# Clonidine versus tramadol for post spinal anesthesia shivering

# A meta-analysis of randomized controlled trials

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## ABSTRACT

الأهداف: مقارنة عقار الكلونيدين بالترامادول في السيطرة على الارتعاش بعد تخدير العمود الفقري.

المنهجية : أجري البحث في الأدبيات المحدثة حتى أغسطس 2020 وأدرجت في هذه الدراسة التجارب المعشاة ذات الشواهد التي تقارن عقار الكلونيدين والترامادول للسيطرة على الارتعاش بعد تخدير العمود الفقري .

النتائج: وجدنا 14 دراسة مع 960 مريض. أظهر عقار الكلونيدين معدل أقل فعالية بالسيطرة على الارتعاش ( OR: 0.59 % 978 فترة الثقة: –0.40 معدل حدوث ( 260-0.80 % 96-12 )، ولكن مع انخفاض معدل حدوث الغثيان والقيء والدوخة. زاد عقار الكلونيدين من معدل حدوث بطء القلب وانخفاض ضغط الدم والتخدير مقارنة بعقار الترامادول.

**الخلاصة**: اظهرت الدراسة أن عقار الترامادول له فعالية أكثر في السيطرة على الارتعاش بالمقارنه مع عقار الكلونيدين، ولكنه يرفع معدل حدوث الغثيان والقىء والدوخة.

**Objectives:** To compare clonidine with tramadol for shivering control following spinal anesthesia.

**Methods:** The literature was searched updated to August 2020, and only randomized controlled trials comparing clonidine and tramadol for shivering control following spinal anesthesia were eligible for this study.

**Results:** Fourteen studies with 960 patients were identified. Clonidine demonstrated a lower effective rate of shivering control (OR: 0.59; 95% CI: 0.40-0.88; p=0.009; I<sup>2</sup>=36%), but with decreased occurrence of nausea, vomiting, and dizziness. Clonidine increased the occurrence of bradycardia, hypotension, and sedation compared to tramadol.

**Conclusion:** Tramadol is more effective for shivering control than clonidine, but with increased occurrence of nausea, vomiting, and dizziness.

#### PROSPERO No: CRD42020207979

Keywords: shivering, spinal anesthesia, clonidine, tramadol

#### Saudi Med J 2021; Vol. 42 (4): 363-362 doi: 10.15537/smj.2021.42.4.20200342

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Received 7th October 2020. Accepted 26th January 2021.

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Shivering frequently occurs in the perioperative period.<sup>1</sup> Various medications have been studied for shivering control, including dexmedetomidine, clonidine, pethidine, tramadol, magnesium sulphate, dexamethasone, and ketamine.<sup>2</sup> Despite availability of numerous drugs for shivering control, no single drug has been found to be effective without any side effects.

In recent years, increasing randomized controlled trials (RCTs) comparing clonidine with tramadol for shivering control following spinal anesthesia have been conducted. Hence, we conducted this meta-analysis to compare clonidine with tramadol for shivering control following spinal anesthesia.

**Methods.** The recommendations of the PRISMA guidelines were followed in this meta-analysis.<sup>3</sup> We



searched Pubmed, Embase, Cochrane library, and Google Scholar, updated to August 2020 without language restrictions. All databases were searched using the following terms: "shivering," "clonidine," "tramadol," "hypothermia," "spinal anesthesia," "intrathecal injection," or "subarachnoid anesthesia." The references of all included articles were manually scanned for additional relevant publications.

Inclusion criteria were as follows: i) the study design is an RCT; ii) the participants were adult patients undergoing surgeries under spinal anesthesia; iii) the intervention of the study involved treating shivering following spinal anesthesia with intravenous clonidine or tramadol. The exclusion criteria were as follows: i) the study is not an RCT; ii) animal studies, meeting papers, editorials, correspondence, case reports or review papers; iii) and the intervention of the study includes clonidine or tramadol combined with other medications for shivering treatment.

The quality of the eligible RCTs were independently assessed by NW and HZ. Study quality was assessed with the Jadad score and the Cochrane risk of bias tool.<sup>4,5</sup> Disagreement was solved by JW. The data from each eligible RCT was separately extracted by JW and YL. Disagreement was also settled by RW. The following data were obtained from each eligible article: number of patients, publication year, study interventions, effective parameters of shivering control (effective rate of shivering control and recurrence rate), and the related complications. The main outcome was the efficacy of shivering control, and the secondary outcome was the related complications (hypotension, bradycardia, sedation, nausea, vomiting, dizziness, dry mouth).

Statistical analysis. Review Manager 5.3 was used for statistical analysis. The efficacy of shivering control and the related complications were displayed by the odds ratio (OR) with 95% confidence intervals (CI). Heterogeneity was estimated by the value of I<sup>2</sup>. If I<sup>2</sup> was less than 50%, data were analyzed utilizing the fixedeffect model, or the random-effects model. P<0.05 was statistically significant.

**Results.** Initially, we found 476 studies. After assessment, 22 full texts were included; however, 8 articles were excluded because they involved children or animals, or were non-RCTs or correspondences.

**Disclosure**. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Thus, 14 RCTs involving 960 patients were eligible for the present study.<sup>6-19</sup> (Figure 1) Table 1 displays the characteristics of the identified RCTs in details and shows that all included studies in this meta-analysis had moderate to high quality. A risk-of-bias overview is shown in Figure 2.

As shown in Figure 3A, 12 studies including 860 participants recorded the effective rate of shivering control, and clonidine was less effective than tramadol (OR: 0.59; 95% CI: 0.40-0.88; p=0.009; I<sup>2</sup>=36%). The difference in shivering recurrence rate was not statistically significant between clonidine and tramadol (OR: 0.82; 95% CI: 0.52-1.31; p=0.41; I<sup>2</sup>=36%). (Figure 3B)

The most common treatment-related complications were evaluated. Clonidine had higher incidences of hypotension (OR: 5.97; 95% CI: 2.76-12.91;

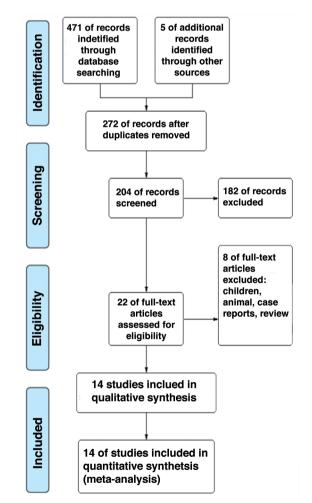
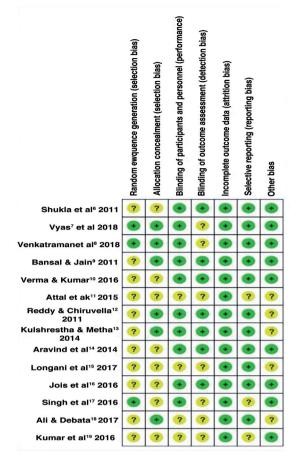


Figure 1 - Flow chart of selected randomized controlled trials.

#### Table 1 - Characteristics of the included trials.

| Author/<br>date                             | Dosage  | Study<br>type | Jadad<br>score | Sample<br>size<br>D/T | Patient characteristics;<br>surgical setting   | Type of anesthesia;<br>drug for anesthesia                    | Degrees of shivering                                   | Outcomes<br>measures        |
|---|---|---------------|----------------|-----------------------|--|---|--|-----------------------------|
| Shukla et al <sup>6</sup><br>2011           | Clonidine<br>0.5µg/kg;<br>tramadol<br>0.5 mg/kg                       | RCT           | 4              | 40/40                 | 18-40 yr, ASA: I;<br>Elective abdominal,<br>orthopaedic and<br>gynaecological surgeries                                      | Spinal anesthesia;<br>0.5% bupivacaine<br>10-15 mg            | Grades 3 or 4  | 1, 2 , 3 , 4,<br>5, 6, 7, 8 |
| Vyas et al <sup>7</sup><br>2018             | Clonidine<br>1 µg/kg;<br>tramadol<br>1 mg/kg                          | RCT           | 4              | 30/30                 | 18-65 yr, ASA: I-II;<br>Elective lower abdominal<br>and lower limb surgeries   | Spinal anesthesia;<br>0.5% heavy<br>bupivacaine               | Grades 1-4<br>for at least 2<br>minutes                | 1, 2 , 3 , 4,<br>5, 6, 7, 8 |
| Venkatraman<br>et al <sup>8</sup><br>2018   | Clonidine<br>1 μg/kg;<br>tramadol<br>1 mg/kg                          | RCT           | 5              | 30/30                 | 18-70 yr, ASA: I-II;<br>Lower abdominal, lower<br>limb, orthopaedic and<br>plastic surgeries                                 | Spinal anesthesia;<br>No mention                              | Grades 2, 3<br>or 4                                    | 1, 2, 3, 4,<br>5, 6,        |
| Bansal & Jain <sup>9</sup><br>2011          | Clonidine 150µg;<br>tramadol<br>50 mg                                 | RCT           | 4              | 30 /30                | 18-65 yr, ASA: I-III;<br>Urological, inguinal, and<br>lower limb surgeries   | Spinal anesthesia;<br>0.5% heavy<br>bupivacaine<br>3.2-3.5 mL | Grade 2 or 3   | 1, 2, 3,<br>5, 6,           |
| Verma &<br>Kumar <sup>10</sup><br>2016      | Clonidine<br>0.5µg/kg;<br>tramadol<br>1.5 mg/kg<br>(maximum<br>100mg) | RCT           | 3              | 30/30                 | 18-45 yr, ASA: I-II;<br>Elective abdominal,<br>gynecological and<br>orthopedic surgeries                                     | Spinal anesthesia;<br>0.5% heavy<br>bupivacaine<br>15 mg      | Grade 2, 3 or<br>grade 4                               | 1, 2, 3, 4,<br>5, 6         |
| Attal et al <sup>11</sup><br>2015           | Clonidine<br>50µg;<br>tramadol<br>50 mg                               | RCT           | 3              | 30/30                 | 18-40 yr, ASA: I-II;<br>Elective lower abdominal<br>and lower limb surgeries   | Spinal anesthesia;<br>0.5% heavy<br>bupivacaine<br>3.5 mL     | Grade 3 or 4<br>for at least 2<br>minutes              | 1, 2 , 3 , 4,<br>5, 6, 8    |
| Reddy &<br>Chiruvella <sup>12</sup><br>2011 | Clonidine<br>50µg IV;<br>tramadol<br>50 mg IV                         | RCT           | 4              | 45/45                 | 18-35 yr, ASA: I-II;<br>Elective or emergency<br>caesarean section   | Spinal anesthesia;<br>0.5% heavy<br>bupivacaine<br>10 mg      | Grade 3 or 4<br>for at least 3<br>minutes              | 1, 2 , 4, 5,<br>6, 8        |
| Kulshrestha <sup>13</sup><br>2014           | Clonidine<br>50µg IV;<br>tramadol<br>50 mg IV                         | RCT           | 4              | 45/45                 | 18-35 yr, ASA: I-II;<br>Elective Elective Lower<br>Segment Caesarean<br>Section  | Spinal anesthesia;<br>0.5% bupivacaine<br>12mg                | Grade 3 or 4<br>for at least 3<br>minutes              | 1, 2 , 3 , 4,<br>5, 6, 7, 8 |
| Aravind et al <sup>14</sup><br>2014         | Clonidine<br>1 µg/kg;<br>tramadol<br>1 mg/kg IV                       | RCT           | 4              | 40/40                 | 18-40 yr, ASA: I-II;<br>Various surgeries  | Spinal anesthesia;<br>0.5% heavy<br>bupivacaine               | Grade 2, 3 or<br>grade 4<br>for at least 2<br>minutes. | 1, 2, 5                     |
| Longani et al <sup>15</sup><br>2017         | Clonidine<br>150µg IV;<br>tramadol<br>50 mg IV                        | RCT           | 3              | 40/40                 | 25-50 yr, ASA: I-II;<br>Elective lower stomach<br>and lower appendage<br>surgeries,  | Spinal anesthesia;<br>0.5% bupivacaine<br>14 mg               | Grade 3 or 4<br>for at least 2<br>minutes              | 1, 2 , 3, 4,<br>5, 8        |
| Jois et al <sup>16</sup><br>2016            | Clonidine<br>0.5µg/kg IV;<br>tramadol<br>0.5 mg/kg IV                 | RCT           | 4              | 40/40                 | 25-50 yr, ASA: I-II;<br>Lower abdominal and<br>lower limb surgeries  | Spinal anesthesia<br>0.5% heavy<br>bupivacaine 2-4mL          | Grade 3 or 4   | 1, 2, 3, 4,<br>5, 6, 7, 8   |
| Singh et al <sup>17</sup><br>2016           | Clonidine<br>0.5µg/kg IV;<br>tramadol<br>0.5 mg/kg IV                 | RCT           | 4              | 30/30                 | 20-50 yr, ASA: I-II;<br>elective lower abdominal,<br>lower limb orthopaedic<br>and gynaecological<br>surgeries               | Spinal anesthesia<br>0.5% heavy<br>bupivacaine 15 mg          | Grade 3 or 4   | 1, 2 , 3 , 4,<br>5, 6, 8    |
| Ali &<br>Debata <sup>18</sup><br>2017       | Clonidine<br>50µg IV;<br>tramadol<br>50 mg IV                         | RCT           | 3              | 30/30                 | 18-60 yr, ASA: I-II;<br>elective lower abdominal<br>and lower limb surgery<br>under spinal anesthesia                        | Spinal anesthesia<br>0.5% heavy<br>bupivacaine                | Grade 1, 2<br>or 3                                     | 2, 5                        |
| Kumar et al <sup>19</sup><br>2016           | Clonidine<br>0.6µg/kg IV;<br>tramadol<br>1.0 mg/kg IV                 | RCT           | 3              | 20/20                 | 18-60 yr, ASA: I-II;<br>elective lower abdominal<br>surgeries,orthopaedics<br>lower limb surgeries and<br>plastic surgeries. | Spinal anesthesia<br>0.5% heavy<br>bupivacaine 15 mg          | Grades 3 or 4  | 3                           |

RCT: randomized controlled trial, ASA: American Society of Anesthesiologists, YR: year, IR: intravenous, Outcome measures: 1) Effective rate of shivering control, 2) Time to cease shivering, 3) Recurrent rate of shivering, 4) The incidence of bradycardia and hypotension, 5) The incidence of nausea and vomiting, 6) The incidence of sedation, 7) The incidence of dizziness, 8) The incidence of dry mouth



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Figure 2 - Risk of bias evaluation.

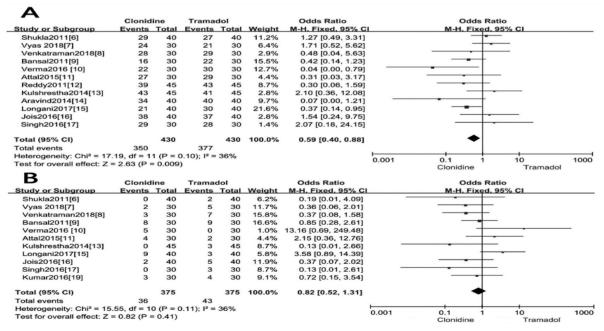


Figure 3 - A) Forest plot for effective rate of shivering control, B) and recurrent rate of shivering.

| Chudu on Cub man  | Clonid   |  | Tramad   |   | Mainh  | Odds Ratio   |       | Odds Rat                              |   |    |
|---|--|--|--|---|--|--|-------|---------------------------------------|---|----|
| Study or Subgroup   | Events   |  |  | Total<br>40   | Weight<br>6 7%   | M-H, Fixed, 95% C<br>7.56 [0.38, 151.28]   |       | M-H, Fixed, 9                         | -   |    |
| Shukla2011[6]<br>Vyas 2018[7]   | 3  | 40<br>30   | 0  | 40<br>30  | 6.7%<br>6.2%   | 7.56 [0.38, 151.28]<br>10.36 [0.53, 201.45]  |       |                                       |   |    |
| Venkatraman2018[8]  | 4  | 30   | 2  | 30  | 25.3%  | 2.15 [0.36, 12.76]   |       |                                       |   |    |
| Verma2016 [10]  | 10   | 30   | 3  | 30  | 29.2%  | 4.50 [1.09, 18.50]   |       |                                       |   |    |
| Attal2015[11]   | 4  | 30   | 0  | 30  | 6.2%   | 10.36 [0.53, 201.45]   |       |                                       |   | -  |
| Reddy2011[12]   | 0  | 45   | 0  | 45  |  | Not estimable  |       |                                       |   |    |
| Kulshrestha2014[13]   | 5  | 45   | 0  | 45  |  | 12.36 [0.66, 230.48]   |       |                                       |   | _  |
| Longani2017[15]   | 2  | 40   | 0  | 40  | 6.9%   | 5.26 [0.24, 113.11]  |       |                                       |   |    |
| Jois2016[16]  | 4  | 40   | 0  | 40  | 6.5%   | 9.99 [0.52, 191.90]  |       |                                       |   |    |
| Singh2016[17]   | 3  | 30   | 0  | 30  | 6.5%   | 7.76 [0.38, 157.14]  |       |                                       | ·   |    |
| Total (95% CI)  |  | 360  |  | 360   | 100.0%   | 5.97 [2.76, 12.91]   |       |                                       | •   |    |
| Total events  | 39   | 000  | 5  | 000   |  | 0.01 [2.10, 12.01]   |       |                                       |   |    |
| Heterogeneity: $Chi^2 = 2$ .  |  | P = 0.9  |  | 6   |  |  | -     |                                       |   |    |
| Test for overall effect: Z  |  |  |  | -   |  |  | 0.001 | 0.1 1<br>Clonidine                    | 10<br>Tramadal  | 1  |
| Bradycardia   |  |  |  |   |  |  |       |                                       | Tramadol  |    |
|   | Clonidir   |  | Tramad   |   |  | Odds Ratio   |       | Odds Ra                               |   |    |
| tudy or Subgroup<br>Shukla2011[6]   | Events 2   | 40   | Events 1   | Total<br>40   | Weight<br>14.7%  | M-H. Fixed, 95% Cl<br>2.05 [0.18, 23.59]   | P     | M-H. Fixed. S                         | 95% CI  | _  |
| Vyas 2018[7]  | 2  | 30   | 0  | 30  | 7.1%   | 5.35 [0.25, 116.31]  |       |                                       | -   |    |
| Venkatraman2018[8]  | 2  | 30   | 0  | 30  | 7.1%   | 5.35 [0.25, 116.31]  |       |                                       | -   |    |
| Verma2016 [10]  | 3  | 30   | 1  | 30  | 13.9%  | 3.22 [0.32, 32.89]   |       |                                       | -   |    |
| Attal2015[11]<br>Reddy2011[12]  | 2 2  | 30<br>45   | 0  | 30<br>45  | 7.1%<br>14.8%  | 5.35 [0.25, 116.31]<br>2.05 [0.18, 23.41]  |       |                                       |   |    |
| Kulshrestha2014[13]   | 3  | 45   | 1  | 45  | 14.4%  | 3.14 [0.31, 31.42]   |       |                                       | -   |    |
| Longani2017[15]   | 4  | 40   | 0  | 40  | 6.9%   | 9.99 [0.52, 191.90]  |       |                                       | -   | -  |
| Jois2016[16]  | 4  | 40   | 1  | 40  | 13.9%  | 4.33 [0.46, 40.61]   |       |                                       | -   |    |
| Singh2016[17]   | 0  | 30   | 0  | 30  |  | Not estimable  |       |                                       |   |    |
| otal (95% CI)   |  | 360  |  | 360   | 100.0%   | 3.94 [1.69, 9.20]  |       |                                       | •   |    |
| otal events   | 24   |  | 5  |   |  |  |       |                                       |   |    |
| eterogeneity: Chi <sup>2</sup> = 1.12   | 2, df = 8 (P   |  | 0); I <sup>2</sup> = 0%  |   |  |  | 0.001 | 0.1 1                                 | 10  |    |
| est for overall effect: Z =   | 3.17 (P =  | 0.002)   |  |   |  |  | 0.001 | Clonidine                             | Tramadol  |    |
| Sedation  | Clonidi  | ne   | Tramad   | lol   |  | Odds Ratio   |       | Odds Ra                               | tio   |    |
| tudy or Subgroup  | Events   |  | Events   |   | Weight   | M-H, Fixed, 95% C  |       | M-H, Fixed, S                         |   |    |
| Shukla2011[6]   | 10   | 40   | 5  | 40  | 11.8%  | 2.33 [0.72, 7.59]  |       |                                       |   |    |
| Vyas 2018[7]<br>Venkatraman2018[8]  | 30<br>25   | 30   | 30<br>18   | 30<br>30  | 9.4%   | Not estimable  |       |                                       | -   |    |
| Bansal2011[9]   | 25   | 30   | 3  | 30  | 6.0%   | 3.33 [1.00, 11.14]<br>5.21 [1.28, 21.24]   |       |                                       | -   |    |
| Verma2016 [10]  | 10   | 30   | 2  | 30  | 4.2%   | 7.00 [1.38, 35.48]   |       | -                                     | -   |    |
| Attal2015[11]   | 18   | 30   | 6  | 30  | 7.5%   | 6.00 [1.89, 19.04]   |       |                                       |   |    |
| Reddy2011[12]<br>Kulshrestha2014[13]  | 2<br>15  | 45   | 8  | 45<br>45  | 24.0%<br>10.5%   | 0.22 [0.04, 1.08]<br>4.00 [1.31, 12.23]  |       | -  -                                  |   |    |
| Jois2016[16]  | 9  | 40   | 4  | 40  | 9.8%   | 2.61 [0.73, 9.32]  |       |                                       | -   |    |
| Singh2016[17]   | 14   | 30   | 10   | 30  | 16.8%  | 1.75 [0.62, 4.97]  |       |                                       |   |    |
| otal (95% CI)   |  | 350  |  | 350   | 100.0%   | 2.67 [1.80, 3.94]  |       |                                       | •   |    |
| otal events   | 144  | 000  | 91   |   | 1001070  | 2101 [1100; 0104]  |       |                                       |   |    |
|   | ting   | 0.000  | 06); I <sup>2</sup> = 40<br>01)<br>Tramado   |   |  | Odds Ratio   | 0.001 | 0.1 1<br>Clonidine<br>Odds Rat        | 10<br>Tramadol<br><b>io</b>   |    |
| Test for overall effect: Z = Nausea and vomi<br>Study or Subgroup<br>Shukia2011[6]  | ting<br>Clonidin<br>Events   | 0.0000<br>ne<br>Total  | Tramado  | ol<br>Fotal   |  | M-H. Random, 95% C   | 1     |                                       | Tramadol<br>io  | 1  |
| Nausea and vomi   | ting<br><sub>Clonidin</sub>  | 0.0000   | D1)<br>Tramado   | ol  | <u>Weight</u><br>5.8%<br>6.4%  |  | 1     | Clonidine<br>Odds Rat                 | Tramadol<br>io  |    |
| Nausea and vomi<br>Study or Subgroup<br>Shukla2011[6]<br>Vyas 2018[7]<br>Venkatraman2018[8]   | ting<br>Clonidin<br>Events<br>0<br>0<br>1  | 0.0000<br>ne<br><u>Total</u><br>40<br>30<br>30   | 01)<br>Tramado<br>Events ]<br>39<br>14<br>4  | <b>5</b><br>Fotal<br>40<br>30<br>30   | 5.8%<br>6.4%<br>7.6%   | M-H. Random. 95% C<br>0.00 [0.00, 0.01]<br>0.02 [0.00, 0.33]<br>0.22 [0.02, 2.14]  | 1     | Clonidine<br>Odds Rat                 | Tramadol<br>io  |    |
| Nausea and vomi<br><u>Study or Subgroup</u><br>Shukia2011[6]<br>Vyas 2018[7]<br>Venkatraman2018[8]<br>Bansal2011[9]   | ting<br>Clonidii<br>Events<br>0<br>0<br>1<br>4   | 0.0000<br>ne<br><u>Total</u><br>40<br>30<br>30<br>30   | 01)<br>Tramado<br>Events 1<br>39<br>14<br>4<br>5   | 51<br><u>Fotal</u><br>40<br>30<br>30<br>30  | 5.8%<br>6.4%<br>7.6%<br>9.3%   | M-H. Random. 95% C<br>0.00 [0.00, 0.01]<br>0.02 [0.00, 0.33]<br>0.22 [0.02, 2.14]<br>0.77 [0.19, 3.20]   | 1     | Clonidine<br>Odds Rat                 | Tramadol<br>io  |    |
| Nausea and vomi<br>Study or Subgroup<br>Shukla2011[6]<br>Vyas 2018[7]<br>Venkatraman2018[8]   | ting<br>Clonidin<br>Events<br>0<br>0<br>1  | 0.0000<br>ne<br><u>Total</u><br>40<br>30<br>30   | 01)<br>Tramado<br>Events ]<br>39<br>14<br>4  | <b>5</b><br>Fotal<br>40<br>30<br>30   | 5.8%<br>6.4%<br>7.6%   | M-H. Random. 95% C<br>0.00 [0.00, 0.01]<br>0.02 [0.00, 0.33]<br>0.22 [0.02, 2.14]<br>0.77 [0.19, 3.20]<br>1.80 [0.39, 8.32]<br>0.06 [0.00, 1.15]   | 1     | Clonidine<br>Odds Rat                 | Tramadol<br>io  |    |
| Nausea and vomi<br>Study or Subgroup<br>Shukia2011[6]<br>Vyas 2018[7]<br>Venkatraman2018[8]<br>Bansal2011[9]<br>Verma2016 [10]<br>Attal2015[11]<br>Reddy2011[12]  | Clonidin<br>Events<br>0<br>0<br>1<br>4<br>5<br>0<br>4  | 0.0000<br>ne<br><u>Total</u><br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>45   | 01)<br>Tramado<br>Events 1<br>39<br>14<br>4<br>5<br>3<br>6<br>12   | 51<br>Fotal<br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>45   | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.1%<br>6.3%<br>9.7%   | M-H. Random. 95% C<br>0.00 [0.00, 0.01]<br>0.02 [0.00, 0.33]<br>0.22 [0.02, 2.14]<br>0.77 [0.19, 3.20]<br>1.80 [0.39, 8.32]<br>0.06 [0.00, 1.15]<br>0.27 [0.08, 0.91]  | 1     | Clonidine<br>Odds Rat                 | Tramadol<br>io  |    |
| Nausea and vomi<br>Study or Subgroup<br>Shukia2011[6]<br>Vyas 2018[7]<br>Venkatraman2018[8]<br>Bansal2011[9]<br>Verma2016 [10]<br>Attal2015[11]<br>Reddy2011[12]<br>Kulshrestha2014[13]   | Clonidin<br>Events<br>0<br>0<br>1<br>4<br>5<br>0<br>4<br>0   | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>45  | Tramado<br>Events 1<br>39<br>14<br>4<br>5<br>3<br>6<br>12<br>41  | 51<br>Fotal<br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>45<br>45   | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.1%<br>6.3%<br>9.7%<br>6.3%   | M-H. Random. 95% C<br>0.00 [0.00, 0.01]<br>0.02 [0.00, 0.33]<br>0.22 [0.02, 2.14]<br>0.77 [0.19, 3.20]<br>1.80 [0.39, 8.32]<br>0.06 [0.00, 1.15]<br>0.27 [0.08, 0.91]<br>0.00 [0.00, 0.02]   | 1     | Clonidine<br>Odds Rat                 | Tramadol<br>io  |    |
| Nausea and vomi<br><u>Study or Subgroup</u><br>Shukia2011[6]<br>Vyas 2018[7]<br>Venkatraman2018[8]<br>Bansal2011[9]<br>Verma2016 [10]<br>Attai2015[11]<br>Reddy2011[12]<br>Kulshrestha2014[13]<br>Aravind2014[14]   | Clonidii<br>Events<br>0<br>1<br>4<br>5<br>0<br>4<br>0<br>2   | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>45<br>40  | D1)<br>Tramado<br>Events 1<br>39<br>4<br>5<br>3<br>6<br>12<br>41<br>5  | bl<br><b>Total</b><br>40<br>30<br>30<br>30<br>30<br>30<br>45<br>45<br>40  | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.1%<br>6.3%<br>6.3%<br>6.3%<br>8.7%   | M-H. Random. 95% C<br>0.00 [0.00, 0.01]<br>0.02 [0.00, 0.33]<br>0.22 [0.02, 2.14]<br>0.77 [0.19, 3.20]<br>1.80 [0.39, 8.32]<br>0.06 [0.00, 1.15]<br>0.27 [0.08, 0.91]<br>0.00 [0.00, 0.02]<br>0.37 [0.07, 2.02]  | 1     | Clonidine<br>Odds Rat                 | Tramadol<br>io  |    |
| Nausea and vomi<br>Study or Subgroup<br>Shukia2011[6]<br>Vyas 2018[7]<br>Venkatraman2018[8]<br>Bansal2011[9]<br>Verma2016 [10]<br>Attal2015[11]<br>Reddy2011[12]<br>Kulshrestha2014[13]   | ting<br>Clonidii<br>Events<br>0<br>0<br>1<br>4<br>5<br>0<br>4<br>5<br>0<br>4<br>0<br>2<br>0<br>3   | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>45  | Tramado<br>Events 1<br>39<br>14<br>4<br>5<br>3<br>6<br>12<br>41  | 51<br>Fotal<br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>45<br>45   | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.1%<br>6.3%<br>9.7%<br>6.3%   | M-H. Random. 95% C<br>0.00 [0.00, 0.01]<br>0.02 [0.00, 0.33]<br>0.22 [0.02, 2.14]<br>0.77 [0.19, 3.20]<br>1.80 [0.39, 8.32]<br>0.06 [0.00, 1.15]<br>0.27 [0.08, 0.91]<br>0.00 [0.00, 0.02]   | 1     | Clonidine<br>Odds Rat                 | Tramadol<br>io  |    |
| Nausea and vomi<br><u>Study or Subgroup</u><br>Shukla2011[6]<br>Vyas 2018[7]<br>Venkatraman2018[8]<br>Bansal2011[9]<br>Verma2016 [10]<br>Verma2016 [10]<br>Attal2015[11]<br>Reddy2011[12]<br>Kulshrestha2014[13]<br>Aravind2014[14]<br>Longani2017[15]<br>Jois2016[16]<br>Singh2016[17]   | ting<br>Clonidii<br>Events<br>0<br>0<br>1<br>4<br>5<br>0<br>4<br>0<br>2<br>0<br>3<br>0<br>3<br>0   | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>45<br>40<br>40<br>40<br>30  | D1)<br>Tramado<br>Events 1<br>39<br>14<br>4<br>5<br>6<br>12<br>41<br>5<br>5<br>5<br>12<br>19   | <b>Fotal</b><br>40<br>30<br>30<br>30<br>30<br>45<br>45<br>45<br>40<br>40<br>30  | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.1%<br>6.3%<br>6.3%<br>6.3%<br>6.3%<br>6.3%<br>9.4%   | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.00 (0.00, 0.02)<br>0.37 (0.07, 2.02]<br>0.08 (0.00, 1.49)<br>0.19 (0.05, 0.73)<br>0.01 (0.00, 0.17)   | 1     | Clonidine<br>Odds Rat                 | Tramadol<br>io  |    |
| Nausea and vomi           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Venkatraman2018[8]           Bansal2011[9]           Verma2016 [10]           Attal2015[11]           Reddy2011[12]           Kuishrestha2014[13]           Aravind2014[14]           Longani2017[15]  | ting<br>Clonidii<br>Events<br>0<br>0<br>1<br>4<br>5<br>0<br>4<br>5<br>0<br>4<br>0<br>2<br>0<br>3   | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>45<br>45<br>40<br>40  | D1)<br>Tramado<br>Events 1<br>39<br>14<br>5<br>3<br>6<br>12<br>41<br>5<br>5<br>12  | <b>Fotal</b><br>40<br>30<br>30<br>30<br>30<br>45<br>45<br>45<br>40<br>40  | 5.8%<br>6.4%<br>9.3%<br>9.1%<br>6.3%<br>9.7%<br>6.3%<br>8.7%<br>6.3%<br>9.4%   | M-H. Random. 95% C<br>0.00 [0.00, 0.01]<br>0.02 [0.00, 0.33]<br>0.22 [0.02, 2.14]<br>0.77 [0.19, 3.20]<br>1.80 [0.39, 8.32]<br>0.06 [0.00, 1.15]<br>0.27 [0.08, 0.91]<br>0.00 [0.00, 0.02]<br>0.37 [0.07, 2.02]<br>0.08 [0.00, 1.49]<br>0.19 [0.05, 0.73]  | 1     | Clonidine<br>Odds Rat                 | Tramadol<br>io  |    |
| Nausea and vomi           Shukla2011[6]           Vyas 2018[7]           Venkatraman2018[8]           Bansal2011[9]           Verma2016 [10]           Attal2015[11]           Reddy2011[12]           Kulshrestha2014[13]           Jois2016[16]           Singh2016[17]           Ali2017[18]           Total (95% Cl)  | ting<br>Clonidin<br>Events<br>0<br>1<br>4<br>5<br>0<br>4<br>0<br>2<br>0<br>0<br>3<br>0<br>2<br>2<br>2  | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>45<br>40<br>40<br>40<br>30  | D1)<br>Tramado<br>Events 1<br>39<br>14<br>4<br>5<br>3<br>6<br>12<br>41<br>5<br>12<br>5<br>12<br>19<br>6  | Fotal         Fotal           40         30           30         30           30         30           45         40           40         30           30         30   | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.1%<br>6.3%<br>6.3%<br>6.3%<br>6.3%<br>6.3%<br>9.4%   | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.00 (0.00, 0.02)<br>0.37 (0.07, 2.02]<br>0.08 (0.00, 1.49)<br>0.19 (0.05, 0.73)<br>0.01 (0.00, 0.17)   | 1     | Clonidine<br>Odds Rat                 | Tramadol<br>io  |    |
| Nausea and vomi           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Venkatraman2018[8]           Bansal2011[9]           Verma2016 [10]           Attal2015[11]           Redy2011[12]           Kulshrestha2014[13]           Aravind2014[14]           Longani2017[15]           Jois2016[16]           Singh2016[17]           Ail2017[18]           Total (95% CI)           Total events  | <b>Events</b><br><b>Events</b><br>0<br>0<br>1<br>4<br>5<br>0<br>4<br>0<br>2<br>0<br>3<br>0<br>2<br>21  | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>30<br>45<br>45<br>40<br>40<br>30<br>30<br>45<br>45<br>40<br>40<br>30<br>30<br>45<br>45<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40  | Tramado<br>Events 1<br>39<br>14<br>5<br>3<br>6<br>12<br>41<br>5<br>5<br>12<br>19<br>6<br>12  | Iotal         Y           40         30           30         30           30         45           45         40           40         30           30         30   | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.1%<br>6.3%<br>9.7%<br>6.3%<br>9.4%<br>6.3%<br>9.4%<br>8.8%   | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32]<br>0.06 (0.00, 1.15]<br>0.27 (0.08, 0.91)<br>0.00 (0.00, 0.02]<br>0.37 (0.07, 2.02]<br>0.08 (0.00, 1.49]<br>0.19 (0.05, 0.73)<br>0.01 (0.00, 0.17]<br>0.29 (0.05, 1.55]<br>0.10 [0.03, 0.31]   |       | Clonidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>io  |    |
| Nausea and vomi           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Venkatraman2018[8]           Bansal2011[9]           Verma2016 [10]           Attal2015[11]           Reddy2011[12]           Kuishrestha2014[13]           Aravind2014[14]           Longani2017[15]           Jois2016[16]           Singh2016[17]           Ali2017[18]           Total (95% CI)  | <b>Events</b><br><b>Events</b><br><b>Events</b><br><b>1</b><br><b>4</b><br><b>5</b><br><b>0</b><br><b>1</b><br><b>1</b><br><b>1</b><br><b>5</b><br><b>0</b><br><b>1</b><br><b>1</b><br><b>1</b><br><b>2</b><br><b>0</b><br><b>2</b><br><b>1</b><br><b>1</b><br><b>2</b><br><b>1</b><br><b>2</b><br><b>1</b><br><b>1</b><br><b>2</b><br><b>1</b><br><b>1</b><br><b>1</b><br><b>1</b><br><b>1</b><br><b>1</b><br><b>1</b><br><b>1</b>  | 0.0000<br>ne<br><u>Total</u><br>40<br>30<br>30<br>30<br>30<br>45<br>40<br>40<br>30<br>30<br>45<br>40<br>40<br>30<br>30<br>45<br>45<br>40<br>30<br>30<br>45<br>45<br>40<br>30<br>30<br>45<br>40<br>30<br>30<br>50<br>50<br>50<br>50<br>50<br>50<br>50<br>50<br>50<br>5  | 201)<br>Tramado<br>Events 1<br>39<br>14<br>4<br>5<br>6<br>12<br>12<br>12<br>19<br>6<br>171<br>If = 12 (P -   | Iotal         Y           40         30           30         30           30         45           45         40           40         30           30         30   | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.1%<br>6.3%<br>9.7%<br>6.3%<br>9.4%<br>6.3%<br>9.4%<br>8.8%   | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32]<br>0.06 (0.00, 1.15]<br>0.27 (0.08, 0.91)<br>0.00 (0.00, 0.02]<br>0.37 (0.07, 2.02]<br>0.08 (0.00, 1.49]<br>0.19 (0.05, 0.73)<br>0.01 (0.00, 0.17]<br>0.29 (0.05, 1.55]<br>0.10 [0.03, 0.31]   | 1     | Clonidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>95% Cl<br>  |    |
| Nausea and vomi<br>Study or Subgroup<br>Shukia2011[6]<br>Vyas 2018[7]<br>Vernaz018[7]<br>Vernaz016[10]<br>Attai2015[11]<br>Reddy2011[12]<br>Kulshrestha2014[13]<br>Aravind2014[14]<br>Longani2017[15]<br>Jois2016[16]<br>Singh2016[17]<br>Ali2017[18]<br>Total events<br>Heterogeneity: Tau <sup>2</sup> = 3.0<br>Test for overall effect: Z  | <b>Events</b><br><b>Events</b><br>0<br>0<br>1<br>4<br>0<br>2<br>0<br>3<br>0<br>2<br>21<br>05; Chi <sup>a</sup> = 5<br>= 4.01 (P <  | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>30<br>45<br>45<br>40<br>40<br>40<br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>45<br>45<br>45<br>40<br>40<br>40<br>50<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>6   | D1)<br>Tramado<br>Events 1<br>39<br>14<br>4<br>5<br>3<br>6<br>12<br>41<br>5<br>5<br>12<br>41<br>6<br>5<br>12<br>41<br>5<br>5<br>12<br>41<br>5<br>5<br>12<br>41<br>5<br>5<br>12<br>41<br>5<br>5<br>12<br>4<br>5<br>5<br>12<br>4<br>5<br>5<br>12<br>4<br>5<br>5<br>12<br>4<br>5<br>5<br>12<br>4<br>5<br>5<br>12<br>4<br>5<br>5<br>5<br>12<br>4<br>5<br>5<br>12<br>4<br>5<br>5<br>5<br>5<br>5<br>12<br>4<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5   | Image: constraint of the second se | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.1%<br>6.3%<br>9.7%<br>6.3%<br>9.4%<br>6.3%<br>9.4%<br>8.8%   | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 [0.00, 0.33]<br>0.22 [0.02, 2.14]<br>0.77 [0.19, 3.20]<br>1.80 [0.39, 8.32]<br>0.06 [0.00, 1.15]<br>0.27 [0.08, 0.91]<br>0.00 [0.00, 0.02]<br>0.37 [0.07, 2.02]<br>0.08 [0.00, 1.49]<br>0.19 [0.05, 0.73]<br>0.01 [0.00, 0.17]<br>0.29 [0.05, 1.55]<br>0.10 [0.03, 0.31]<br>6%   |       | Clonidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>95% Cl<br>-<br>-<br>10<br>Tramadol  |    |
| Nausea and vomi<br>Study or Subgroup<br>Shukla2011[6]<br>Vyas 2018[7]<br>Venkatraman2018[8]<br>Bansal2011[9]<br>Verma2016 [10]<br>Attal2015[11]<br>Reddy2011[12]<br>Kulshrestha2014[13]<br>Aravind2014[14]<br>Longani2017[15]<br>Jois2016[16]<br>Singh2016[17]<br>Ali2017[18]<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> = 3.0<br>Test for overall effect: Z =  | Clonidii<br>Events<br>0<br>0<br>1<br>4<br>5<br>0<br>4<br>0<br>2<br>0<br>3<br>0<br>2<br>2<br>0<br>5; Chi <sup>2</sup> = 5<br>= 4.01 (P <<br>Clonidi   | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>40<br>40<br>40<br>40<br>30<br>30<br>45<br>40<br>40<br>50.62, c<br>0.0001<br>line  | D1)<br>Tramado<br>Events 1<br>39<br>14<br>4<br>5<br>12<br>41<br>5<br>12<br>12<br>19<br>15<br>12<br>19<br>17<br>19<br>17<br>19<br>17<br>19<br>17<br>19<br>16<br>17<br>19<br>16<br>12<br>12<br>19<br>14<br>12<br>12<br>12<br>14<br>15<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12  | Image: state  | 5.8%<br>6.4%<br>7.6%<br>9.1%<br>6.3%<br>9.7%<br>6.3%<br>8.7%<br>6.3%<br>9.4%<br>6.4%<br>8.8%<br>100.0%   | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.00 (0.00, 0.02)<br>0.37 (0.07, 2.02)<br>0.38 (0.00, 1.49)<br>0.19 (0.05, 0.73)<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio   |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br><u>95% Cl</u><br>-<br>10<br>Tramadol<br><b>tio</b>  |    |
| Nausea and vomi<br>Study or Subgroup<br>Shukia2011[6]<br>Vyas 2018[7]<br>Vernkatraman2018[8]<br>Bansal2011[9]<br>Verma2016 [10]<br>Attai2015[11]<br>Reddy2011[12]<br>Kulshrestha2014[13]<br>Longani2017[15]<br>Jois2016[16]<br>Singh2016[17]<br>Ali2017[18]<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> = 3.0<br>Test for overall effect: Z =<br>Dizziness<br>Study or Subgroup  | ting<br>Clonidii<br>Events<br>0<br>0<br>1<br>4<br>5<br>0<br>1<br>4<br>5<br>0<br>2<br>0<br>2<br>0<br>2<br>0<br>2<br>0<br>2<br>0<br>2<br>0<br>2<br>0<br>2<br>0<br>0<br>1<br>4<br>5<br>0<br>0<br>0<br>1<br>1<br>4<br>5<br>0<br>0<br>0<br>1<br>1<br>4<br>5<br>0<br>0<br>0<br>0<br>1<br>1<br>4<br>0<br>0<br>0<br>0<br>0<br>1<br>1<br>4<br>5<br>0<br>0<br>0<br>0<br>0<br>1<br>1<br>4<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0  | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>45<br>40<br>40<br>40<br>30<br>30<br>45<br>45<br>40<br>40<br>30<br>30<br>30<br>45<br>45<br>40<br>50<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>6   | Tramado<br>Events 1<br>39<br>14<br>5<br>3<br>6<br>12<br>41<br>5<br>5<br>12<br>19<br>6<br>171<br>171<br>171<br>172<br>P -<br>Tramac<br>Events   | ol       fotal       40       30       30       30       30       30       40       40       40       40       40       40       40       40       30       30       40   <  | 5.8%<br>6.4%<br>7.6%<br>9.1%<br>6.3%<br>9.7%<br>6.3%<br>8.7%<br>6.3%<br>9.4%<br>6.4%<br>8.8%<br>100.0%<br>101.1 <sup>2</sup> = 7   | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32]<br>0.06 (0.00, 1.15]<br>0.27 (0.00, 0.02]<br>0.37 (0.00, 0.02]<br>0.37 (0.00, 1.49]<br>0.19 (0.05, 0.73)<br>0.01 (0.00, 0.17]<br>0.29 (0.05, 1.55]<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H. Fixed, 95% C   |       | Clonidine<br>Odds Rat<br>M-H. Random. | Tramadol<br><u>95% Cl</u><br>-<br>10<br>Tramadol<br><b>tio</b>  |    |
| Nausea and vomi<br>Study or Subgroup<br>Shukla2011[6]<br>Vyas 2018[7]<br>Vernkatraman2018[8]<br>Bansal2011[9]<br>Verma2016 [10]<br>Attai2015[11]<br>Reddy2011[12]<br>Kulshrestha2014[13]<br>Aravind2014[14]<br>Longani2017[15]<br>Jois2016[16]<br>Singh2016[17]<br>Ali2017[18]<br>Total events<br>Heterogeneity: Tau <sup>2</sup> = 3.0<br>Test for overall effect: Z =<br>Dizziness  | Clonidii<br>Events<br>0<br>0<br>1<br>4<br>5<br>0<br>4<br>0<br>2<br>0<br>3<br>0<br>2<br>2<br>0<br>5; Chi <sup>2</sup> = 5<br>= 4.01 (P <<br>Clonidi   | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>40<br>40<br>40<br>40<br>30<br>30<br>45<br>40<br>40<br>50.62, c<br>0.0001<br>line  | D1)<br>Tramado<br>Events 1<br>39<br>14<br>4<br>5<br>12<br>41<br>5<br>12<br>12<br>19<br>15<br>12<br>19<br>17<br>19<br>17<br>19<br>17<br>19<br>17<br>19<br>16<br>17<br>19<br>16<br>12<br>12<br>19<br>14<br>12<br>12<br>12<br>14<br>15<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12<br>12  | Image: state  | 5.8%<br>6.4%<br>9.3%<br>9.1%<br>6.3%<br>9.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.3%<br>8.8%<br>100.0%<br>01): I <sup>2</sup> = 7<br>Weight<br>39.5%   | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.00 (0.00, 0.02)<br>0.37 (0.07, 2.02)<br>0.38 (0.00, 1.49)<br>0.19 (0.05, 0.73)<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio   |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br><u>95% Cl</u><br>-<br>10<br>Tramadol<br><b>tio</b>  |    |
| Study or Subgroup         Shukla2011[6]         Vyas 2018[7]         Venkatraman2018[8]         Bansal2011[9]         Verma2016 [10]         Attal2015[11]         Reddy2011[12]         Kulshrestha2014[13]         Longani2017[15]         Jois2016[16]         Singh2016[17]         Attai2017[18]         Total (95% CI)         Total events         Heterogeneity: Tau <sup>2</sup> = 3.0         Test for overall effect: Z =         Dizzziness         Study or Subgroup   | ting<br>Clonidii<br>Events<br>0<br>0<br>1<br>4<br>5<br>0<br>1<br>4<br>5<br>0<br>2<br>0<br>2<br>0<br>2<br>0<br>2<br>0<br>2<br>0<br>2<br>0<br>2<br>0<br>2<br>0<br>0<br>1<br>4<br>5<br>0<br>0<br>0<br>1<br>1<br>4<br>5<br>0<br>0<br>0<br>1<br>1<br>4<br>5<br>0<br>0<br>0<br>0<br>1<br>1<br>4<br>0<br>0<br>0<br>0<br>0<br>1<br>1<br>4<br>5<br>0<br>0<br>0<br>0<br>0<br>1<br>1<br>4<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0  | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>45<br>40<br>40<br>40<br>30<br>30<br>45<br>45<br>40<br>40<br>30<br>30<br>30<br>45<br>45<br>40<br>50<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>60<br>6   | Tramado<br>Events 1<br>39<br>14<br>5<br>3<br>6<br>12<br>41<br>5<br>5<br>12<br>19<br>6<br>171<br>171<br>171<br>172<br>P -<br>Tramac<br>Events   | ol       fotal       40       30       30       30       30       30       40       40       40       40       40       40       40       40       30       30       40   <  | 5.8%<br>6.4%<br>7.6%<br>9.1%<br>6.3%<br>9.7%<br>6.3%<br>8.7%<br>6.3%<br>9.4%<br>6.4%<br>8.8%<br>100.0%<br>101.1 <sup>2</sup> = 7   | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32]<br>0.06 (0.00, 1.15]<br>0.27 (0.00, 0.02]<br>0.37 (0.07, 2.02]<br>0.08 (0.07, 2.02]<br>0.08 (0.00, 1.49]<br>0.19 (0.05, 0.73)<br>0.01 (0.00, 0.17]<br>0.29 (0.05, 1.55]<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H. Fixed, 95% C  |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br><u>95% Cl</u><br>-<br>10<br>Tramadol<br><b>tio</b>  |    |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Vyas 2018[7]           Vyas 2018[7]           Varna2016[10]           Attai2011[9]           Attai2015[11]           Attai2015[11]           Attai2014[9]           Jois2014[14]           Longani2017[15]           Jois2016[17]           Ali2017[18]           Total events           Heterogeneity: Tau <sup>2</sup> = 3.0           Test for overall effect: Z =           Dizziness           Study or Subgroup           Shukla2011[6]  | Clonidii<br>Events<br>0<br>0<br>1<br>4<br>5<br>4<br>0<br>2<br>2<br>0<br>5; Chi <sup>2</sup> = 5<br>= 4.01 (P <<br>Clonid<br>Events<br>0<br>0<br>0<br>2   | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>45<br>40<br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>3   | D1)<br>Tramadc<br>Events 1<br>39<br>14<br>4<br>5<br>3<br>6<br>12<br>41<br>5<br>5<br>12<br>19<br>6<br>171<br>If = 12 (P -<br>)<br>Tramac<br><u>Events</u><br>22   | Image: style="text-align: center;">          Image: style="text-align: center;">             for align: style="text-align: center;"             for align: style="text-align: center;"             for align: style="text-align: style="text-align: s                 | 5.8%<br>6.4%<br>9.3%<br>9.1%<br>6.3%<br>9.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.3%<br>8.8%<br>100.0%<br>01): I <sup>2</sup> = 7<br>Weight<br>39.5%   | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.00, 0.02)<br>0.37 (0.07, 2.02)<br>0.08 (0.00, 1.49)<br>0.19 (0.05, 0.73)<br>0.01 (0.00, 0.17)<br>0.29 (0.05, 1.55)<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H, Fixed, 95% C<br>0.01 [0.00, 0.18]  |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br><u>95% Cl</u><br>-<br>10<br>Tramadol<br><b>tio</b>  |    |
| Nausea and vomi       Study or Subgroup       Shukla2011[6]       Vyas 2018[7]       Vernaz018 [10]       Hansal2011[9]       Vermaz016 [10]       Attai2015[11]       Reddy2011[12]       Kuishrestha2014[13]       Aravind2014[14]       Longani2017[15]       Jois2016[16]       Singh2016[17]       Ati2017[18]       Total (95% CI)       Total events       Heterogeneity: Tau <sup>2</sup> = 3.0.       Test for overall effect: Z =       Dizziness       Study or Subgroup       Shukla2011[[6]       Vyas 2018[7]   | ting<br>Clonidii<br>Events<br>0<br>1<br>4<br>5<br>0<br>4<br>0<br>2<br>0<br>3<br>0<br>2<br>21<br>05: Chi <sup>2</sup> = 5<br>= 4.01 (P <<br>Clonid<br>Events<br>0<br>0<br>0<br>1<br>1<br>1<br>5<br>0<br>0<br>1<br>1<br>1<br>5<br>0<br>0<br>1<br>1<br>1<br>5<br>0<br>0<br>1<br>1<br>1<br>5<br>0<br>0<br>1<br>1<br>1<br>5<br>0<br>0<br>1<br>1<br>1<br>5<br>0<br>0<br>1<br>1<br>1<br>5<br>0<br>0<br>0<br>1<br>1<br>1<br>5<br>0<br>0<br>0<br>1<br>1<br>1<br>5<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0  | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>40<br>40<br>40<br>30<br>30<br>45<br>40<br>40<br>30<br>30<br>45<br>40<br>40<br>50.62, c<br>0.0001<br>line<br>Total   | D1)<br>Tramade<br>Events 1<br>39<br>14<br>4<br>5<br>12<br>41<br>5<br>12<br>19<br>6<br>171<br>171<br>171<br>171<br>171<br>171<br>171  | ol<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>45<br>45<br>40<br>40<br>30<br>30<br>460<br>Col<br>Total<br>40<br>30<br>30<br>30<br>30<br>30<br>45<br>45<br>45<br>40<br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>3   | $\begin{array}{c} 5.8\% \\ 6.4\% \\ 7.6\% \\ 9.3\% \\ 9.1\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 8.7\% \\ 6.3\% \\ 8.7\% \\ 6.4\% \\ 8.8\% \\ 100.0\% \\ 01); \ l^2 = 7 \\ \hline \\$ | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.00 (0.00, 0.02)<br>0.37 (0.07, 2.02)<br>0.38 (0.00, 0.48)<br>0.19 (0.05, 0.73)<br>0.19 (0.05, 0.73)<br>0.19 (0.05, 0.73)<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H. Fixed, 95% C<br>0.01 [0.00, 0.18]<br>0.06 [0.00, 1.15]  |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br><u>95% Cl</u><br>-<br>10<br>Tramadol<br><b>tio</b>  |    |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Venkatraman2018[8]           Bansal2011[9]           Verma2016 [10]           Attai2011[1]           Reddy2011[12]           Kulshrestha2014[13]           Aravind2014[14]           Longani2017[15]           Jois2016[16]           Singh2016[17]           Ali2017[18]           Total (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = 3.1           Test for overall effect: Z =           Dizziness           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]  | Clonidi<br>Events<br>0<br>0<br>1<br>4<br>5<br>0<br>4<br>4<br>0<br>2<br>0<br>3<br>3<br>0<br>2<br>0<br>5; Chi <sup>2</sup> = 5<br>= 4.01 (P <<br>Clonid<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>30<br>46<br>40<br>40<br>30<br>30<br>46<br>40<br>30<br>30<br>46<br>40<br>30<br>30<br>46<br>40<br>30<br>30<br>46<br>40<br>30<br>30<br>46<br>40<br>30<br>30<br>46<br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>3   | Tramade<br>Events 3<br>39<br>14<br>4<br>5<br>6<br>12<br>41<br>5<br>5<br>12<br>19<br>6<br>171<br>171<br>171<br>172<br>19<br>6<br>171<br>172<br>19<br>6<br>172<br>19<br>6<br>22<br>6<br>22   | A0       30       30       30       30       30       30       40       30       40       30       40       30       40       30       40       30       40       30       460       60       dol       10       30       45  | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.1%<br>6.3%<br>9.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.4%<br>8.8%<br>100.0%<br>01): I <sup>2</sup> = 7<br><u>Weight</u><br>39.5%  | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.03, 0.31)<br>0.07 (0.00, 0.02)<br>0.37 (0.00, 0.02)<br>0.37 (0.00, 0.77, 2.02)<br>0.05 (0.00, 1.49)<br>0.19 (0.00, 0.149)<br>0.19 (0.00, 0.149)<br>0.19 (0.00, 0.149)<br>0.10 (0.00, 0.17)<br>0.29 (0.05, 1.55)<br>0.10 [0.00, 0.17]<br>0.20 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H. Fixed, 95% C<br>0.01 [0.00, 0.18]<br>0.06 [0.00, 1.15]<br>0.01 [0.00, 0.20]   |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br><u>95% Cl</u><br>-<br>10<br>Tramadol<br><b>tio</b>  |    |
| Nausea and vomi<br>Study or Subgroup<br>Shukla2011[6]<br>Vyas 2018[7]<br>Venkatraman2018[8]<br>Bansal2011[9]<br>Verma2016 [10]<br>Attal2011[1]<br>Reddy2011[12]<br>Kulshrestha2014[13]<br>Aravind2014[14]<br>Longani2017[15]<br>Jois2016[16]<br>Jois2016[17]<br>Ali2017[18]<br>Total events<br>Heterogeneity: Tau <sup>2</sup> = 3.1<br>Total events<br>Heterogeneity: Tau <sup>2</sup> = 3.1<br>Total events<br>Heterogeneity: Tau <sup>2</sup> = 3.1<br>Shukla2011[6]<br>Vyas 2018[7]<br>Kulshrestha2014[13]  | Clonidi<br>Events<br>0<br>0<br>1<br>4<br>5<br>0<br>4<br>4<br>0<br>2<br>0<br>3<br>3<br>0<br>2<br>0<br>5; Chi <sup>2</sup> = 5<br>= 4.01 (P <<br>Clonid<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>30<br>46<br>40<br>40<br>30<br>30<br>46<br>40<br>30<br>30<br>46<br>40<br>30<br>30<br>46<br>40<br>30<br>30<br>46<br>40<br>30<br>30<br>46<br>40<br>30<br>30<br>46<br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>3   | Tramade<br>Events 3<br>39<br>14<br>4<br>5<br>6<br>12<br>41<br>5<br>5<br>12<br>19<br>6<br>171<br>171<br>171<br>172<br>19<br>6<br>171<br>172<br>19<br>6<br>172<br>19<br>6<br>22<br>6<br>22   | A0       30       30       30       30       30       30       40       30       40       30       40       30       40       30       40       30       40       30       460       60       dol       10       30       45  | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.1%<br>6.3%<br>9.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.4%<br>8.8%<br>100.0%<br>01): I <sup>2</sup> = 7<br><u>Weight</u><br>39.5%  | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.03, 0.31)<br>0.07 (0.00, 0.02)<br>0.37 (0.00, 0.02)<br>0.37 (0.00, 0.77, 2.02)<br>0.05 (0.00, 1.49)<br>0.19 (0.00, 0.149)<br>0.19 (0.00, 0.149)<br>0.19 (0.00, 0.149)<br>0.10 (0.00, 0.17)<br>0.29 (0.05, 1.55)<br>0.10 [0.00, 0.17]<br>0.20 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H. Fixed, 95% C<br>0.01 [0.00, 0.18]<br>0.06 [0.00, 1.15]<br>0.01 [0.00, 0.20]   |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br><u>95% Cl</u><br>-<br>10<br>Tramadol<br><b>tio</b>  |    |
| Nausea and vomi       Study or Subgroup       Shukla2011[6]       Vyas 2018[7]       Verna2018 [10]       Hansal2011[9]       Verma2016 [10]       Attai2015[11]       Reddy2011[12]       Kulshrestha2014[13]       Aravind2014[14]       Longani2017[15]       Jois2016[16]       Singh2016[17]       Atleo17[18]       Total (95% CI)       Total events       Heterogeneity: Tau <sup>2</sup> = 3.0.       Test for overall effect: Z =       Dizziness       Study or Subgroup       Shukla2011[6]       Vyas 2018[7]       Kulshrestha2014[13]       Jois2016[16]   | Clonidi<br>Events<br>0<br>0<br>1<br>4<br>5<br>0<br>4<br>4<br>0<br>2<br>0<br>3<br>3<br>0<br>2<br>0<br>5; Chi <sup>2</sup> = 5<br>= 4.01 (P <<br>Clonid<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>45<br>45<br>40<br>40<br>30<br>30<br>30<br>30<br>30<br>45<br>50.62, c<br>0.0001<br>line<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>45<br>45<br>40<br>30<br>30<br>30<br>30<br>30<br>45<br>45<br>45<br>40<br>30<br>30<br>30<br>45<br>45<br>45<br>40<br>30<br>30<br>30<br>30<br>45<br>45<br>45<br>45<br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>3  | Tramade<br>Events 3<br>39<br>14<br>4<br>5<br>6<br>12<br>41<br>5<br>5<br>12<br>19<br>6<br>171<br>171<br>171<br>172<br>19<br>6<br>171<br>172<br>19<br>6<br>172<br>19<br>6<br>22<br>6<br>22   | 40       30       30       30       30       30       30       45       40       40       30       460       460       460       30       460       30       460       30       460       40       30       45       40       40  | $5.8\% \\ 6.4\% \\ 7.6\% \\ 9.3\% \\ 9.1\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.4\% \\ 8.7\% \\ 6.4\% \\ 8.8\% \\ 100.0\% \\ 101); l^2 = 7 \\ \hline Weight \\ 39.5\% \\ 39.5\% \\ 9.6\% \\ \hline$                                      | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.09 (0.00, 0.02)<br>0.37 (0.07, 2.02)<br>0.38 (0.00, 0.48)<br>0.19 (0.05, 0.73)<br>0.19 (0.05, 1.55)<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H, Fixed, 95% C<br>0.01 [0.00, 0.18]<br>0.06 [0.00, 1.15]<br>0.01 [0.00, 0.20]<br>0.08 [0.00, 1.49]   |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br><u>95% Cl</u><br>-<br>10<br>Tramadol<br><b>tio</b>  |    |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Venkatraman2018[8]           Bansal2011[9]           Verma2016 [10]           Verma2016 [11]           Reddy2011[12]           Kulshrestha2014[13]           Aravind2014[14]           Longani2017[15]           Jois2016[16]           Singh2016[17]           Ali2017[18]           Total events           Heterogeneity: Tau <sup>2</sup> = 3.1           Total events           Bukal2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total (95% CI)  | Clonidii<br>Events<br>Clonidii<br>Events<br>0<br>0<br>0<br>2<br>05; Chi <sup>≥</sup> = 5<br>= 4.01 (P <<br>Clonid<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | 0.0000<br>ne<br>Total<br>400<br>30<br>30<br>30<br>30<br>30<br>45<br>40<br>40<br>40<br>40<br>40<br>40<br>50.62, c<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40   | D1)<br>Tramadc<br>Events 1<br>39<br>14<br>4<br>5<br>3<br>6<br>12<br>41<br>5<br>5<br>12<br>19<br>6<br>171<br>171<br>16<br>Events<br>22<br>6<br>22<br>5<br>55  | I         I           40         30           30         30           30         30           460         460           400         100           400         400           400         30           45         40           400         30           45         40           400         155   | $5.8\% \\ 6.4\% \\ 7.6\% \\ 9.3\% \\ 9.1\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.4\% \\ 8.7\% \\ 6.4\% \\ 8.8\% \\ 100.0\% \\ 101); l^2 = 7 \\ \hline Weight \\ 39.5\% \\ 39.5\% \\ 9.6\% \\ \hline$                                      | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.09 (0.00, 0.02)<br>0.37 (0.07, 2.02)<br>0.38 (0.00, 0.48)<br>0.19 (0.05, 0.73)<br>0.19 (0.05, 1.55)<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H, Fixed, 95% C<br>0.01 [0.00, 0.18]<br>0.06 [0.00, 1.15]<br>0.01 [0.00, 0.20]<br>0.08 [0.00, 1.49]   |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>95% Cl<br>-<br>10<br>Tramadol<br>tio<br>95% Cl  | 10 |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Vyas 2018[7]           Vyas 2018[7]           Vyas 2018[7]           Vyas 2018[7]           Varna2016[10]           Attai2011[9]           Attai2015[11]           Attai2015[11]           Attai2014[14]           Longani2017[15]           Jois2016[17]           Ali2017[18]           Total events           Heterogeneity: Tau <sup>2</sup> = 3.4           Test for overall effect: Z =           Dizziness           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total (95% CI)           Total events   | ting<br>Clonidii<br>Events<br>0<br>1<br>4<br>5<br>0<br>4<br>0<br>2<br>0<br>3<br>0<br>2<br>21<br>0<br>5; Chi <sup>2</sup> = 5<br>= 4.01 (P <<br>Clonid<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | o.oood           ne           Total           40           30           30           30           30           30           30           30           30           40           30           30           40           30           40           30           40           30           40           30           40           30           460           50.62, c           0.0001           100           30           40           30           40           30           30           40           30           40           30           40           30           40           30           40           50           60           70           75   | Tramade<br>Events 3<br>39<br>14<br>4<br>5<br>12<br>41<br>5<br>12<br>19<br>6<br>171<br>171<br>171<br>171<br>171<br>171<br>171   | I         I           40         30           30         30           30         30           460         460           400         100           400         400           400         30           45         40           400         30           45         40           400         155   | $5.8\% \\ 6.4\% \\ 7.6\% \\ 9.3\% \\ 9.1\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.4\% \\ 8.7\% \\ 6.4\% \\ 8.8\% \\ 100.0\% \\ 101); l^2 = 7 \\ \hline Weight \\ 39.5\% \\ 39.5\% \\ 9.6\% \\ \hline$                                      | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.09 (0.00, 0.02)<br>0.37 (0.07, 2.02)<br>0.38 (0.00, 0.48)<br>0.19 (0.05, 0.73)<br>0.19 (0.05, 1.55)<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H, Fixed, 95% C<br>0.01 [0.00, 0.18]<br>0.06 [0.00, 1.15]<br>0.01 [0.00, 0.20]<br>0.08 [0.00, 1.49]   |       | Clonidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>95% CI<br>  | 10 |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Verna2016 [10]           Attai2015[11]           Reddy2011[12]           Kulshrestha2014[13]           Aravind2014[14]           Longani2017[15]           Jois2016[16]           Singh2016[17]           Ali2017[18]           Total (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = 3.0           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total (95% CI)           Total events  | ting<br>Clonidii<br>Events<br>0<br>1<br>4<br>5<br>0<br>4<br>0<br>2<br>0<br>3<br>0<br>2<br>21<br>0<br>5; Chi <sup>2</sup> = 5<br>= 4.01 (P <<br>Clonid<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | o.oood           ne           Total           40           30           30           30           30           30           30           30           30           40           30           30           40           30           40           30           40           30           40           30           40           30           460           50.62, c           0.0001           100           30           40           30           40           30           30           40           30           40           30           40           30           40           30           40           50           60           70           75   | Tramade<br>Events 3<br>39<br>14<br>4<br>5<br>12<br>41<br>5<br>12<br>19<br>6<br>171<br>171<br>171<br>171<br>171<br>171<br>171   | I         I           40         30           30         30           30         30           460         460           400         100           400         400           400         30           45         40           400         30           45         40           400         155   | $5.8\% \\ 6.4\% \\ 7.6\% \\ 9.3\% \\ 9.1\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.4\% \\ 8.7\% \\ 6.4\% \\ 8.8\% \\ 100.0\% \\ 101); l^2 = 7 \\ \hline Weight \\ 39.5\% \\ 39.5\% \\ 9.6\% \\ \hline$                                      | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.09 (0.00, 0.02)<br>0.37 (0.07, 2.02)<br>0.38 (0.00, 0.48)<br>0.19 (0.05, 0.73)<br>0.19 (0.05, 1.55)<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H, Fixed, 95% C<br>0.01 [0.00, 0.18]<br>0.06 [0.00, 1.15]<br>0.01 [0.00, 0.20]<br>0.08 [0.00, 1.49]   |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>95% Cl<br>-<br>10<br>Tramadol<br>tio<br>95% Cl  | 10 |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Venkatraman2018[8]           Bansal2011[9]           Verma2016 [10]           Attai2011[11]           Reddy2011[12]           Kulshrestha2014[13]           Aravind2014[14]           Longani2017[15]           Jois2016[16]           Singh2016[17]           Ali2017[18]           Total events           Heterogeneity: Tau <sup>2</sup> = 3.0           Dizziness           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Test for overall effect: Z   | ting<br>Clonidii<br>Events<br>0<br>1<br>4<br>5<br>0<br>4<br>0<br>2<br>0<br>3<br>0<br>2<br>21<br>0<br>5; Chi <sup>2</sup> = 5<br>= 4.01 (P <<br>Clonid<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | o.oood           ne           Total           40           30           30           30           30           30           30           30           30           40           30           30           40           30           40           30           40           30           40           30           40           30           460           50.62, c           0.0001           100           30           40           30           40           30           30           40           30           40           30           40           30           40           30           40           50           60           70           75   | Tramade<br>Events 3<br>39<br>14<br>4<br>5<br>12<br>41<br>5<br>12<br>19<br>6<br>171<br>171<br>171<br>171<br>171<br>171<br>171   | I         I           40         30           30         30           30         30           460         460           400         100           400         400           400         30           45         40           400         30           45         40           400         155   | $5.8\% \\ 6.4\% \\ 7.6\% \\ 9.3\% \\ 9.1\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.4\% \\ 8.7\% \\ 6.4\% \\ 8.8\% \\ 100.0\% \\ 101); l^2 = 7 \\ \hline Weight \\ 39.5\% \\ 39.5\% \\ 9.6\% \\ \hline$                                      | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.09 (0.00, 0.02)<br>0.37 (0.07, 2.02)<br>0.38 (0.00, 0.48)<br>0.19 (0.05, 0.73)<br>0.10 (0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H. Fixed, 95% C<br>0.01 [0.00, 0.18]<br>0.06 [0.00, 1.15]<br>0.01 [0.00, 0.20]<br>0.08 [0.00, 1.49]  |       | Clonidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>95% CI<br>  | 10 |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Venkatraman2018[8]           Bansal2011[9]           Verma2016 [10]           Attai2011[11]           Reddy2011[12]           Kulshrestha2014[13]           Aravind2014[14]           Longani2017[15]           Jois2016[16]           Singh2016[17]           Ali2017[18]           Total events           Heterogeneity: Tau <sup>2</sup> = 3.0           Dizziness           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Test for overall effect: Z   | Clonidii<br>Events<br>0<br>0<br>1<br>4<br>0<br>0<br>2<br>0<br>3<br>0<br>0<br>5; Chi <sup>p</sup> = 5<br>= 4.01 (P <<br>Clonid<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | 0.0000           ne           Total           400           300           300           300           45           400           300           45           400           300           450           400           300           450           400           300           450           400           300           450           400           300           450           400           300           450           400           300           450           400           300           450           400           300           450           400           300           450           400           300           455           400           155           400           400           400           400           400  | Tramade<br>Events 1<br>39<br>14<br>4<br>5<br>3<br>6<br>12<br>41<br>5<br>5<br>12<br>41<br>19<br>6<br>171<br>171<br>16<br>171<br>12<br>19<br>6<br>7<br>7<br>7<br>7<br>7<br>8<br>6<br>22<br>6<br>22<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5  | I         I           40         30           30         30           30         30           30         30           30         30           460         40           400         40           400         40           300         30           460         40           400         30           400         30           400         30           400         30           400         30           400         30           400         30           400         30           5         40           155         40  | $5.8\% \\ 6.4\% \\ 7.6\% \\ 9.3\% \\ 9.1\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.4\% \\ 8.7\% \\ 6.4\% \\ 8.8\% \\ 100.0\% \\ 101); l^2 = 7 \\ \hline Weight \\ 39.5\% \\ 39.5\% \\ 9.6\% \\ \hline$                                      | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.03, 1.65)<br>0.27 (0.06, 0.91]<br>0.00 (0.00, 2.02)<br>0.37 (0.06, 0.91]<br>0.00 (0.00, 2.02)<br>0.37 (0.00, 0.149]<br>0.19 (0.00, 0.17)<br>0.29 (0.05, 1.55)<br>0.10 [0.00, 0.17]<br>0.29 (0.05, 1.55)<br>0.10 [0.00, 0.17]<br>0.29 (0.05, 1.55)<br>0.10 [0.00, 0.17]<br>0.29 (0.05, 1.55)<br>0.10 [0.00, 0.17]<br>0.01 [0.00, 0.18]<br>0.01 [0.00, 0.20]<br>0.08 [0.00, 1.49]<br>0.02 [0.01, 0.09]  |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>95% CI<br>10<br>Tramadol<br>tio<br>95% CI<br>10<br>Tramadol<br>10<br>Tramadol   | 10 |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Vyas 2018[7]           Vyes 2018[7]           Vyes 2018[7]           Vyes 2018[7]           Vyes 2018[7]           Verma2016[10]           Attai2011[9]           Verma2016[10]           Attai2015[11]           Reddy2011[12]           Kulshrestha2014[13]           Jois2016[16]           Singh2016[17]           Ali2017[18]           Total (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = 3.1           Test for overall effect: Z +           Dizziness           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Test for overall effect: Z           Dry mouth           tudy or Subgroup   | ting<br>Clonidii<br>Events<br>0<br>1<br>4<br>5<br>0<br>4<br>0<br>2<br>0<br>3<br>0<br>2<br>21<br>0<br>5; Chi <sup>2</sup> = 5<br>= 4.01 (P <<br>Clonid<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>30<br>40<br>40<br>40<br>30<br>40<br>40<br>30<br>40<br>40<br>30<br>40<br>40<br>30<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>4   | Tramade<br>Events 3<br>39<br>14<br>4<br>5<br>12<br>41<br>5<br>12<br>19<br>6<br>171<br>171<br>171<br>171<br>171<br>171<br>171   | ol<br>Total 1<br>40<br>30<br>30<br>30<br>30<br>30<br>45<br>45<br>40<br>40<br>30<br>460<br>460<br>460<br>460<br>155<br>%   | $5.8\% \\ 6.4\% \\ 7.6\% \\ 9.3\% \\ 9.1\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.3\% \\ 6.4\% \\ 8.7\% \\ 6.4\% \\ 8.8\% \\ 100.0\% \\ 101); l^2 = 7 \\ \hline Weight \\ 39.5\% \\ 39.5\% \\ 9.6\% \\ \hline$                                      | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.09 (0.00, 0.02)<br>0.37 (0.07, 2.02)<br>0.38 (0.00, 0.48)<br>0.19 (0.05, 0.73)<br>0.10 (0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H. Fixed, 95% C<br>0.01 [0.00, 0.18]<br>0.06 [0.00, 1.15]<br>0.01 [0.00, 0.20]<br>0.08 [0.00, 1.49]  |       | Clonidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>10<br>10<br>Tramadol<br>tio<br>10<br>Tramadol<br>10<br>Tramadol<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10 | 10 |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Venkatraman2018[8]           Bansal2011[9]           Verma2016 [10]           Attal2013[11]           Reddy2011[12]           Kulshrestha2014[13]           Aravind2014[14]           Longani2017[15]           Jois2016[16]           Singh2016[17]           All2017[18]           Total (95% CI)           Total (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = 3.           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Test for overall effect: Z           Dry mouth           tu   | ting<br>Clonidii<br>Events<br>0<br>0<br>1<br>4<br>0<br>2<br>0<br>2<br>21<br>0<br>5; Chi <sup>2</sup> = 5<br>21<br>0<br>2<br>Clonidi<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | 0.0000<br>Total<br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>40<br>40<br>40<br>30<br>40<br>40<br>30<br>40<br>40<br>30<br>40<br>40<br>30<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>4   | Tramade<br>Events 3<br>39<br>14<br>4<br>5<br>12<br>41<br>5<br>12<br>19<br>6<br>12<br>19<br>17<br>19<br>14<br>5<br>12<br>19<br>10<br>12<br>19<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5  | ol<br>Total 1<br>40<br>30<br>30<br>30<br>30<br>30<br>45<br>45<br>40<br>40<br>30<br>460<br>460<br>460<br>460<br>155<br>%   | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.1%<br>6.3%<br>6.3%<br>6.3%<br>6.3%<br>6.3%<br>6.4%<br>6.4%<br>6.4%<br>001); I <sup>2</sup> = 7<br>Weight<br>39.5%<br>11.4%<br>39.5%<br>9.6%  | M-H. Random, 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.00 (0.00, 0.02)<br>0.37 (0.07, 2.02)<br>0.38 (0.00, 1.49)<br>0.19 (0.05, 0.73)<br>0.01 (0.00, 0.17)<br>0.29 (0.05, 1.55)<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H. Fixed, 95% C<br>0.01 [0.00, 0.18]<br>0.06 [0.00, 1.15]<br>0.01 [0.00, 0.20]<br>0.08 [0.00, 1.49]<br>0.02 [0.01, 0.09]<br>Odds Ratio   |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>10<br>10<br>Tramadol<br>tio<br>10<br>Tramadol<br>10<br>Tramadol<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10 | 10 |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Verma2016 [10]           Verma2016 [10]           Attai2011[9]           Verma2016 [10]           Attai2011[9]           Verma2016 [10]           Attai2011[12]           Kulshrestha2014[13]           Aravind2014[14]           Longani2017[15]           Jois2016[16]           Singh2016[17]           Ali2017[18]           Total (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = 3.0           Test for overall effect: Z =           Dizziness           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Test for overall effect: Z           Dry mouth           tudy or Subgroup           Shukla2011[6]           Vyas 2018[7]   | Clonidin<br>Events<br>0<br>0<br>1<br>4<br>5<br>0<br>0<br>2<br>0<br>3<br>0<br>2<br>0<br>3<br>0<br>2<br>0<br>3<br>0<br>2<br>0<br>3<br>0<br>2<br>0<br>3<br>0<br>2<br>0<br>3<br>0<br>2<br>0<br>3<br>0<br>2<br>0<br>0<br>3<br>0<br>2<br>0<br>0<br>3<br>0<br>2<br>0<br>0<br>3<br>0<br>2<br>0<br>0<br>1<br>4<br>0<br>4<br>0<br>0<br>1<br>4<br>0<br>2<br>0<br>0<br>3<br>0<br>0<br>2<br>0<br>0<br>1<br>4<br>0<br>2<br>0<br>0<br>1<br>4<br>0<br>0<br>0<br>1<br>4<br>0<br>0<br>2<br>0<br>0<br>0<br>1<br>4<br>0<br>0<br>2<br>0<br>0<br>0<br>2<br>0<br>0<br>0<br>0<br>1<br>4<br>0<br>0<br>2<br>0<br>0<br>0<br>0<br>2<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0 | 0.0000<br><b>Total</b><br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>45<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40   | Tramade<br>Events 3<br>39<br>14<br>4<br>5<br>5<br>12<br>41<br>5<br>5<br>12<br>19<br>6<br>171<br>171<br>12<br>6<br>171<br>12<br>6<br>22<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5  | I         I           40         30           30         30           30         30           30         30           40         40           40         40           40         30           40         40           40         30           30         30           460         30           460         30           460         30           400         30           300         30           400         30           300         30           400         30           300         30           400         30           300         30           400         30           300         30           400         30           50         40           155         %           60         60           60         60           60         60   | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.4%<br>8.8%<br>100.0%<br>100.0%<br>11.4%<br>39.5%<br>11.4%<br>39.5%<br>11.4%<br>39.5%<br>11.4%<br>39.5%<br>11.4%<br>7.2%<br>7.1%                                      | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.06 (0.00, 0.22)<br>0.37 (0.07, 2.02)<br>0.37 (0.07, 2.02)<br>0.37 (0.07, 2.02)<br>0.37 (0.07, 2.02)<br>0.37 (0.07, 2.02)<br>0.37 (0.07, 2.02)<br>0.37 (0.07, 2.02)<br>0.08 (0.07, 1.49)<br>0.10 [0.00, 0.18]<br>0.01 [0.00, 0.20]<br>0.08 [0.00, 1.49]<br>0.02 [0.01, 0.09]<br>0.02 [0.01, 0.09]<br>0.08 [0.12, 77.80]<br>3.10 (0.12, 77.83]  |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>10<br>10<br>Tramadol<br>tio<br>10<br>Tramadol<br>10<br>Tramadol<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10 | 10 |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Venkatramar2018[8]           Bansal2016[9]           Verma2016[10]           Attai2015[11]           Attai2016[11]           Attai2016[11]           Attai2016[11]           Attai2016[11]           Attai2016[11]           Aravind214[14]           Longani2017[15]           Jois2016[16]           Singh2016[17]           Ali2017[18]           Total (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = 3.4           Pizziness           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total (95% CI)   | ting<br>Clonidii<br>Events<br>0<br>0<br>1<br>4<br>0<br>2<br>0<br>2<br>2<br>0<br>5; Chi <sup>2</sup> = 5<br>= 4.01 (P <<br>Clonidi<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>30<br>45<br>40<br>40<br>40<br>30<br>40<br>40<br>30<br>40<br>40<br>30<br>40<br>40<br>30<br>40<br>40<br>30<br>45<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40  | Tramade<br>Events 1<br>39<br>14<br>4<br>5<br>5<br>12<br>41<br>5<br>5<br>12<br>41<br>5<br>5<br>12<br>41<br>17<br>17<br>19<br>6<br>12<br>41<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5   | ol<br>[Total]<br>40<br>30<br>30<br>30<br>30<br>45<br>40<br>40<br>40<br>30<br>460<br>40<br>30<br>460<br>40<br>30<br>460<br>40<br>30<br>45<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40  | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.1%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.4%<br>8.8%<br>100.0%<br>100.0%<br>100.0%<br>11.4%<br>39.5%<br>11.4%<br>39.5%<br>100.0%   | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.09 (0.00, 0.02)<br>0.37 (0.07, 2.02)<br>0.08 (0.00, 1.49)<br>0.19 (0.05, 0.73)<br>0.01 (0.00, 0.17)<br>0.29 (0.05, 1.55)<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H. Fixed, 95% C<br>0.01 [0.00, 1.15]<br>0.01 [0.00, 0.20]<br>0.08 [0.00, 1.49]<br>0.02 [0.01, 0.09]<br>0.02 [0.01, 0.09]<br>0.02 [0.01, 0.09]<br>3.00 [0.12, 77.80]<br>3.10 [0.12, 79.23]  |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>10<br>10<br>Tramadol<br>tio<br>10<br>Tramadol<br>10<br>Tramadol<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10 | 10 |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Venkatraman2018[8]           Bansal2011[9]           Verma2016 [10]           Attai2011[1]           Reddy2011[12]           Kulshrestha2014[13]           Aravind2014[14]           Longani2017[15]           Jois2016[16]           Singh2016[17]           Ali2017[18]           Total (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = 3.1           Test for overall effect: Z =           Dizziness           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Test for overall effect: Z           Dry mouth           Heterogeneity: Chi <sup>2</sup> = 1.           Test for overall effect: Z           Dry mouth           Heterogeneity: Chi <sup>2</sup> = 1.           Test for overall effect: Z           Dry mouth           Rudy or Subgroup           Shukla2011[6]           Vyas 2018[7]           Atta12015[11]           Reddy201   | ting<br>Clonidin<br>Events<br>0<br>0<br>1<br>4<br>5<br>0<br>2<br>0<br>3<br>0<br>2<br>2<br>0<br>5<br>Clorid<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0  | 0.0000<br>ne<br>Total<br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>45<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40  | Tramade<br>Events 3<br>39<br>14<br>4<br>5<br>5<br>5<br>12<br>19<br>6<br>171<br>16<br>171<br>16<br>171<br>16<br>171<br>16<br>22<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5  | ol<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>45<br>40<br>45<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40   | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.4%<br>8.8%<br>100.0%<br>01): I <sup>2</sup> = 7<br><u>Weight</u><br>39.5%<br>11.4%<br>39.5%<br>11.4%<br>9.6%<br>100.0%   | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.09 (0.00, 0.22)<br>0.37 (0.07, 2.02)<br>0.37 (0.07, 2.02)<br>0.08 (0.07, 1.49]<br>0.01 [0.00, 0.149]<br>0.02 [0.01, 0.09]<br>0.02 [0.01, 0.09]<br>0.08 [0.12, 77.80]<br>3.10 [0.12, 79.23]<br>3.10 (0.12, 79.23]<br>1.00 (0.13, 7.43]  |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>10<br>10<br>Tramadol<br>tio<br>10<br>Tramadol<br>10<br>Tramadol<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10 | 10 |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Anvind2014[14]           Longani2017[15]           Jois2016[16]           Singh2016[16]           Total (95% CI)           Total (95% CI)           Total (95% CI)           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = 3.4           Heterogeneity: Tau <sup>2</sup> = 3.4           Jois2016[16]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Test for overall effect: Z           Ory mouth           tudy or Subgroup           Shukla2011[6]           Vyas 2018[7]           Atta1201   | ting<br>Clonidin<br>Events<br>0<br>0<br>1<br>4<br>0<br>0<br>2<br>2<br>05; Chi <sup>2</sup> = 5<br>= 4.01 (P <<br>Clonidi<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0  | 0.0000<br>1000000000000000000000000000000000000  | Tramade<br>Events 1<br>39<br>14<br>4<br>5<br>3<br>6<br>12<br>41<br>5<br>5<br>12<br>19<br>6<br>171<br>17<br>19<br>6<br>171<br>12<br>19<br>6<br>171<br>12<br>19<br>6<br>171<br>12<br>19<br>6<br>172<br>19<br>10<br>10<br>12<br>41<br>10<br>12<br>41<br>12<br>19<br>6<br>12<br>41<br>12<br>19<br>6<br>12<br>12<br>19<br>6<br>12<br>12<br>19<br>6<br>12<br>12<br>19<br>6<br>12<br>12<br>12<br>19<br>6<br>12<br>12<br>19<br>6<br>12<br>12<br>12<br>19<br>6<br>12<br>12<br>12<br>19<br>6<br>12<br>12<br>12<br>12<br>12<br>19<br>6<br>171<br>171<br>12<br>12<br>19<br>6<br>22<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5  | ol<br>Total<br>400<br>30<br>30<br>30<br>30<br>45<br>40<br>40<br>40<br>30<br>45<br>40<br>40<br>30<br>45<br>40<br>40<br>40<br>40<br>30<br>45<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40  | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.4%<br>8.8%<br>100.0%<br>100.0%<br>11.4%<br>39.5%<br>11.4%<br>39.5%<br>11.4%<br>9.6%<br>100.0%  | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.09 (0.00, 0.02)<br>0.37 (0.07, 2.02)<br>0.08 (0.00, 1.49)<br>0.19 (0.05, 0.73)<br>0.01 (0.00, 0.17)<br>0.29 (0.05, 1.55)<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H. Fixed, 95% C<br>0.01 [0.00, 0.18]<br>0.06 [0.00, 1.15]<br>0.01 [0.00, 0.20]<br>0.08 [0.00, 1.49]<br>0.02 [0.01, 0.09]<br>0.02 [0.01, 0.09]<br>3.00 [0.12, 77.80]<br>3.10 [0.12, 79.23]<br>1.00 (0.13, 7.43]<br>1.49 (0.38, 149.40]  |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>10<br>10<br>Tramadol<br>tio<br>10<br>Tramadol<br>10<br>Tramadol<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10 | 10 |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Venkatraman2018[8]           Bansal2011[9]           Verma2016 [10]           Attai2011[12]           Kulshrestha2014[13]           Aravind2014[14]           Longani2017[15]           Jois2016[16]           Singh2016[17]           Ali2017[18]           Total events           Heterogeneity: Tau <sup>2</sup> = 3.1           Total events           Heterogeneity: Tau <sup>2</sup> = 3.1           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Vyas 2018[7]           Kulshrestha2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Test for overall effect: Z           Ory mouth           tady or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Test for overall effect: Z           Ory mouth  | ting<br>Clonidii<br>Events<br>0<br>0<br>1<br>4<br>5<br>0<br>2<br>0<br>2<br>21<br>0<br>5<br>Clonidi<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0  | 0.0000<br><b>Total</b><br>40<br>30<br>30<br>30<br>30<br>30<br>30<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>4  | Tramade<br>Events 3<br>39<br>14<br>4<br>5<br>3<br>6<br>12<br>41<br>5<br>5<br>5<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>6<br>22<br>55<br>55<br>55<br>55<br>55<br>50<br>10<br>11<br>19<br>6<br>22<br>5<br>50<br>00<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>1  | ol<br>Total<br>40<br>30<br>30<br>30<br>30<br>40<br>45<br>40<br>40<br>30<br>30<br>45<br>40<br>40<br>30<br>30<br>460<br>40<br>30<br>30<br>45<br>40<br>40<br>40<br>40<br>30<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>4   | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.4%<br>8.8%<br>100.0%<br>01): I <sup>2</sup> = 7<br>Weight<br>39.5%<br>11.4%<br>9.6%<br>100.0%<br>Weight<br>7.2%<br>7.1%<br>7.1%<br>28.6%<br>6.9%<br>29.2%                            | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.27 (0.08, 0.91)<br>0.09 (0.00, 0.02)<br>0.37 (0.07, 2.02)<br>0.37 (0.07, 2.02)<br>0.37 (0.07, 2.02)<br>0.38 (0.07, 2.02)<br>0.38 (0.00, 1.49)<br>0.19 (0.05, 0.73)<br>0.10 (0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H, Fixed, 95% C<br>0.01 [0.00, 0.18]<br>0.05 [0.00, 1.49]<br>0.08 [0.00, 1.49]<br>0.02 [0.01, 0.09]<br>0.02 [0.01, 0.09]<br>0.02 [0.01, 7.780]<br>3.10 [0.12, 77,23]<br>3.10 [0.12, 79,23]<br>1.00 (0.13, 7.43]<br>7.49 [0.38, 149.40]<br>0.49 [0.04, 5.60]                         |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>10<br>10<br>Tramadol<br>tio<br>10<br>Tramadol<br>10<br>Tramadol<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10 | 10 |
| Shukia2011[6]           Shukia2011[6]           Vyas 2018[7]           Vyas 2018[7]           Vyas 2018[7]           Vyas 2018[7]           Vyas 2018[7]           Venkatraman2018[8]           Bansal2011[9]           Verma2016[10]           Attai2015[11]           Reddy2011[12]           Kulshrestha2014[13]           Jois2016[16]           Singh2016[17]           Ali2017[18]           Total (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = 3.0           Dizziness           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Total (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Test for overall effect: Z           Ory mouth           tudy or Subgroup           Shukla2011[6]           Vyas 2018[7]           Attai2015[11]           Reddy2015[11]           Reddy2015[11]           Kulshrestha2014[13]           Jois2016[1   | ting<br>Clonidin<br>Events<br>0<br>0<br>1<br>4<br>0<br>0<br>2<br>2<br>05; Chi <sup>2</sup> = 5<br>= 4.01 (P <<br>Clonidi<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0  | 0.0000<br>1000000000000000000000000000000000000  | Tramade<br>Events 1<br>39<br>14<br>4<br>5<br>3<br>6<br>12<br>41<br>5<br>5<br>12<br>19<br>6<br>171<br>17<br>19<br>6<br>171<br>12<br>19<br>6<br>171<br>12<br>19<br>6<br>171<br>12<br>19<br>6<br>172<br>19<br>10<br>10<br>12<br>41<br>10<br>12<br>41<br>12<br>19<br>6<br>12<br>41<br>12<br>19<br>6<br>12<br>12<br>19<br>6<br>12<br>12<br>19<br>6<br>12<br>12<br>19<br>6<br>12<br>12<br>12<br>19<br>6<br>12<br>12<br>19<br>6<br>12<br>12<br>12<br>19<br>6<br>12<br>12<br>12<br>19<br>6<br>12<br>12<br>12<br>12<br>12<br>19<br>6<br>171<br>171<br>12<br>12<br>19<br>6<br>22<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5  | ol<br>Total<br>400<br>30<br>30<br>30<br>30<br>45<br>40<br>40<br>40<br>300<br>460<br>40<br>40<br>300<br>45<br>40<br>40<br>40<br>30<br>45<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40   | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.4%<br>8.8%<br>100.0%<br>100.0%<br>11.4%<br>39.5%<br>11.4%<br>39.5%<br>11.4%<br>9.6%<br>100.0%  | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.07 (0.06, 0.91]<br>0.00 (0.07, 2.02]<br>0.37 (0.06, 0.91]<br>0.00 (0.07, 2.02]<br>0.37 (0.06, 0.91]<br>0.01 [0.00, 0.17]<br>0.19 (0.05, 0.73]<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H. Fixed, 95% C<br>0.01 [0.00, 0.18]<br>0.06 [0.00, 1.16]<br>0.01 [0.00, 0.20]<br>0.08 [0.00, 1.49]<br>0.02 [0.01, 0.09]<br>0.02 [0.01, 0.09]<br>0.02 [0.01, 0.09]<br>0.01 (2, 79, 23]<br>1.00 [0.12, 79, 23]<br>1.00 [0.3, 14, 4.0]<br>0.49 [0.04, 5.60]<br>0.26 [0.24, 113, 11]                        |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>10<br>10<br>Tramadol<br>tio<br>10<br>Tramadol<br>10<br>Tramadol<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10 | 10 |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Vyenkatraman2018[8]           Bansal2011[9]           Verma2016[10]           Attai2011[12]           Kulshrestha2014[13]           Aravind2014[14]           Longani2017[15]           Jois2016[16]           Singh2016[17]           Alli2017[18]           Total (95% CI)           Total (95% CI)           Total (95% CI)           Dizziness           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total (95% CI)           Total events           Heterogeneity: Chi² = 1.           Test for overall effect: Z           Dizziness           Stuky or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Shukla2011[6]           Vyas 2018[7]           Attai2015[11]           Reddy2015[11]           Reddy2015[11]           Kulshrestha2014[13]           Jois2016[16]           Singh2016[16] <td>ting<br/>Clonidin<br/>Events<br/>0<br/>0<br/>1<br/>4<br/>0<br/>2<br/>0<br/>2<br/>2<br/>0<br/>5; Chi<sup>2</sup> = 5<br/>2<br/>1<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0</td> <td>0.0000<br/>1000000000000000000000000000000000000</td> <td>Tramade<br/>Events 3<br/>39<br/>14<br/>5<br/>5<br/>12<br/>41<br/>5<br/>5<br/>12<br/>19<br/>6<br/>171<br/>171<br/>171<br/>12<br/>19<br/>6<br/>171<br/>171<br/>12<br/>19<br/>6<br/>171<br/>171<br/>12<br/>19<br/>6<br/>172<br/>19<br/>6<br/>22<br/>5<br/>55<br/>55<br/>54);  <sup>2</sup> = 0<br/>001)<br/>Tramade<br/>Events 0<br/>0<br/>0<br/>0<br/>2<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0</td> <td>ol<br/>Total<br/>40<br/>30<br/>30<br/>30<br/>30<br/>45<br/>40<br/>40<br/>40<br/>30<br/>460<br/>40<br/>30<br/>40<br/>40<br/>30<br/>45<br/>40<br/>40<br/>40<br/>30<br/>45<br/>40<br/>40<br/>40<br/>40<br/>40<br/>40<br/>40<br/>40<br/>40<br/>40</td> <td>5.8%<br/>6.4%<br/>7.6%<br/>9.3%<br/>9.7%<br/>6.3%<br/>8.7%<br/>6.3%<br/>8.7%<br/>6.3%<br/>8.4%<br/>8.8%<br/>100.0%<br/>100.0%<br/>100.0%<br/>100.0%<br/>100.0%<br/>100.0%<br/>100.0%<br/>100.0%</td> <td>M-H. Random. 95% C<br/>0.00 (0.00, 0.01)<br/>0.02 (0.00, 0.31)<br/>0.22 (0.02, 2.14)<br/>0.77 (0.19, 3.20)<br/>1.80 (0.39, 8.32)<br/>0.06 (0.00, 1.15)<br/>0.07 (0.06, 0.91]<br/>0.00 (0.07, 2.02)<br/>0.08 (0.00, 1.49)<br/>0.19 (0.05, 0.73)<br/>0.01 [0.00, 0.17]<br/>0.29 (0.05, 1.55]<br/>0.10 [0.03, 0.31]<br/>6%<br/>Odds Ratio<br/>M-H. Fixed, 95% C<br/>0.01 [0.00, 0.18]<br/>0.06 [0.00, 1.15]<br/>0.01 [0.00, 0.18]<br/>0.06 [0.00, 1.49]<br/>0.02 [0.01, 0.09]<br/>0.02 [0.01, 0.09]<br/>0.02 [0.01, 0.09]<br/>3.10 [0.12, 79.23]<br/>3.10 [0.12, 79.23]<br/>3.10 [0.13, 7.43]<br/>7.49 [0.38, 149.40]<br/>0.49 [0.04, 5.60]<br/>5.26 [0.24, 113.11]<br/>5.35 [0.25, 116.31]</td> <td></td> <td>Cionidine<br/>Odds Rat<br/>M-H. Random.</td> <td>Tramadol<br/>10<br/>10<br/>Tramadol<br/>tio<br/>10<br/>Tramadol<br/>10<br/>Tramadol<br/>10<br/>10<br/>10<br/>10<br/>10<br/>10<br/>10<br/>10<br/>10<br/>10</td> <td>10</td>   | ting<br>Clonidin<br>Events<br>0<br>0<br>1<br>4<br>0<br>2<br>0<br>2<br>2<br>0<br>5; Chi <sup>2</sup> = 5<br>2<br>1<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | 0.0000<br>1000000000000000000000000000000000000  | Tramade<br>Events 3<br>39<br>14<br>5<br>5<br>12<br>41<br>5<br>5<br>12<br>19<br>6<br>171<br>171<br>171<br>12<br>19<br>6<br>171<br>171<br>12<br>19<br>6<br>171<br>171<br>12<br>19<br>6<br>172<br>19<br>6<br>22<br>5<br>55<br>55<br>54);   <sup>2</sup> = 0<br>001)<br>Tramade<br>Events 0<br>0<br>0<br>0<br>2<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | ol<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>40<br>40<br>40<br>30<br>460<br>40<br>30<br>40<br>40<br>30<br>45<br>40<br>40<br>40<br>30<br>45<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40  | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.3%<br>8.4%<br>8.8%<br>100.0%<br>100.0%<br>100.0%<br>100.0%<br>100.0%<br>100.0%<br>100.0%<br>100.0%   | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32)<br>0.06 (0.00, 1.15)<br>0.07 (0.06, 0.91]<br>0.00 (0.07, 2.02)<br>0.08 (0.00, 1.49)<br>0.19 (0.05, 0.73)<br>0.01 [0.00, 0.17]<br>0.29 (0.05, 1.55]<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H. Fixed, 95% C<br>0.01 [0.00, 0.18]<br>0.06 [0.00, 1.15]<br>0.01 [0.00, 0.18]<br>0.06 [0.00, 1.49]<br>0.02 [0.01, 0.09]<br>0.02 [0.01, 0.09]<br>0.02 [0.01, 0.09]<br>3.10 [0.12, 79.23]<br>3.10 [0.12, 79.23]<br>3.10 [0.13, 7.43]<br>7.49 [0.38, 149.40]<br>0.49 [0.04, 5.60]<br>5.26 [0.24, 113.11]<br>5.35 [0.25, 116.31] |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>10<br>10<br>Tramadol<br>tio<br>10<br>Tramadol<br>10<br>Tramadol<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10 | 10 |
| Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Vemkatraman2018[8]           Bansal2011[9]           Verma2016 [10]           Attal2013[11]           Reddy2011[12]           Kulshrestha2014[13]           Aravind2014[14]           Longani2017[15]           Jois2016[16]           Singh2016[17]           All2017[18]           Total (95% CI)           Total (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> = 3.           Test for overall effect: Z =           Dizziness           Study or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kulshrestha2014[13]           Jois2016[16]           Total (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 1.           Test for overall effect: Z           Dry mouth           tudy or Subgroup           Shukla2011[6]           Vyas 2018[7]           Kutal2011[6]           Vyas 2018[7]           Kutal2011[6]           Vyas 2018[7]           Kutal2011[6]           Shukla2011[6]           Sutal   | ting<br>Clonidii<br>Events<br>0<br>0<br>1<br>4<br>0<br>2<br>0<br>2<br>21<br>0<br>2<br>2<br>0<br>0<br>2<br>2<br>0<br>0<br>2<br>2<br>0<br>0<br>2<br>2<br>0<br>0<br>2<br>2<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | 0.0000<br>1000000000000000000000000000000000000  | 21)<br>Tramade<br>Events 3<br>39<br>14<br>4<br>5<br>12<br>41<br>5<br>12<br>19<br>6<br>12<br>19<br>6<br>12<br>19<br>10<br>12<br>12<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5   | ol<br>Total<br>40<br>30<br>30<br>30<br>30<br>45<br>40<br>40<br>40<br>30<br>460<br>40<br>30<br>40<br>40<br>30<br>40<br>40<br>30<br>40<br>40<br>30<br>45<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40  | 5.8%<br>6.4%<br>7.6%<br>9.3%<br>9.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.3%<br>8.7%<br>6.4%<br>8.8%<br>100.0%<br>100.0%<br>100.0%<br>100.0%<br>100.0%<br>100.0%   | M-H. Random. 95% C<br>0.00 (0.00, 0.01)<br>0.02 (0.00, 0.31)<br>0.22 (0.02, 2.14)<br>0.77 (0.19, 3.20)<br>1.80 (0.39, 8.32]<br>0.06 (0.00, 1.15]<br>0.07 (0.06, 0.91]<br>0.00 (0.07, 2.02]<br>0.37 (0.06, 0.91]<br>0.00 (0.07, 2.02]<br>0.37 (0.06, 0.91]<br>0.01 [0.00, 0.17]<br>0.19 (0.05, 0.73]<br>0.10 [0.03, 0.31]<br>6%<br>Odds Ratio<br>M-H. Fixed, 95% C<br>0.01 [0.00, 0.18]<br>0.06 [0.00, 1.16]<br>0.01 [0.00, 0.20]<br>0.08 [0.00, 1.49]<br>0.02 [0.01, 0.09]<br>0.02 [0.01, 0.09]<br>0.02 [0.01, 0.09]<br>0.03, 10 (0.12, 79,23]<br>1.00 [0.13, 7.43]<br>7.49 [0.38, 149,40]<br>0.49 [0.04, 5.60]<br>0.26 [0.24, 113,11]                     |       | Cionidine<br>Odds Rat<br>M-H. Random. | Tramadol<br>10<br>10<br>Tramadol<br>tio<br>10<br>Tramadol<br>10<br>Tramadol<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10 | 10 |
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Figure 4 - Forest plot for related complications (hypotension, bradycardia, sedation, nausea, vomiting, dizziness, dry mouth).

*p*<0.00001; I<sup>2</sup>=0%), bradycardia (OR: 3.94; 95% CI: 1.69-9.20; *p*= 0.002; I<sup>2</sup> = 0%), and sedation (OR: 2.67; 95% CI: 1.80–3.94; *p*<0.00001; I<sup>2</sup>=46%), and lower incidence of dizziness (OR: 0.02; 95% CI: 0.01-0.09; *p*<0.00001; I<sup>2</sup>=0%) compared with tramadol. (**Figure 4**)

Compared with tramadol, clonidine had a lower incidence of nausea and vomiting (OR 0.10; 95% CI: 0.03-0.31; p<0.0001; I<sup>2</sup>=76%) (Figure 4). Sensitivity analysis was performed by taking out every included RCT sequentially. The result was confirmed, and no source of heterogeneity was identified.

The difference in the incidence of dry mouth was not statistically significant between clonidine and tramadol (OR: 2.35; 95% CI: 0.95-5.77; p=0.06;  $I^2$ =0%) (Figure 4).

The funnel plot of the effective rate of shivering control was symmetrical, so there were no potential publication biases.

**Discussion.** The present meta-analysis indicates that tramadol is more effective than clonidine for shivering control following spinal anesthesia. However, the difference is not significant in the shivering recurrence rate between clonidine and tramadol. In terms of complications, tramadol use resulted in higher incidences of nausea, vomiting, and dizziness, while clonidine increased the probability of bradycardia, hypotension, and sedation.

Nausea, vomiting, and dizziness are very distressing for patients and may lead to serious consequences.<sup>20</sup> According to the included RCTs, bradycardia and hypotension could be promptly treated by intravenous drugs. If surgeries are performed under spinal anesthesia, sedation caused by clonidine is beneficial for the patients. In addition, no patients were over sedated in the identified studies.

Clonidine has a high lipid solubility; therefore, it can promptly cross the blood-brain barrier.<sup>21</sup> Hence, clonidine can activate  $\alpha 2$  receptors in the central nervous system to reduce the central thermosensitivity by suppressing the neuronal conductance, consequently reducing the thermoregulatory threshold for shivering.<sup>21</sup> The antishivering mechanism of tramadol possibly results from its opioid or serotonergic and noradrenergic function.<sup>22</sup>

Although the search strategy was designed to be as thorough as possible to identify eligible RCTs, the included RCTs were limited. Tramadol can significantly increase the effective rate of shivering treatment, but in terms of the complications, there is not enough clinical evidence to determine which of the 2, clonidine or tramadol, is better for shivering treatment after spinal anesthesia. Thus, further high-quality evidence from a large sample is needed.

In conclusion, tramadol is more effective than clonidine for shivering treatment, but with increased incidences of nausea, vomiting, and dizziness.

**Acknowledgment.** *The authors gratefully acknowledge Editage* (*www.editage.cn*) *for English language editing.* 

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