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

Li-Xian He,1,2 Yun-Tai Yao,1 Ken Shao,3 Yuan-Yuan Zhao,3,4 Jie Ma4

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 CRD4201914255.
such as priming, dilution and slow injection of opioids, have been used to manage OIC.\(^1\)\(^2\)\(^4\)\(^\text{–}\)\(^9\)\(^1\)\(^1\)\(^5\)\(^\text{–}\)\(^1\)\(^9\)\(^\text{–}\)\(^2\)\(^2\) Unfortunately, the efficacy and safety of those antitussive interventions remain controversial.

Dezocine (DZC), a mixed opioid agonist/antagonist, 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.\(^2\)\(^3\)\(^\text{–}\)\(^2\)\(^7\) Although no longer used clinically in Western countries, DZC has gained popularity in China and been widely used as a perioperative analgesic for decades.\(^2\)\(^4\)\(^\text{–}\)\(^3\)\(^2\) 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 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 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.

---

**Figure 1 Flowchart.**

Records identified through database searching (n = 122)

Additional records identified through other sources (n = 0)

Records after duplicates removed (n = 70)

Records screened (n = 70)

Full-text articles assessed for eligibility (n = 45)

Studies included in qualitative synthesis (n = 33)

Studies included in quantitative synthesis (meta-analysis) (n = 33)

Records excluded (n = 25)

Full-text articles excluded (n = 12)

Review (n=5)

Lack of Control group (n=4)

Lack of endpoints (n=1)

Non-RCT (n=2)
Table 1: Characteristics of the included RCTs and administration protocols of dezocine

| Study            | Language | Age (years) | Sex (M/F) | Type | Dose (μg/kg) | Duration (s) | Timing (min) | n | Dose (mg/kg) | CID | CIC | SCID | SCIC | Adverse effect |
|------------------|----------|-------------|-----------|------|--------------|--------------|--------------|---|--------------|-----|-----|------|------|----------------|
| Qing-Ming et al  | Chinese  | 23–64       | 48/53     | S    | 3.0          | ≤5 s         | 5            | 50 | 5 mg         |     |     |      |      |                 |
| Xiao-Ming and Guang-Hong | Chinese   | 20–60       | 39/41     | S    | 2.0          | ≤2 s         | NR           | 40 | 5 mg         |     |     |      |      |                 |
| Li                | Chinese  | 20–60       | 66/58     | F    | 5.0          | ≤3 s         | 10           | 62 | 0.1          |     |     |      |      |                 |
| Ya-Ping et al 19  | Chinese  | 20–50       | 0/120     | F    | 3.0          | NR           | 10           | 40 | 0.05         |     |     |      |      |                 |
| Li Yan-Juan et al | Chinese  | 23–72       | 134/106   | S    | 0.3          | ≤10 s        | 10           | 80 | 0.05         |     |     |      |      |                 |
| Liu et al 6       | English  | 18–70       | 189/181   | S    | 0.5          | >3 s         | 2            | 185| 0.1          |     |     |      |      |                 |
| Zhen-chen et al   | Chinese  | 28–55       | 39/41     | S    | 0.4          | ≤2 s         | 2            | 40 | 0.1          |     |     |      |      |                 |
| Ming-fang et al 12 | Chinese  | 22–65       | 51/49     | F    | 4.0          | ≤3 s         | 10           | 50 | 0.1          |     |     |      |      |                 |
| Jian-Bin et al 63 | Chinese  | 20–65       | 119/81    | S    | 0.5          | NR           | NR           | 100| 5 mg         |     |     |      |      |                 |
| Liang-Cheng et al | Chinese  | 18–45       | 0/120     | F    | 3.0          | ≤5 s         | 2            | 60 | 0.1          |     |     |      |      |                 |
| Hui et al 15      | Chinese  | 18–65       | 40/80     | F    | 4.0          | ≤5 s         | 2            | 60 | 0.05         |     |     |      |      |                 |
| Tian-yi et al 16  | Chinese  | 24–55       | NR        | S    | 0.4          | NR           | 10           | 35 | 0.1          |     |     |      |      |                 |
| Jie et al 17      | Chinese  | 20–65       | 0/120     | S    | 0.3          | <5 s         | 5            | 60 | 0.05         |     |     |      |      |                 |
| Da-Wei et al 18   | Chinese  | 19–70       | 44/52     | S    | 0.3          | ≤10 s        | 8            | 48 | 0.1          |     |     |      |      |                 |
| Sun et al 4       | Chinese  | 20–60       | 68/52     | F    | 5.0          | ≤2 s         | 10           | 60 | 0.1          |     |     |      |      |                 |
| Li et al 19       | Chinese  | 15–60       | 78/62     | F    | 5.0          | ≤5 s         | 10           | 70 | 0.1          |     |     |      |      |                 |
| Jun-Liang and Rong | Chinese  | 18–70       | 190/180   | S    | 0.5          | NR           | Immediately  | 185| 0.1          |     |     |      |      |                 |
| Zhi-Yong 31       | Chinese  | 22–61       | 67/53     | S    | NR           | NR           | NR           | 60 | 0.05         |     |     |      |      |                 |
| Hui and En-Ming   | Chinese  | 25–65       | 42/58     | S    | 0.3          | <5 s         | 10           | 50 | 0.1          |     |     |      |      |                 |
| Li-Ping 13        | Chinese  | 60–85       | 59/41     | S    | 0.3          | ≤5 s         | 5            | 25 | 0.04         |     |     |      |      |                 |

Continued
### Table 1
Continued

| Study | Language | Age (years) | Sex (M/F) | Type | Dose (μg/kg) | Duration (s) | Timing (min) | n | Dose (mg/kg) | 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 s | 10 | 40 | 0.1 | 40 | 0.2 | 14 | Equal volume | NS | 7.50% | 2.50% | 0 | 0.00% | NR |
| Qing et al 57 | Chinese | 20–65 | 102/98 | S | 0.5 | <3 s | 5 | 50 | 0.1 | 50 | 0.1 | 50 | 5 mL | NS | 6.00% | 2.00% | 0 | 7.50% | NR |
| Xu et al 58 | English | 20–70 | 243/157 | F | 3 | <5 s | Immediately | 100 | 0.025 | 100 | 0.05 | 34 | NS | 12.00% | 4.00% | 0 | 5.00% | NR |
| Ming-Feng and Yu 59 | Chinese | 25–55 | NR | F | 3 | NR | 10 | 30 | 0.05 | 30 | 0.1 | 50 | 5 mL | NS | 56.67% | 13.33% | 0 | 6.67% | DI, DR |
| Jian-Feng and Han-Zhong 60 | 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 61 | 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 62 | Chinese | 20–61 | 19/33 | S | 5 | NR | 5–8 | 26 | 0.1 | 26 | NS | NS | 7.69% | 65.38% | 0 | 19.23% | NR |
| Qin-Shu 63 | Chinese | 39±5 | 61/39 | S | 0.4 | ≤3 s | 1 | 25 | 2 mg | 25 | 2 mg | 25 | 2 mg | Equal volume | NS | 28.00% | 4.00% | 0 | 8.00% | NR |
| Xiao-Zhen et al 64 | Chinese | 18–56 | 92/108 | S | 0.4 | ≤6 s | 3 | 50 | 5 mg | 50 | 2 mL | NS | 16.00% | 44.00% | 0 | 8.00% | NR |
| Tao-Yu et al 65 | 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 66 | 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.
Search strategy
We conducted a systemic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Quality of Reporting of Meta-analysis (PRISMA) Guidelines (online supplemental table 1). 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), 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). 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 to further identify relevant studies.

RESULTS
Characteristics of the included trials
As shown in figure 1, initial literature search generated 70 results. Finally, 33 RCTs involving 4442 patients were included in the meta-analysis. Of the 33 RCTs, 30 were written in Chinese, and the other 3 in English (table 1). The 33 RCTs were performed, respectively, in 2 provincial hospitals, 16 urban hospitals, and 2 county hospitals 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.
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, I²=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, I²=61%) and SIC (5.0% vs 41.5%, OR=0.07, 95% CI 0.04 to 0.12, p<0.00001, I²=55%). 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.

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 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, I²=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
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), Li et al and Ming-Feng and Yu (preoperative medication with phenobarbital) and 53% to 36% for SIC by exclusion of four studies conducted from Jie et al (female patients only), Qing et al (duration of sufentanil injection more than 10 s), Li-Ping and Xiao-Zhen et al (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). 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. Fentanyl and its derivatives sufentanil are commonly used opioid anaesthetics 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. 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 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. This may suggest that sex to some extent contributes to heterogeneity. In addition to that, study from Qing et al 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. Additionally, many factors can contribute to the occurrence of OIC, which can be divided into two categories.

Figure 3 Risk of bias summary.
**Table 2** Quality assessment for primary outcomes

| Effect of DZC on OIC occurrence rate | Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | DZC | Control | Relative (95% CI) | Absolute | Quality | Importance |
|-------------------------------------|-------------------|--------|--------------|---------------|--------------|-------------|---------------------|------|---------|-----------------|----------|---------|------------|
|                                     | 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 | CRITICAL |
|                                     |                   |         |              |               |              |             |                     |      |         | 50%              |          |         | HIGH       |
|                                     |                   |         |              |               |              |             |                     |      |         |                  |          |         |            |
| 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 | CRITICAL |
|                                     |                   |         |              |               |              |             |                     |      |         | 53.9%            |          |         | HIGH       |
|                                     |                   |         |              |               |              |             |                     |      |         |                  |          |         |            |
| 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 | CRITICAL |
|                                     |                   |         |              |               |              |             |                     |      |         | 44.2%            |          |         | HIGH       |
|                                     |                   |         |              |               |              |             |                     |      |         |                  |          |         |            |

DZC, dezocine; FIC, fentanyl-induced cough; OIC, opioid-induced cough; SIC, sufentanil-induced cough.
| Quality assessment for secondary outcomes | Number of patients | Effect | Relative (95% CI) | Absolute | Quality | Importance |
|-----------------------------------------|--------------------|--------|-------------------|----------|---------|------------|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | DZC | Control | | | |
| 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%) | OR 8.06 (1.40 to 46.35) | – | ÅÅÅO IMPORTANT |
| | | | | | | | | | | | | |
| | 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%) | OR 4.91 (0.80 to 30.19) | – | ÅÅÅ HIGH IMPORTANT |
| | | | | | | | | | | | | |
| | 1 Randomised trials | Very serious | No serious inconsistency | No serious indirectness | Serious | None | 4/185 (2.2%) | 0/185 (0%) | OR 9.2 (0.49 to 172.07) | – | ÅOOO VERY LOW CRITICAL |
| | | | | | | | | | | | | |
| | 1 Randomised trials | Serious | No serious indirectness | Very serious | None | 2/48 (4.2%) | 11/48 (22.9%) | not pooled | not pooled | ÅOOO VERY LOW IMPORTANT |
| | | | | | | | | | | | | |
| | 2 Randomised trials | Serious | Very serious | No serious indirectness | Serious | None | 17/233 (7.3%) | 9/233 (3.9%) | OR 1.7 (0.00 to 766.69) | 25 more per 1000 (from 39 fewer to 930 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%) | OR 1.32 (0.03 to 53.18) | 20 more per 1000 (from 65 fewer to 725 more) | ÅÅÅO MODERATE IMPORTANT |

DZC, dezocine.
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). 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
pharmaceutical and non-pharmaceutical interventions has been tested, some proved to be effective, some ineffective and some have side effects. DZC, a mixed κ and μ opioid receptor agonist-antagonist, is not a well-known drug in Western countries. However, DZC is widely applied as perioperative pain analgesic agent in China for decades. The present meta-analysis demonstrated that DZC could significantly suppress both FIC and SIC, with several trials 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/serotonin reuptake inhibition and reduce cough. Whether a central gating mechanisms via

| Study or Subgroup | Dezocine | Control | Odds Ratio | Odds Ratio |
|-------------------|----------|---------|------------|------------|
|                   | Events   | Total   | Weight     | M-H. Random. 95% CI | M-H. Random. 95% CI |
| 9.1.1 Dizziness   |          |         |            |             |                       |
| Wang L 2015 (3)   | 6        | 25      | 25         | 7.2%        | 17.00 [0.90, 320.37]  |
| Yuan 2015 (3)     | 2        | 30      | 30         | 7.0%        | 5.35 [0.25, 116.31]  |
| Zhou 2014         | 2        | 30      | 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: Tau^2 = 0.00; Chi^2 = 0.39, df = 2 (P = 0.82); I^2 = 0% |
| Test for overall effect: Z = 2.34 (P = 0.02) |

| 9.1.2 Drowsiness  |          |         |            |             |                       |
| Wang L 2015 (3)   | 4        | 25      | 25         | 7.2%        | 10.67 [0.54, 209.64] |
| Yuan 2015 (3)     | 1        | 30      | 30         | 6.7%        | 3.10 [0.12, 79.23]   |
| Zhou 2014         | 1        | 30      | 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: Tau^2 = 0.00; Chi^2 = 0.43, df = 2 (P = 0.81); I^2 = 0% |
| Test for overall effect: Z = 1.72 (P = 0.09) |

| 9.1.3 Truncal rigidity |          |         |            |             |                       |
| Wang 2016          | 4        | 185     | 185        | 7.3%        | 9.20 [0.48, 172.07]   |
| Subtotal (95 CI)   | 185      | 185     | 7.3%       |             | 9.20 [0.48, 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      | 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      | 48         | 8.6%        | 0.09 [0.01, 0.76]     |
| Wang 2016           | 16       | 185     | 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: Tau^2 = 17.84; Chi^2 = 12.04, df = 1 (P = 0.0005); I^2 = 92% |
| Test for overall effect: Z = 0.17 (P = 0.86) |

| 9.1.8 Nausea and emesis |          |         |            |             |                       |
| Sheng 2017           | 1        | 48      | 48         | 8.7%        | 0.04 [0.01, 0.34]     |
| Wang 2016            | 20       | 185     | 185        | 7.4%        | 45.95 [2.76, 765.77]  |
| Zhu 2018             | 3        | 30      | 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: Tau^2 = 9.35; Chi^2 = 16.75, df = 2 (P = 0.0002); I^2 = 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: Tau^2 = 4.43; Chi^2 = 44.89, df = 12 (P < 0.0001); I^2 = 73% |
| Test for overall effect: Z = 1.22 (P = 0.22) |
| Test for subarous differences: Chi^2 = 15.06, df = 5 (P = 0.01); I^2 = 66.8% |

Figure 5 Possible adverse effects.
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 colleagues4 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.

**Contributors** L-XH and Y-TY were involved in the study design, data collection, data analysis and drafting the manuscript, and responsible for the overall content as the guarantors. KS, Y-YZ and JM participated in data collection. All authors have read and approved the manuscript. LX-H and Y-TY are responsible for the overall content as the guarantors.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**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.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

**ORCID iDs**

Li-Xian He http://orcid.org/0000-0002-6632-7335

---

**Table 4** Reliability of results

| 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 I² (%) | P | Analysis model | OR 95% CI | Overall effect 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.
REFERENCES

1. El Baisari 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, Kasaya 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 dexametomidine 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 JG, et al. The effect of lidocaine on remifentanil-induced cough. *Anaesth Analg* 2008;83:495–6.

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. Hanamand A, Safavi M, Khaledinejadi F, et al. 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. *Anaesthesiology* 2010;65:897–703.

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 Anaesth* 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. *Anaesth 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;53:1226–9.

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 Zhonglan Univ* 2017;18:589–92.

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 anesthetics. *Anesth Analg* 1978;57:563–6.

24. Liu R, Huang X-P, Yeliseev A, et al. Molecular targets of dezocine and their clinical implications. *Anesthesiology* 2014;120:714–23.

25. Wang Y-H, Chai J-F, Xu X-J, et al. Pharmacological characterization of dezocine, a potent analgesic acting as a μ partial agonist and δ partial agonist. *Sci Rep* 2018;8:14087.
Open access

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 Dezocine 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.