95% CI)		**330**		**151**	**25.2%**	**0.22 [0.07, 0.68]**
Total events	56		58			
Heterogeneity: Tau² = 1.11; Chi² = 13.75, df = 4 (P = 0.008); I² = 71%						
Test for overall effect: Z = 2.61 (P = 0.009)						
6.1.2 Dezocine 0.1 mg/kg						
Gao 2013 (2)	7	40	7	13	5.3%	0.18 [0.05, 0.71]
Pi 2015	6	50	34	50	6.1%	0.06 [0.02, 0.18]
Qiu L 2016	1	60	15	60	3.7%	0.05 [0.01, 0.40]
Sun 2011	0	60	42	60	2.5%	0.00 [0.00, 0.06]
Wang 2015	1	70	53	70	3.7%	0.00 [0.00, 0.04]
Wang Z 2015	4	30	16	30	5.5%	0.13 [0.04, 0.48]
Wang Z 2016	5	30	15	30	5.7%	0.20 [0.06, 0.66]
Wu 2014 (1)	3	40	10	14	4.6%	0.03 [0.01, 0.17]
Xu 2015 (3)	0	100	13	33	2.5%	0.01 [0.00, 0.13]
Yuan 2015 (2)	4	30	6	10	4.6%	0.10 [0.02, 0.53]
Zhang 2013	1	40	18	40	3.7%	0.03 [0.00, 0.25]
Subtotal (95% CI)		**550**		**410**	**47.9%**	**0.05 [0.02, 0.11]**
Total events	32		229			
Heterogeneity: Tau² = 0.88; Chi² = 23.21, df = 10 (P = 0.01); I² = 57%						
Test for overall effect: Z = 7.59 (P < 0.00001)						
6.1.3 Dezocine 0.15-0.3 mg/kg						
Gao 2013 (3)	6	40	7	13	5.2%	0.15 [0.04, 0.61]
Wu 2014 (2)	1	40	8	13	3.3%	0.02 [0.00, 0.16]
Wu 2014 (3)	0	40	8	13	2.3%	0.01 [0.00, 0.16]
Yuan 2015 (3)	2	30	6	10	4.0%	0.05 [0.01, 0.32]
Subtotal (95% CI)		**150**		**49**	**14.9%**	**0.04 [0.01, 0.16]**
Total events	9		29			
Heterogeneity: Tau² = 0.65; Chi² = 4.85, df = 3 (P = 0.18); I² = 38%						
Test for overall effect: Z = 4.73 (P < 0.00001)						
6.1.4 Dezocine 5mg						
Bian 2012	1	50	15	50	3.7%	0.05 [0.01, 0.38]
Chen 2013	2	40	18	40	4.8%	0.06 [0.01, 0.30]
Zhang 2016	1	30	14	30	3.6%	0.04 [0.00, 0.33]
Subtotal (95% CI)		**120**		**120**	**12.1%**	**0.05 [0.02, 0.15]**
Total events	4		47			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 2 (P = 0.93); I² = 0%						
Test for overall effect: Z = 5.40 (P < 0.00001)						
Total (95% CI)		**1150**		**730**	**100.0%**	**0.07 [0.04, 0.12]**
Total events	101		363			
Heterogeneity: Tau² = 0.99; Chi² = 55.82, df = 22 (P < 0.0001); I² = 61%						
Test for overall effect: Z = 9.45 (P < 0.00001)						
Test for subgroup differences: Chi² = 5.24, df = 3 (P = 0.16), I² = 42.7%						



Study or Subgroup	Dezocine Events	Dezocine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
7.1.1 Dezocine 0.04-0.08 mg/kg						
Li 2017 (1)	2	80	13	40	3.5%	0.05 [0.01, 0.25]
Shen 2014	5	60	17	60	3.2%	0.23 [0.08, 0.67]
Wang 2017	10	60	33	60	5.6%	0.16 [0.07, 0.38]
Wang L 2015 (1)	7	25	4	9	0.9%	0.49 [0.10, 2.36]
Wang L 2015 (2)	3	25	3	8	0.8%	0.23 [0.03, 1.48]
Subtotal (95% CI)		**250**		**177**	**14.0%**	**0.18 [0.10, 0.30]**
Total events	27		70			
Heterogeneity: Chi² = 4.21, df = 4 (P = 0.38); I² = 5%						
Test for overall effect: Z = 6.41 (P < 0.00001)						
7.1.2 Dzocine 0.1 mg/kg						
Fang 2016	6	62	39	62	7.2%	0.06 [0.02, 0.17]
Li 2017 (2)	1	80	14	40	3.8%	0.02 [0.00, 0.19]
Liu 2015	0	185	59	185	12.2%	0.01 [0.00, 0.09]
Meng 2013	0	40	29	40	6.0%	0.00 [0.00, 0.08]
Ruan 2017	2	35	20	35	3.9%	0.05 [0.01, 0.22]
Sheng 2017	0	48	31	48	6.4%	0.01 [0.00, 0.10]
Wang 2016	0	185	59	185	12.2%	0.01 [0.00, 0.09]
Wang H 2015	1	50	16	50	3.2%	0.04 [0.01, 0.34]
Wu 2014 (1)	3	50	40	50	7.7%	0.02 [0.00, 0.06]
Wu 2014 (2)	1	50	4	50	0.8%	0.23 [0.03, 2.18]
Zhao 2017	2	26	17	26	3.2%	0.04 [0.01, 0.23]
Zhou 2014	0	30	8	30	1.7%	0.04 [0.00, 0.79]
Zhu 2018	1	30	4	30	0.8%	0.22 [0.02, 2.14]
Subtotal (95% CI)		**871**		**831**	**68.9%**	**0.03 [0.02, 0.04]**
Total events	17		340			
Heterogeneity: Chi² = 16.90, df = 12 (P = 0.15); I² = 29%						
Test for overall effect: Z = 14.00 (P < 0.00001)						
7.1.3 Dezocine 0.12 mg/kg						
Wang L 2015 (3)	2	25	3	8	0.9%	0.14 [0.02, 1.11]
Subtotal (95% CI)		**25**		**8**	**0.9%**	**0.14 [0.02, 1.11]**
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
7.1.4 Dezocine 2-5mg						
Qiu 2016	5	100	45	100	8.8%	0.06 [0.02, 0.17]
Zheng 2018 (1)	7	25	6	9	1.3%	0.19 [0.04, 1.00]
Zheng 2018 (2)	1	25	4	8	1.2%	0.04 [0.00, 0.47]
Zheng 2018 (3)	1	25	4	8	1.2%	0.04 [0.00, 0.47]
Zheng 2019	8	50	22	50	3.8%	0.24 [0.09, 0.62]
Subtotal (95% CI)		**225**		**175**	**16.2%**	**0.11 [0.06, 0.20]**
Total events	22		81			
Heterogeneity: Chi² = 5.51, df = 4 (P = 0.24); I² = 27%						
Test for overall effect: Z = 7.44 (P < 0.00001)						
Total (95% CI)		**1371**		**1191**	**100.0%**	**0.06 [0.05, 0.08]**
Total events	68		494			
Heterogeneity: Chi² = 49.24, df = 23 (P = 0.001); I² = 53%						
Test for overall effect: Z = 18.60 (P < 0.00001)						
Test for subgroup differences: Chi² = 28.88, df = 3 (P < 0.00001), I² = 89.6%						




SE(log[OR])
OR
Subgroups
Fentanyl
Sufentanil
A
Incidence of mild FIC
Incidence of mild SIC
B
Incidence of moderate FIC
Incidence of moderate SIC
C
Incidence of severe FIC
Incidence of severe SIC
D

Supplemental Table 1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract, page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction, page 4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction, page 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods, page 5-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods—Study inclusion criteria, page 6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods—Search strategy, page 6

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Methods—Search strategy, page 6, and Supplemental Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods—Study inclusion criteria, page 6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods—Data abstraction, page 7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods—Data abstraction, page 7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods—Study quality assessmen, page 7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods—Statistical analysis, page 8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods—Statistical analysis, page 8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods—Statistical analysis, page 7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods—Statistical analysis, page 7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results-Search results page 9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results-Meta-analysis, page 9-
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results-Study quality and risk bias, page 9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results-Meta-analysis, page 10-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results-Meta-analysis, page 10-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results-Meta-analysis, page 12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results- page 12
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion- Page 13-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion- Page 15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion- Page 16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding- Page 16

Supplemental Table 2. 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

Ovid

No.	**Search items**
#1	dezocine.mp. [mp=title, abstract, full text, caption text]
#2	(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").mp. [mp=title, abstract, full text, caption text]
#3	(cough or coughs or coughing or antitussive or anti-tussive).mp. [mp=title, abstract, full text, caption text]
#4	("randomized controlled trial" or "controlled clinical trial" or randomized or placebo or randomly).mp. [mp=title, abstract, full text, caption text]
#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)	