### Literature Search Terms:

((insomnia OR "Sleep Initiation and Maintenance Disorders"[Mesh]) AND ((clinical trial) OR (randomized controlled trial)) NOT "Editorial"[Publication Type] NOT "Letter"[Publication Type] NOT "Comment"[Publication Type] NOT "Case Reports"[Publication Type] NOT "Biography"[Publication Type] NOT "Review"[Publication Type] NOT (transient[TI]) NOT (animals[mh] NOT humans[mh]))

### Suvorexant - Summary of Findings Tables

#### Table S1 – Summary of Findings table for suvorexant 10 mg for the treatment of chronic insomnia

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 10 mg Suvorexant vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (PSG)</td>
<td>⊕⊕⊕⊝⊝ low</td>
<td>The mean sleep latency in the suvorexant group was 2.3 minutes lower (13.68 lower to 9.08 higher)</td>
<td>175 (1 study)^A</td>
</tr>
<tr>
<td>Wake After Sleep Onset* (PSG)</td>
<td>⊕⊕⊕ ⊝ low</td>
<td>The mean wake after sleep onset in the suvorexant group was 21.5 minutes lower (36.34 to 6.66 lower)</td>
<td>175 (1 study)^A</td>
</tr>
<tr>
<td>Sleep Efficiency (PSG)</td>
<td>⊕⊕⊕⊕ ⊝ low</td>
<td>The mean sleep efficiency in the suvorexant group was 4.7 percent higher (0.97 to 8.43 higher)</td>
<td>175 (1 study)^A</td>
</tr>
</tbody>
</table>

^ Critical Outcome, used to determine Quality of Evidence
1 95% CI (-13.68 to 9.08) crosses the Clinical Significance Threshold (10 min)
2 Study funded by industry
3 95% CI (-36.34 to -6.66) crosses the Clinical Significance Threshold (20 min)
4 95% CI (0.97 to 8.43) crosses the Clinical Significance Threshold (5%)

#### Table S2 – Summary of Findings table for suvorexant 15/20 mg for the treatment of chronic insomnia

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 15/20 mg Suvorexant vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (PSG)</td>
<td>⊕⊕⊕ ⊝ low</td>
<td>The mean sleep latency in the suvorexant group was 8.1 minutes lower (13.85 lower to 2.35 lower)</td>
<td>423 (1 study)^A</td>
</tr>
<tr>
<td>Sleep Latency (Subjective)</td>
<td>⊕⊕⊕ ⊝ moderate</td>
<td>The mean sleep latency in the suvorexant group was 5.2 minutes lower (10.1 to 0.3 lower)</td>
<td>567 (1 study)^A</td>
</tr>
<tr>
<td>Total Sleep Time* (Subjective)</td>
<td>⊕⊕⊕ ⊝ moderate</td>
<td>The mean total sleep time in the suvorexant group was 10.6 minutes higher (1.79 to 19.41 higher)</td>
<td>567 (1 study)^A</td>
</tr>
<tr>
<td>Wake After Sleep Onset* (PSG)</td>
<td>⊕⊕⊕ ⊝ low</td>
<td>The mean wake after sleep onset in the suvorexant group was 16.60 minutes lower (24.87 to 8.33 lower)</td>
<td>567 (1 study)^A</td>
</tr>
</tbody>
</table>

^ Critical Outcome, used to determine Quality of Evidence
1 95% CI (-13.85 to -2.35) crosses the Clinical Significance Threshold (10 min)
2 Study funded by industry
3 95% CI (-24.87 to -8.33) crosses the Clinical Significance Threshold (20 min)
Table S3 – Summary of Findings table for suvorexant 20 mg for the treatment of chronic insomnia

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 20 mg Suvorexant vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (PSG)</td>
<td>⊕⊕⊕⊕ ⊕ ⊕ ⊕ moderate²</td>
<td>The mean sleep latency in the suvorexant group was 22.3 minutes lower (33.77 to 10.83 lower)</td>
<td>173 (1 study)⁴</td>
</tr>
<tr>
<td>Wake After Sleep Onset* (PSG)</td>
<td>⊕⊕⊕⊕⊕ ⊕⊕⊕⊕⊕ ⊕⊕⊕⊕⊕ low²</td>
<td>The mean wake after sleep onset in the suvorexant group was 28.1 minutes lower (43.07 to 13.13 lower)</td>
<td>173 (1 study)⁴</td>
</tr>
<tr>
<td>Sleep Efficiency (PSG)</td>
<td>⊕⊕⊕⊕⊕ ⊕⊕⊕⊕⊕ moderate²</td>
<td>The mean sleep efficiency in the suvorexant group was 10.4 percent higher (6.65 to 14.15 higher)</td>
<td>173 (1 study)⁴</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence
² 95% CI (-43.07 to -13.13) crosses Clinical Significance Threshold (20 min)
³ Study funded by industry

Eszopiclone - Meta-Analyses and Summary of Findings Tables

Figure S1 – Meta-analysis of data for PSG-determined sleep latency in response to eszopiclone 2 mg

Figure S2 – Meta-analysis of data for subjectively-determined sleep latency in response to eszopiclone 2 mg

Figure S3 – Meta-analysis of data for subjectively-determined total sleep time in response to eszopiclone 2 mg

Figure S4 – Meta-analysis of data for PSG-determined wake after sleep onset in response to eszopiclone 2 mg
Figure S5 – Meta-analysis of data for subjectively-determined wake after sleep onset in response to eszopiclone 2 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [SD]</th>
<th>Total Mean [SD]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankil-Haasch, 2010</td>
<td>63.96 (6.05)</td>
<td>145</td>
<td>59.05 (5.63)</td>
<td>146</td>
<td>-4.47 (-16.83, 7.90)</td>
</tr>
<tr>
<td>Ermak, 2018</td>
<td>76.82 (7.26)</td>
<td>63</td>
<td>56.6 (4.83)</td>
<td>83</td>
<td>1.5% (12.40 - 5.69, 70.38)</td>
</tr>
<tr>
<td>McCall, 2006</td>
<td>77.3 (6.17)</td>
<td>133</td>
<td>68.1 (5.3)</td>
<td>122</td>
<td>30.7% (-10.60 - 22.37, 0.77)</td>
</tr>
<tr>
<td>Scharr, 2006</td>
<td>54.1 (6.1)</td>
<td>73</td>
<td>57.4 (5.8)</td>
<td>90</td>
<td>14.0% (-13.20 - 31.51, 4.51)</td>
</tr>
<tr>
<td>Zammit, 2004</td>
<td>53.4 (6.1)</td>
<td>104</td>
<td>49.1 (3.6)</td>
<td>99</td>
<td>30.3% (4.20 - 7.38, 15.86)</td>
</tr>
</tbody>
</table>

Total (95% CI): 524 | 510 | 100.0% | -4.74 (-11.87, 2.39) |

Heterogeneity: Tau² = 0.03; Ch² = 4.55; df = 4 (P = 0.34); P = 12%
Test for overall effect: Z = 1.30 (P = 0.19)

Figure S6 – Meta-analysis of data for subjectively-determined quality of sleep in response to eszopiclone 2 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [SD]</th>
<th>Total Mean [SD]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ermak, 2008</td>
<td>57.2 (20.9)</td>
<td>63</td>
<td>44.4 (18.9)</td>
<td>63</td>
<td>19.7% (0.62 [0.27, 0.98])</td>
</tr>
<tr>
<td>Scharr, 2005</td>
<td>7.5 (1.7)</td>
<td>79</td>
<td>6.6 (1.9)</td>
<td>80</td>
<td>25.3% (0.50 [0.18, 0.81])</td>
</tr>
<tr>
<td>Uchimura, 2012</td>
<td>8.3 (1.8)</td>
<td>80</td>
<td>5.2 (1.9)</td>
<td>71</td>
<td>22.8% (0.59 [0.25, 0.93])</td>
</tr>
<tr>
<td>Zammit, 2004</td>
<td>54.4 (16.7)</td>
<td>104</td>
<td>49 (16.1)</td>
<td>99</td>
<td>33.0% (0.29 [0.02, 0.57])</td>
</tr>
</tbody>
</table>

Total (95% CI): 315 | 313 | 100.0% | 0.47 [0.32, 0.63] |

Heterogeneity: Tau² = 0.04; Ch² = 2.01; df = 3 (P = 0.42); P = 0%
Test for overall effect: Z = 5.66 (P < 0.00001)

Figure S7 – Meta-analysis of data for PSG-determined sleep efficiency in response to eszopiclone 2 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [SD]</th>
<th>Total Mean [SD]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCall, 2006</td>
<td>78.9 (9)</td>
<td>133</td>
<td>73.4 (6)</td>
<td>122</td>
<td>56.8% (5.00 [3.79, 8.21])</td>
</tr>
<tr>
<td>Zammit, 2004</td>
<td>86.2 (9.8)</td>
<td>104</td>
<td>82.9 (11.7)</td>
<td>93</td>
<td>43.2% (1.30 [0.35, 6.25])</td>
</tr>
</tbody>
</table>

Total (95% CI): 237 | 221 | 100.0% | 4.83 [2.21, 7.46] |

Heterogeneity: Tau² = 1.92; Ch² = 2.06; df = 1 (P = 0.15); P = 51%
Test for overall effect: Z = 3.61 (P = 0.0003)

Figure S8 – Meta-analysis of data for PSG-determined number of awakenings in response to eszopiclone 2 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [SD]</th>
<th>Total Mean [SD]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI [#]</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCall, 2006</td>
<td>9.1 (3.3)</td>
<td>133</td>
<td>9.5 (3.3)</td>
<td>122</td>
<td>56.5% (-0.40 [-2.11, 0.41])</td>
</tr>
<tr>
<td>Zammit, 2004</td>
<td>7.3 (4)</td>
<td>104</td>
<td>8.5 (4.5)</td>
<td>99</td>
<td>43.5% (0.80 [0.37, 1.97])</td>
</tr>
</tbody>
</table>

Total (95% CI): 237 | 221 | 100.0% | 0.12 [-1.04, 1.29] |

Heterogeneity: Tau² = 0.46; Ch² = 2.72; df = 1 (P = 0.10); P = 58%
Test for overall effect: Z = 0.21 (P = 0.84)

Figure S9 – Meta-analysis of data for subjectively-determined number of awakenings in response to eszopiclone 2 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [SD]</th>
<th>Total Mean [SD]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI [#]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ermak, 2008</td>
<td>3 (1.4)</td>
<td>63</td>
<td>3.7 (2.1)</td>
<td>63</td>
<td>7.9% (0.70 [-1.32, -0.68])</td>
</tr>
<tr>
<td>McCall, 2006</td>
<td>2 (1)</td>
<td>133</td>
<td>2.3 (1)</td>
<td>122</td>
<td>58.9% (-0.35 [-0.55, -0.65])</td>
</tr>
<tr>
<td>Scharr, 2005</td>
<td>1.5 (1.1)</td>
<td>79</td>
<td>1.8 (1)</td>
<td>80</td>
<td>28.6% (-0.30 [-0.63, 0.83])</td>
</tr>
<tr>
<td>Zammit, 2004</td>
<td>2.9 (1.7)</td>
<td>104</td>
<td>3.2 (1.9)</td>
<td>99</td>
<td>12.4% (-0.39 [-0.88, 0.20])</td>
</tr>
</tbody>
</table>

Total (95% CI): 379 | 364 | 100.0% | -0.33 [-0.51, -0.16] |

Heterogeneity: Tau² = 0.00; Ch² = 1.48; df = 3 (P = 0.69); P = 9%
Test for overall effect: Z = 3.71 (P = 0.0002)
Figure S10– Meta-analysis of data for the occurrence of dizziness in response to eszopiclone 2 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Eszopiclone 2 mg Events</th>
<th>Placebo Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erman 2008</td>
<td>0</td>
<td>53</td>
<td>53</td>
<td>36%</td>
<td>0.05 [0.11, 0.01]</td>
</tr>
<tr>
<td>McCall 2006</td>
<td>12</td>
<td>133</td>
<td>145</td>
<td>146</td>
<td>0.10 [0.04, 0.16]</td>
</tr>
<tr>
<td>Uchimura 2012</td>
<td>3</td>
<td>104</td>
<td>107</td>
<td>99</td>
<td>0.03 [-0.02, 0.08]</td>
</tr>
<tr>
<td>Zammit 1971</td>
<td>0</td>
<td>69</td>
<td>69</td>
<td>71</td>
<td>0.00 [-0.03, 0.03]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>369</strong></td>
<td><strong>355</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>6</strong></td>
<td><strong>0.00 [0.04, 0.05]</strong></td>
</tr>
</tbody>
</table>

Total events 15, Heterogeneity: Tau² = 0.00, Chi² = 10.93, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 0.18 (P = 0.85)

Figure S11– Meta-analysis of data for the occurrence of dry mouth in response to eszopiclone 2 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Eszopiclone 2 mg Events</th>
<th>Placebo Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCall 2006</td>
<td>16</td>
<td>133</td>
<td>149</td>
<td>150</td>
<td>0.10 [0.04, 0.16]</td>
</tr>
<tr>
<td>Zammit 1971</td>
<td>6</td>
<td>104</td>
<td>110</td>
<td>101</td>
<td>0.03 [-0.02, 0.08]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>237</strong></td>
<td><strong>221</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>4</strong></td>
<td><strong>0.06 [-0.01, 0.14]</strong></td>
</tr>
</tbody>
</table>

Total events 21, Heterogeneity: Tau² = 0.00, Chi² = 4.02, df = 1 (P = 0.04); I² = 75%
Test for overall effect: Z = 1.62 (P = 0.11)

Figure S12– Meta-analysis of data for the occurrence of headache in response to eszopiclone 2 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Eszopiclone 2 mg Events</th>
<th>Placebo Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancoli-Israel 2010</td>
<td>20</td>
<td>145</td>
<td>165</td>
<td>165</td>
<td>0.01 [-0.03, 0.09]</td>
</tr>
<tr>
<td>Erman 2008</td>
<td>4</td>
<td>63</td>
<td>65</td>
<td>65</td>
<td>-0.03 [-0.13, 0.06]</td>
</tr>
<tr>
<td>Schaefer 2005</td>
<td>12</td>
<td>79</td>
<td>91</td>
<td>91</td>
<td>0.00 [-0.11, 0.11]</td>
</tr>
<tr>
<td>Zammit 1971</td>
<td>14</td>
<td>104</td>
<td>118</td>
<td>118</td>
<td>0.05 [-0.03, 0.14]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>391</strong></td>
<td><strong>388</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>44</strong></td>
<td><strong>0.01 [-0.03, 0.06]</strong></td>
</tr>
</tbody>
</table>

Total events 60, Heterogeneity: Tau² = 0.00, Chi² = 1.80, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.57 (P = 0.57)

Figure S13– Meta-analysis of data for the occurrence of somnolence in response to eszopiclone 2 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Eszopiclone 2 mg Events</th>
<th>Placebo Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erman 2008</td>
<td>2</td>
<td>63</td>
<td>65</td>
<td>65</td>
<td>0.00 [-0.03, 0.06]</td>
</tr>
<tr>
<td>McCall 2006</td>
<td>12</td>
<td>133</td>
<td>145</td>
<td>145</td>
<td>0.02 [-0.05, 0.08]</td>
</tr>
<tr>
<td>Schaefer 2005</td>
<td>3</td>
<td>76</td>
<td>79</td>
<td>79</td>
<td>-0.05 [-0.12, 0.03]</td>
</tr>
<tr>
<td>Uchimura 2012</td>
<td>8</td>
<td>104</td>
<td>112</td>
<td>112</td>
<td>0.05 [-0.01, 0.11]</td>
</tr>
<tr>
<td>Zammit 1971</td>
<td>2</td>
<td>69</td>
<td>71</td>
<td>71</td>
<td>0.01 [-0.03, 0.06]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>448</strong></td>
<td><strong>435</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>22</strong></td>
<td><strong>0.01 [-0.02, 0.04]</strong></td>
</tr>
</tbody>
</table>

Total events 27, Heterogeneity: Tau² = 0.00, Chi² = 3.98, df = 4 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)
Figure S14 – Meta-analysis of data for the occurrence of unpleasant taste in response to eszopiclone 2 mg

Table S4 – Summary of Findings table for eszopiclone 2 mg for the treatment of chronic insomnia

References: Ancoli-Israel 2010(A); Erman 2008(B); McCall 2006(C); Scharf 2005(D); Uchimura 2012(E); Zammit 2004(F)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of evidence (GRADE)</th>
<th>Absolute Difference 2 mg Eszopiclone vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (PSG)</td>
<td>⊕⊕⊕⊕⊕ low²</td>
<td>The mean sleep latency in the eszopiclone groups was 14.87 minutes lower (24.27 to 5.47 lower)</td>
<td>598 (3 studies)⁴,E,F</td>
</tr>
<tr>
<td>Sleep Latency (Subjective)</td>
<td>⊕⊕⊕⊕⊕ low³</td>
<td>The mean sleep latency in the eszopiclone groups was 17.78 minutes lower (28.52 to 7.04 lower)</td>
<td>1174 (6 studies)⁴,A,B,C,D,E,F</td>
</tr>
<tr>
<td>Total Sleep Time* (Subjective)</td>
<td>⊕⊕⊕⊕⊕ low²,⁴</td>
<td>The mean total sleep time in the eszopiclone groups was 27.53 minutes higher (18.29 to 36.76 higher)</td>
<td>743 (4 studies)⁴,B,C,D,F</td>
</tr>
<tr>
<td>Wake After Sleep Onset* (PSG)</td>
<td>⊕⊕⊕⊕ moderate⁵</td>
<td>The mean wake after sleep onset in the eszopiclone groups was 10.02 minutes lower (17.27 to 2.77 lower)</td>
<td>458 (2 studies)⁵,F</td>
</tr>
<tr>
<td>Wake After Sleep Onset (Subjective)</td>
<td>⊕⊕⊕⊕ moderate⁵</td>
<td>The mean wake after sleep onset in the eszopiclone groups was 4.74 minutes lower (11.87 lower to 2.39 higher)</td>
<td>1034 (5 studies)⁵,A,B,C,D,F</td>
</tr>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⊕⊕⊕⊕ moderate⁵,⁶</td>
<td>The mean quality of sleep in the eszopiclone groups was 0.47 standard deviations higher (0.32 to 0.63 higher)</td>
<td>628 (4 studies)⁵,B,D,E,F</td>
</tr>
<tr>
<td>Sleep Efficiency (PSG)</td>
<td>⊕⊕⊕⊕ low⁶</td>
<td>The mean sleep efficiency in the eszopiclone groups was 4.83 percent higher (2.21 to 7.46 higher)</td>
<td>458 (2 studies)⁶,F</td>
</tr>
<tr>
<td>Sleep Efficiency (Subjective)</td>
<td>⊕⊕⊕⊕ moderate⁵</td>
<td>The mean sleep efficiency in the eszopiclone groups was 0.30 percent lower (0.79 lower to 0.19 higher)</td>
<td>203 (1 study)⁶,F</td>
</tr>
<tr>
<td>Number of Awakening (PSG)</td>
<td>⊕⊕⊕⊕ moderate⁵</td>
<td>The mean number awakening in the eszopiclone groups was 0.12 awakenings higher (1.04 lower to 1.29 higher)</td>
<td>458 (2 studies)⁵,F</td>
</tr>
<tr>
<td>Number of Awakenings (Subjective)</td>
<td>⊕⊕⊕⊕ moderate⁵</td>
<td>The mean number of awakenings in the eszopiclone groups was 0.33 awakenings lower (0.51 to 0.16 lower)</td>
<td>743 (4 studies)⁵,B,C,D,F</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence
1 95% CI (-24.27, -5.47) crosses Clinical Significance (10 min)
2 All studies funded by industry
3 95% CI (-33.81, -6.35) crosses Clinical Significance (20 min)
4 95% CI (18.29, 36.76) crosses Clinical Significance (20 min)
5 95% CI (2.21, 7.46) crosses Clinical Significance (5%)
6 95% CI (0.37, 0.76) crosses Clinical Significance (SMD 0.5)
Table S5 – Summary of Findings table for eszopiclone 3 mg for the treatment of chronic insomnia

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 3 mg Eszopiclone vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (PSG)</td>
<td>⊕⊕⊕⊕ very low</td>
<td>The mean sleep latency in the eszopiclone groups was 13.63 minutes lower (23.56 to 3.7 lower)</td>
<td>405 (3 studies)A,D,F</td>
</tr>
<tr>
<td>Sleep Latency (Subjective)</td>
<td>⊕⊕⊕ low</td>
<td>The mean sleep latency in the eszopiclone groups was 25.00 minutes lower (36.07 to 13.94 lower)</td>
<td>1630 (4 studies)B,C,E,F</td>
</tr>
<tr>
<td>Total Sleep Time* (Subjective)</td>
<td>⊕⊕⊕⊕ moderate</td>
<td>The mean total sleep time in the eszopiclone groups was 57.10 minutes higher (37.45 to 76.75 higher)</td>
<td>1630 (4 studies)B,C,E,F</td>
</tr>
<tr>
<td>Wake After Sleep Onset* (PSG)</td>
<td>⊕⊕⊕ moderate</td>
<td>The mean wake after sleep onset in the eszopiclone groups was 14.69 minutes lower (17.68 to 11.69 lower)</td>
<td>266 (2 studies)A,F</td>
</tr>
<tr>
<td>Wake After Sleep Onset (Subjective)</td>
<td>⊕⊕⊕ low</td>
<td>The mean wake after sleep onset in the eszopiclone groups was 15.14 minutes lower (22.11 to 8.16 lower)</td>
<td>1630 (4 studies)B,C,E,F</td>
</tr>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⊕⊕⊕ low</td>
<td>The mean quality of sleep in the eszopiclone groups was 1.49 standard deviations higher (0.84 to 2.14 higher)</td>
<td>1769 (6 studies)A,B,C,D,E,F</td>
</tr>
<tr>
<td>Sleep Efficiency (PSG)</td>
<td>⊕⊕⊕⊕ low</td>
<td>The mean sleep efficiency in the eszopiclone groups was 5.61 percent higher (3.64 to 7.58 higher)</td>
<td>266 (2 studies)A,F</td>
</tr>
<tr>
<td>Number of Awakenings (Subjective)</td>
<td>⊕⊕⊕⊕ very low</td>
<td>The mean number awakenings in the eszopiclone groups was 0.76 awakenings lower (1.49 to 0.02 lower)</td>
<td>1503 (3 studies)C,E,F</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence
1 Heterogeneity ($I^2 = 88\%$) greater than allowance (75%)
2 95% CI (-23.56, -3.70) crosses Clinical Significance (10 min)
3 All studies funded by industry
4 95% CI (-36.07, -13.94) crosses Clinical Significance (20 min)
5 Heterogeneity ($I^2 = 93\%$) greater than allowance (75%)
6 95% CI (-1.49, -0.02) crosses Clinical Significance (0.5 awakenings)
7 Heterogeneity ($I^2 = 93\%$) greater than allowance (75%)
### Zaleplon - Summary of Findings Tables

**Table S6** – Summary of Findings table for zaleplon 5 mg for the treatment of chronic insomnia

References: Hedner 2000(A)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 5 mg Zaleplon vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⊕⊕⊕⊝ moderate¹</td>
<td>The mean quality of sleep in the zaleplon group was 0.10 points* lower (0.27 lower to 0.07 higher)</td>
<td>277 (1 study)²</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence
¹ Study funded by Industry
² 7-point scale (1=excellent, 7=extremely poor)

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**Table S7** – Summary of Findings table for zaleplon 10 mg for the treatment of chronic insomnia

References: Hedner 2000(A); Walsh 2000(B)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 10 mg Zaleplon vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (PSG)</td>
<td>⊕⊕⊕⊝ low³</td>
<td>The mean sleep latency in the zaleplon group was 9.50 minutes lower (18.80 to 0.19 lower)</td>
<td>94 (1 study)²</td>
</tr>
<tr>
<td>Sleep Latency (Subjective)</td>
<td>⊕⊕⊕⊝ low³</td>
<td>The mean sleep latency in the zaleplon group was 11.40 minutes lower (27.36 lower to 4.56 higher)</td>
<td>92 (1 study)²</td>
</tr>
<tr>
<td>Total Sleep Time* (Subjective)</td>
<td>⊕⊕⊕⊝ low⁴</td>
<td>The mean total sleep time in the zaleplon group was 21.50 minutes higher (5.60 lower to 48.6 higher)</td>
<td>93 (1 study)²</td>
</tr>
<tr>
<td>Wake After Sleep Onset* (PSG)</td>
<td>⊕⊕⊕⊝ moderate³</td>
<td>The mean wake after sleep onset in the zaleplon group was 2.10 minutes lower (10.23 lower to 6.03 higher)</td>
<td>92 (1 study)²</td>
</tr>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⊕⊕⊕⊝ moderate³</td>
<td>The mean quality of sleep in the zaleplon group was 0.10 points* lower (0.27 lower to 0.07 higher)</td>
<td>283 (1 study)²</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence
¹ Funding source not specified, author disclosures not specified.
² 95% CI (-11.47, 0.93) crosses Clinical Significance
³ 95% CI (-5.60, 48.60) crosses Clinical Significance
⁴ 7-point scale (1=excellent, 7=extremely poor)

---

### Zolpidem - Meta-Analyses and Summary of Findings Tables

**Table S8** – Summary of Findings table for zolpidem 6.25 mg for the treatment of chronic insomnia

References: Walsh 2008

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 6.25 mg Zolpidem vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (PSG)</td>
<td>⊕⊕⊕⊝ low³</td>
<td>The mean sleep latency in the zolpidem group was 5.27 minutes lower (11.47 lower to 0.93 higher)</td>
<td>199 (1 study)¹</td>
</tr>
<tr>
<td>Wake After Sleep Onset* (PSG)</td>
<td>⊕⊕⊕⊝ low³</td>
<td>The mean wake after sleep onset in the zolpidem group was 13.03 minutes lower (22.5 to 3.55 lower)</td>
<td>199 (1 study)¹</td>
</tr>
<tr>
<td>Sleep Efficiency (PSG)</td>
<td>⊕⊕⊕⊝ moderate³</td>
<td>The mean sleep efficiency in the zolpidem group was 1.60 percent higher (1.4 lower to 4.6 higher)</td>
<td>199 (1 study)¹</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence
¹ Funding source not specified, author disclosures not specified.
² 95% CI (-11.47, 0.93) crosses Clinical Significance
³ 95% CI (-22.5, -3.55) crosses Clinical Significance (20 min)
Figure S23 – Meta-analysis of data for PSG-determined sleep latency in response to zolpidem 10 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total Mean [min]</th>
<th>SD [min]</th>
<th>Total Weight</th>
<th>Mean Difference IV, Random, 95% CI [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermann, 1993</td>
<td>20</td>
<td>7</td>
<td>11</td>
<td>41.7</td>
<td>15</td>
<td>10.4% [16.38, -12.54]</td>
</tr>
<tr>
<td>Randel, 2012</td>
<td>14.2</td>
<td>2.2</td>
<td>44</td>
<td>29.72</td>
<td>18.9</td>
<td>20.5% [24.06, -7.07]</td>
</tr>
<tr>
<td>Schott, 1994</td>
<td>25.8</td>
<td>1.7</td>
<td>22</td>
<td>25.8</td>
<td>22</td>
<td>16.1% [14.8, 12.4]</td>
</tr>
<tr>
<td>Uchino, 2012</td>
<td>14.3</td>
<td>2.8</td>
<td>70</td>
<td>37.6</td>
<td>37.8</td>
<td>18.5% [33.48, -12.04]</td>
</tr>
<tr>
<td>Ware, 1997</td>
<td>17.2</td>
<td>3.4</td>
<td>34</td>
<td>42.2</td>
<td>5</td>
<td>39.9% [28.2, -5.6]</td>
</tr>
</tbody>
</table>

Total Mean [min] = 181

Heterogeneity: Tau² = 52.89; Chi² = 17.97, df = 4 (P = 0.001); I² = 78%
Test for overall effect: Z = 3.84 (P = 0.002)

Figure S24 – Meta-analysis of data for subjectively-determined sleep latency in response to zolpidem 10 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total Mean [min]</th>
<th>SD [min]</th>
<th>Total Weight</th>
<th>Mean Difference IV, Random, 95% CI [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsey, 2004</td>
<td>20</td>
<td>2.4</td>
<td>66</td>
<td>37</td>
<td>3.1</td>
<td>17.2% [3.96, 7.04]</td>
</tr>
<tr>
<td>Elie, 1999</td>
<td>30.8</td>
<td>7.8</td>
<td>64</td>
<td>54.4</td>
<td>39.3</td>
<td>63.3% [35.49, -11.74]</td>
</tr>
<tr>
<td>Erman, 2008</td>
<td>30.9</td>
<td>7.8</td>
<td>64</td>
<td>54.4</td>
<td>39.3</td>
<td>63.3% [35.49, -11.74]</td>
</tr>
<tr>
<td>Hermann, 1993</td>
<td>40.5</td>
<td>10.1</td>
<td>11</td>
<td>73.6</td>
<td>10</td>
<td>12.0% [48.96, -23.74]</td>
</tr>
<tr>
<td>Jacobs, 2004</td>
<td>45</td>
<td>3.2</td>
<td>14</td>
<td>66.6</td>
<td>17</td>
<td>14.4% [47.07, 0.27]</td>
</tr>
<tr>
<td>Parks, 2004</td>
<td>38.4</td>
<td>3.1</td>
<td>95</td>
<td>65.1</td>
<td>52.3</td>
<td>9.0% [39.05, -4.36]</td>
</tr>
<tr>
<td>Randel, 2012</td>
<td>27.33</td>
<td>3.1</td>
<td>44</td>
<td>38.6</td>
<td>35</td>
<td>8.1% [23.12, 14.1]</td>
</tr>
<tr>
<td>Schott, 1994</td>
<td>38.4</td>
<td>2.2</td>
<td>22</td>
<td>96.6</td>
<td>39.5</td>
<td>23.5% [36.78, 0.30]</td>
</tr>
<tr>
<td>Uchino, 2012</td>
<td>20.4</td>
<td>2.6</td>
<td>70</td>
<td>62</td>
<td>47</td>
<td>11.9% [34.6, -21.48]</td>
</tr>
<tr>
<td>Walsh, 1998</td>
<td>45.1</td>
<td>5.1</td>
<td>91</td>
<td>64.7</td>
<td>4.8</td>
<td>17.2% [17.72, -16.48]</td>
</tr>
</tbody>
</table>

Total Mean [min] = 543

Heterogeneity: Tau² = 43.12; Chi² = 174.88; df = 9 (P < 0.00001); I² = 95%
Test for overall effect: Z = 3.16 (P = 0.0007)

Figure S25 – Meta-analysis of data for PSG-determined total sleep time in response to zolpidem 10 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total Mean [min]</th>
<th>SD [min]</th>
<th>Total Weight</th>
<th>Mean Difference IV, Random, 95% CI [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermann, 1993</td>
<td>381.3</td>
<td>10</td>
<td>11</td>
<td>380.3</td>
<td>10</td>
<td>57.8% [55.7, 39.43]</td>
</tr>
<tr>
<td>Randel, 2012</td>
<td>411.2</td>
<td>3.7</td>
<td>44</td>
<td>371.36</td>
<td>42</td>
<td>42.4% [18.67, 60.81]</td>
</tr>
</tbody>
</table>

Total Mean [min] = 55

Heterogeneity: Tau² = 85.49; Chi² = 1.97; df = 1 (P = 0.16); I² = 49%
Test for overall effect: Z = 3.14 (P = 0.002)

Figure S26 – Meta-analysis of data for subjectively-determined total sleep time in response to zolpidem 10 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total Mean [min]</th>
<th>SD [min]</th>
<th>Total Weight</th>
<th>Mean Difference IV, Random, 95% CI [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elie, 1999</td>
<td>324.7</td>
<td>3.3</td>
<td>24</td>
<td>353</td>
<td>25</td>
<td>10.9% [26.38, 5.53]</td>
</tr>
<tr>
<td>Erman, 2008</td>
<td>430.7</td>
<td>4.6</td>
<td>64</td>
<td>382</td>
<td>63</td>
<td>0.9% [78.2, 17.76]</td>
</tr>
<tr>
<td>Hermann, 1993</td>
<td>372.7</td>
<td>12</td>
<td>11</td>
<td>327.4</td>
<td>10</td>
<td>19.4% [45.3, 90.6]</td>
</tr>
<tr>
<td>Jacobs, 2004</td>
<td>343.4</td>
<td>7.6</td>
<td>14</td>
<td>206.8</td>
<td>9.6</td>
<td>4.2% [46.3, 11.2]</td>
</tr>
<tr>
<td>Parks, 2004</td>
<td>417</td>
<td>6.4</td>
<td>95</td>
<td>359.8</td>
<td>77.1</td>
<td>17.0% [57.28, 77.28]</td>
</tr>
<tr>
<td>Randel, 2012</td>
<td>402.7</td>
<td>7.8</td>
<td>41</td>
<td>300</td>
<td>47</td>
<td>12.4% [12.00, 14.73]</td>
</tr>
<tr>
<td>Schott, 1994</td>
<td>369</td>
<td>6.5</td>
<td>22</td>
<td>396</td>
<td>23</td>
<td>9.9% [13.00, 50.71]</td>
</tr>
<tr>
<td>Walsh, 1998</td>
<td>378.6</td>
<td>5.3</td>
<td>91</td>
<td>344.6</td>
<td>5.3</td>
<td>24.4% [34.29, 35.72]</td>
</tr>
</tbody>
</table>

Total Mean [min] = 435

Heterogeneity: Tau² = 238.50; Chi² = 24.48; df = 7 (P < 0.00001); I² = 71%
Test for overall effect: Z = 3.85 (P = 0.0001)

Figure S27 – Meta-analysis of data for PSG-determined wake after sleep onset in response to zolpidem 10 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total Mean [min]</th>
<th>SD [min]</th>
<th>Total Weight</th>
<th>Mean Difference IV, Random, 95% CI [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermann, 1993</td>
<td>34.7</td>
<td>7</td>
<td>11</td>
<td>80</td>
<td>12</td>
<td>78.2% [-25.30, -16.79]</td>
</tr>
<tr>
<td>Randel, 2012</td>
<td>58.25</td>
<td>3.2</td>
<td>44</td>
<td>84.3</td>
<td>45.2</td>
<td>21.8% [-28.05, -9.91]</td>
</tr>
</tbody>
</table>

Total Mean [min] = 55

Heterogeneity: Tau² = 0.00; Chi² = 0.01; df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 6.63 (P < 0.00001)
**Figure S38** – Meta-analysis of data for the occurrence of taste perversion in response to zolpidem 10 mg

**Table S9** – Summary of Findings table for zolpidem 10 mg for the treatment of chronic insomnia

**References:** Dorsey 2004(A); Elie 1999(B); Erman 2008(C); Herrmann 1993(D); Jacobs 2004(E); Perlis 2004(F); Randal 2012(G); Scharf 1994(H); Staner 2005(I); Uchimura 2012(J); Walsh 1998(K); Ware 1997(L)

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### Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 10 mg Zolpidem vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep Latency</strong> (PSG)</td>
<td>⊙⊙⊙⊙ very low¹,²,³</td>
<td>The mean sleep latency in the zolpidem groups was 11.65 minutes lower (19.15 to 4.15 lower)</td>
<td>366 (5 studies)²,⁹,¹,²,³</td>
</tr>
<tr>
<td><strong>Sleep Latency</strong> (Subjective)</td>
<td>⊙⊙⊙⊙ very low¹,²,³</td>
<td>The mean sleep latency in the zolpidem groups was 19.55 minutes lower (24.90 to 14.20 lower)</td>
<td>1101 (10 studies)²,⁹,¹,²,³</td>
</tr>
<tr>
<td><strong>Total Sleep Time</strong> (PSG)</td>
<td>⊙⊙⊙ low¹,²,³</td>
<td>The mean total sleep time in the zolpidem groups was 28.91 minutes higher (10.85 to 46.97 higher)</td>
<td>112 (2 studies)²,³</td>
</tr>
<tr>
<td><strong>Total Sleep Time</strong> (Subjective)</td>
<td>⊙⊙⊙ low¹,²,³</td>
<td>The mean total sleep time in the zolpidem groups was 30.04 minutes higher (15.12 to 44.96 higher)</td>
<td>890 (8 studies)²,³</td>
</tr>
<tr>
<td><strong>Wake After Sleep Onset</strong> (PSG)</td>
<td>⊙⊙⊙ low¹,²,³</td>
<td>The mean wake after sleep onset in the zolpidem groups was 25.46 minutes lower (32.99 to 17.94 lower)</td>
<td>112 (2 studies)²,³</td>
</tr>
<tr>
<td><strong>Wake After Sleep Onset</strong> (Subjective)</td>
<td>⊙⊙⊙ low¹,²,³</td>
<td>The mean wake after sleep onset in the zolpidem groups was 13.57 minutes lower (19.84 to 7.30 lower)</td>
<td>784 (6 studies)²,³</td>
</tr>
<tr>
<td><strong>Quality of Sleep</strong> (Subjective)</td>
<td>⊙⊙⊙ very low¹,²,³</td>
<td>The mean quality of sleep in the zolpidem groups was 0.64 standard deviations higher (0.03 to 1.26 higher)</td>
<td>638 (6 studies)²,³</td>
</tr>
<tr>
<td><strong>Sleep Efficiency</strong> (PSG)</td>
<td>⊙⊙⊙ low¹,²,³</td>
<td>The mean sleep efficiency in the zolpidem groups was 6.12 percent higher (4.39 to 7.85 higher)</td>
<td>226 (4 studies)²,³</td>
</tr>
<tr>
<td><strong>Number of Awakenings</strong> (PSG)</td>
<td>⊙⊙⊙ moderate³</td>
<td>The mean number of awakenings in the zolpidem groups was 0.95 awakenings lower (1.41 to 0.49 lower)</td>
<td>113 (2 studies)²,³</td>
</tr>
<tr>
<td><strong>Number of Awakenings</strong> (Subjective)</td>
<td>⊙⊙⊙ low¹,²,³</td>
<td>The mean number of awakenings in the zolpidem groups was 0.31 awakenings lower (0.45 to 0.17 lower)</td>
<td>720 (6 studies)²,³</td>
</tr>
</tbody>
</table>

---

* Critical Outcome, used to determine Quality of Evidence
1 Heterogeneity (I² = 78%) greater than allowance (75%)
2 95% CI (-19.15, -4.15) crosses Clinical Significance (10 min)
3 Studies funded by industry
4 Heterogeneity (I² = 95%) greater than allowance (75%)
5 95% CI (-24.90, -14.20) crosses Clinical Significance (20 min)
6 Heterogeneity (I² = 92%) greater than allowance (75%)
7 95% CI (15.12, 44.96) crosses Clinical Significance (30 min)
8 Heterogeneity (I² = 87%) greater than allowance (75%)
9 95% CI (4.39, 7.85) crosses Clinical Significance (5%)
10 Heterogeneity (I² = 92%) greater than allowance (75%)
11 95% CI (0.3, 1.26) crosses Clinical Significance (SMD 0.5)
12 95% CI (10.85, 46.97) crosses Clinical Significance (20 min)
13 95% CI (-32.99, -17.4) crosses Clinical Significance (20 min)
Table S10 – Summary of Findings table for zolpidem 12.5 mg for the treatment of chronic insomnia

References: Roth 2006

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 12.5 Zolpidem vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (PSG)</td>
<td>⊕⊕⊕⊕⊕ low</td>
<td>The mean sleep latency in the zolpidem group was 8.19 minutes lower (15.22 to 1.15 lower)</td>
<td>212</td>
</tr>
<tr>
<td>Wake After Sleep Onset* (PSG)</td>
<td>⊕⊕⊕⊕⊕ low</td>
<td>The mean wake after sleep onset in the zolpidem group was 19.99 minutes lower (27.33 to 12.64 lower)</td>
<td>212</td>
</tr>
<tr>
<td>Sleep Efficiency (PSG)</td>
<td>⊕⊕⊕⊕⊕ moderate</td>
<td>The mean sleep efficiency in the zolpidem group was 3.9 percent higher (1.38 to 6.41 higher)</td>
<td>212</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence
1 Funding source not specified, author disclosures not specified.
2 95% CI (-15.22, 1.15) crosses Clinical Significance (10 min)
3 95% CI (-27.33, -12.64) crosses Clinical Significance (20 min)

Triazolam - Summary of Findings Table

Table S11 – Summary of Findings table for triazolam 0.25 mg for the treatment of chronic insomnia

References: Roehrs 2001

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 0.25 mg Triazolam vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (Subjective)</td>
<td>⊕⊕⊕⊕⊕ high</td>
<td>The mean sleep latency in the triazolam group was 9.20 minutes lower (22.3 lower to 3.9 higher)</td>
<td>64</td>
</tr>
<tr>
<td>Total Sleep Time (Subjective)</td>
<td>⊕⊕⊕⊝ moderate</td>
<td>The mean total sleep time in the triazolam group was 25.20 minutes higher (9.12 lower to 59.52 higher)</td>
<td>64</td>
</tr>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⊕⊕⊕⊕⊕ high</td>
<td>The mean quality of sleep in the triazolam group was 0.37 points lower (0.66 to 0.07 lower)</td>
<td>64</td>
</tr>
<tr>
<td>Number of Awakenings (Subjective)</td>
<td>⊕⊕⊕⊕ low</td>
<td>The mean number of awakenings in the triazolam group was 0.37 awakenings lower (1.7 lower to 0.96 higher)</td>
<td>64</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence
1 95% CI (-9.12, 59.52) crosses Clinical Significance (30 min)
2 95% CI (-1.7, 0.96) crosses Clinical Significance (0.5 awakenings)
3 4-point scale (1=good, 4=poor)

Temazepam - Meta-Analyses and Summary of Findings Tables

Figure S39 – Meta-analysis of data for subjectively-determined sleep latency in response to temazepam 15 mg

Figure S40 – Meta-analysis of data for subjectively-determined total sleep time in response to temazepam 15 mg
### Table S12 – Summary of Findings table for temazepam 15 mg for the treatment of chronic insomnia

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 15 mg Temazepam vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (PSG)</td>
<td>⊖⊕⊕⊕ high</td>
<td>The mean sleep latency in the temazepam group was 37.1 minutes lower (52.8 to 21.31 lower)</td>
<td>34 (1 study)C</td>
</tr>
<tr>
<td>Sleep Latency (Subjective)</td>
<td>⊖⊕⊕⊕ moderate</td>
<td>The mean sleep latency in the temazepam group was 20.06 minutes lower (39.05 to 1.07 lower)</td>
<td>72 (2 studies)A,C</td>
</tr>
<tr>
<td>Total Sleep Time* (PSG)</td>
<td>⊖⊕⊕⊕ high</td>
<td>The mean total sleep time in the temazepam group was 99.1 minutes higher (63.4 to 134.7 lower)</td>
<td>34 (1 study)C</td>
</tr>
<tr>
<td>Total Sleep Time (Subjective)</td>
<td>⊖⊕⊕⊕ moderate</td>
<td>The mean total sleep time in the temazepam groups was 64.41 minutes higher (8.07 to 120.76 higher)</td>
<td>72 (2 studies)A,C</td>
</tr>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⊖⊕⊕⊕ moderate</td>
<td>The mean quality of sleep in the temazepam group was 0.25 standard deviations higher (0.2 lower to 0.7 higher)</td>
<td>39 (2 studies)A,B</td>
</tr>
<tr>
<td>Sleep Efficiency (PSG)</td>
<td>⊖⊕⊕⊕ moderate</td>
<td>The mean sleep efficiency in the temazepam group was 13.3 percent higher (3.9 to 22.6 higher)</td>
<td>34 (1 study)C</td>
</tr>
<tr>
<td>Sleep Efficiency (Subjective)</td>
<td>⊖⊕⊕⊕ moderate</td>
<td>The mean sleep efficiency in the temazepam group was 14.1 percent higher (5.8 to 22.3 higher)</td>
<td>34 (1 study)C</td>
</tr>
<tr>
<td>Number of Awakenings (Subjective)</td>
<td>⊖⊕⊕⊕ moderate</td>
<td>The mean number of awakenings in the temazepam group was 0.5 awakenings lower (1.29 lower to 0.29 higher)</td>
<td>38 (1 study)A</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence
1. 95% CI (-0.2, 0.7) crosses Clinical Significance (0.5 SMD)
2. 95% CI (-39.05, -1.07) crosses Clinical Significance (20 min)
3. 95% CI (-21.31, 52.8) crosses Clinical Significance (30 min)
4. 95% CI (0.28, 1.66) crosses Clinical Significance (1.0 cm)
5. 95% CI (1.29, 0.29) crosses Clinical Significance (5%)
**Ramelteon - Meta-Analyses and Summary of Findings Table**

**Figure S42 – Meta-analysis of data for PSG-determined sleep latency in response to ramelteon 8 mg**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohnase, 2011</td>
<td>22.12</td>
<td>18.16</td>
<td>61</td>
<td>35.27</td>
<td>40.68</td>
<td>-13.15 [-24.23, -1.97]</td>
</tr>
<tr>
<td>Rohlf, 2007</td>
<td>30.8</td>
<td>25.51</td>
<td>61</td>
<td>47.07</td>
<td>41.27</td>
<td>-6.97 [-11.97, -1.97]</td>
</tr>
<tr>
<td>Zambreni, 2007</td>
<td>31.5</td>
<td>24.51</td>
<td>139</td>
<td>61.5</td>
<td>61.7</td>
<td>-10.67 [-16.77, -4.57]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>300</td>
<td></td>
<td>292</td>
<td>100</td>
<td>-9.57 [12.75, -6.38]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 6.55; Chi² = 21.31, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 5.39 (P < 0.00001)

**Figure S43 – Meta-analysis of data for subjectively-determined sleep latency in response to ramelteon 8 mg**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohnase, 2011</td>
<td>37.0</td>
<td>25.51</td>
<td>61</td>
<td>47.07</td>
<td>41.27</td>
<td>-9.27 [-14.35, -4.21]</td>
</tr>
<tr>
<td>Rohlf, 2007</td>
<td>59.9</td>
<td>3.95</td>
<td>100</td>
<td>59.2</td>
<td>5.8</td>
<td>-3.70 [8.55, -6.05]</td>
</tr>
<tr>
<td>Zambreni, 2007</td>
<td>44.8</td>
<td>3.95</td>
<td>139</td>
<td>61.5</td>
<td>3.7</td>
<td>-16.70 [-17.67, -6.83]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>300</td>
<td></td>
<td>292</td>
<td>100</td>
<td>-11.44 [14.50, -3.31]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 43.28; Chi² = 147.30, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 2.76 (P = 0.006)

**Figure S44 – Meta-analysis of data for PSG-determined total sleep time in response to ramelteon 8 mg**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohnase, 2011</td>
<td>498.2</td>
<td>48.23</td>
<td>61</td>
<td>394.7</td>
<td>52.35</td>
<td>12.65 [4.69, 29.61]</td>
</tr>
<tr>
<td>Mayer, 2003</td>
<td>345.39</td>
<td>3.83</td>
<td>159</td>
<td>360.11</td>
<td>3.255</td>
<td>17.93 [0.50, 3.89]</td>
</tr>
<tr>
<td>Rohlf, 2007</td>
<td>302.5</td>
<td>6.03</td>
<td>100</td>
<td>385.9</td>
<td>4.12</td>
<td>-11.55 [16.98, -4.68]</td>
</tr>
<tr>
<td>Zambreni, 2007</td>
<td>391.6</td>
<td>4.04</td>
<td>139</td>
<td>385.0</td>
<td>4.12</td>
<td>-6.59 [4.03, 6.67]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>459</td>
<td></td>
<td>458</td>
<td>100</td>
<td>6.58 [13.60, 11.80]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 22.55; Chi² = 133.95, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 2.47 (P = 0.01)

**Figure S45 – Meta-analysis of data for subjectively-determined total sleep time in response to ramelteon 8 mg**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohnase, 2011</td>
<td>377.05</td>
<td>70.92</td>
<td>61</td>
<td>371.88</td>
<td>61.06</td>
<td>5.33 [10.13, 20.61]</td>
</tr>
<tr>
<td>Mayer, 2003</td>
<td>345.39</td>
<td>4.33</td>
<td>159</td>
<td>349.43</td>
<td>4.345</td>
<td>-1.04 [5.03, 3.17]</td>
</tr>
<tr>
<td>Rohlf, 2007</td>
<td>337.6</td>
<td>6.82</td>
<td>100</td>
<td>353.3</td>
<td>6.68</td>
<td>3.04 [1.26, 4.84]</td>
</tr>
<tr>
<td>Zambreni, 2007</td>
<td>395.45</td>
<td>5.9</td>
<td>139</td>
<td>347.1</td>
<td>6.7</td>
<td>16.89 [15.95, 16.88]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>459</td>
<td></td>
<td>458</td>
<td>100</td>
<td>5.70 [7.65, 19.04]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 183.34; Chi² = 717.67, df = 3 (P < 0.00001); I² = 100%
Test for overall effect: Z = 0.84 (P = 0.40)

**Figure S46 – Meta-analysis of data for PSG-determined wake after sleep onset in response to ramelteon 8 mg**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohnase, 2011</td>
<td>49.76</td>
<td>39.11</td>
<td>61</td>
<td>46.42</td>
<td>33.48</td>
<td>3.38 [3.68, 10.28]</td>
</tr>
<tr>
<td>Zambreni, 2007</td>
<td>50.9</td>
<td>3.04</td>
<td>139</td>
<td>58.4</td>
<td>3.11</td>
<td>5.59 [2.77, 4.23]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>290</td>
<td></td>
<td>192</td>
<td>100</td>
<td>3.50 [2.77, 4.23]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.06; Chi² = 0.06, df = 1 (P = 0.895); I² = 0%
Test for overall effect: Z = 9.39 (P < 0.00001)

**Figure S47 – Meta-analysis of data for subjectively-determined wake after sleep onset in response to ramelteon 8 mg**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zambreni, 2007</td>
<td>71.3</td>
<td>4.7</td>
<td>139</td>
<td>71.2</td>
<td>4.3</td>
<td>-6.90 [2.63, 0.33]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>290</td>
<td></td>
<td>307</td>
<td>100</td>
<td>5.23 [3.87, 7.72]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 74.78; Chi² = 265.15, df = 1 (P < 0.00001); I² = 100%
Test for overall effect: Z = 9.05 (P = 0.03)
Figure S48 – Meta-analysis of data for PSG-determined quality of sleep in response to ramelteon 8 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayer, 2009</td>
<td>4.01</td>
<td>0.065</td>
<td>155</td>
<td>4.01</td>
<td>0.065</td>
<td>175</td>
<td>43.0%</td>
<td>0.00 [0.01, 0.01]</td>
<td></td>
</tr>
<tr>
<td>Roth, 2007</td>
<td>3.8</td>
<td>0.1</td>
<td>102</td>
<td>3.8</td>
<td>0.1</td>
<td>100</td>
<td>14.1%</td>
<td>0.00 [0.25, 0.20]</td>
<td></td>
</tr>
<tr>
<td>Zammit, 2007</td>
<td>3.6</td>
<td>0.06</td>
<td>139</td>
<td>3.6</td>
<td>0.06</td>
<td>131</td>
<td>42.9%</td>
<td>-0.10 [-0.11, -0.09]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 398 407 100.0% -0.04 [-0.13, 0.05]

Heterogeneity: Tau² = 0.00; Chi² = 66.43; df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.93 (P = 0.35)

Figure S49 – Meta-analysis of data for PSG-determined sleep efficiency in response to ramelteon 8 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohsaka, 2011</td>
<td>84.83</td>
<td>9.44</td>
<td>81</td>
<td>82.26</td>
<td>10.9</td>
<td>81</td>
<td>5.9%</td>
<td>2.57 [1.05, 0.19]</td>
<td></td>
</tr>
<tr>
<td>Roth, 2007</td>
<td>75.5</td>
<td>1.05</td>
<td>103</td>
<td>73.1</td>
<td>1.05</td>
<td>100</td>
<td>46.5%</td>
<td>2.40 [2.11, 2.69]</td>
<td></td>
</tr>
<tr>
<td>Zammit, 2007</td>
<td>81.8</td>
<td>0.84</td>
<td>139</td>
<td>80.4</td>
<td>0.86</td>
<td>131</td>
<td>47.6%</td>
<td>1.40 [1.20, 1.65]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 300 292 100.0% 1.93 [1.00, 2.87]

Heterogeneity: Tau² = 0.47; Chi² = 30.72; df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 4.06 (P < 0.0001)

Figure S50 – Meta-analysis of data for the occurrence of headache in response to ramelteon 8 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events Ramelteon 8 mg</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayer, 2009</td>
<td>18</td>
<td>226</td>
<td>18</td>
<td>223</td>
<td>33.8%</td>
<td>-0.00 [-0.05, 0.05]</td>
</tr>
<tr>
<td>Roth, 2007</td>
<td>3</td>
<td>100</td>
<td>1</td>
<td>100</td>
<td>59.5%</td>
<td>0.02 [0.02, 0.06]</td>
</tr>
<tr>
<td>Zammit, 2007</td>
<td>27</td>
<td>139</td>
<td>24</td>
<td>131</td>
<td>9.7%</td>
<td>0.01 [0.00, 0.10]</td>
</tr>
</tbody>
</table>

Total (95% CI): 467 454 100.0% 0.01 [0.02, 0.04]

Total events: 48 43
Heterogeneity: Tau² = 0.01; Chi² = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.79 (P = 0.43)

Figure S51 – Meta-analysis of data for the occurrence of upper respiratory tract infection in response to ramelteon 8 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events Ramelteon 8 mg</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayer, 2003</td>
<td>13</td>
<td>228</td>
<td>18</td>
<td>223</td>
<td>44.5%</td>
<td>-0.03 [-0.05, 0.05]</td>
</tr>
<tr>
<td>Zammit, 2007</td>
<td>6</td>
<td>138</td>
<td>4</td>
<td>134</td>
<td>55.5%</td>
<td>0.01 [-0.03, 0.05]</td>
</tr>
</tbody>
</table>

Total (95% CI): 307 354 100.0% 0.01 [-0.03, 0.04]

Total events: 24 22
Heterogeneity: Tau² = 0.00; Chi² = 0.20; df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.72)
Table S14 – Summary of Findings table for ramelteon 8 mg for the treatment of chronic insomnia

References: Kohsaka 2011 (A); Mayer 2009(B); Roth 2007(C); Zammit 2007(D)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 8 mg Ramelteon vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (PSG)</td>
<td>⊕⊕⊕⊕ very low1,2,3</td>
<td>The mean sleep latency in the ramelteon groups was 9.57 minutes lower (12.75 to 6.38 lower)</td>
<td>592 (3 studies) A,C,D</td>
</tr>
<tr>
<td>Sleep Latency (Subjective)</td>
<td>⊕⊕⊕ low7,8</td>
<td>The mean sleep latency in the ramelteon groups was 11.44 minutes lower (19.56 to 3.31 lower)</td>
<td>592 (3 studies) A,C,D</td>
</tr>
<tr>
<td>Total Sleep Time (PSG)</td>
<td>⊕⊕ low1,3</td>
<td>The mean total sleep time in the ramelteon groups was 6.58 minutes higher (1.36 to 11.80 higher)</td>
<td>927 (4 studies) A,B,C,D</td>
</tr>
<tr>
<td>Total Sleep Time (Subjective)</td>
<td>⊕⊕ low1,6</td>
<td>The mean total sleep time in the ramelteon groups was 5.70 minutes higher (7.65 lower to 19.04 higher)</td>
<td>927 (4 studies) A,B,C,D</td>
</tr>
<tr>
<td>Wake After Sleep Onset (PSG)</td>
<td>⊕⊕⊕ moderate8</td>
<td>The mean wake after sleep onset in the ramelteon groups was 3.50 minutes higher (2.77 to 4.23 higher)</td>
<td>392 (2 study) A,D</td>
</tr>
<tr>
<td>Wake After Sleep Onset (Subjective)</td>
<td>⊕⊕ low1,6</td>
<td>The mean wake after sleep onset in the ramelteon groups was 5.23 minutes higher (6.77 lower to 17.24 higher)</td>
<td>605 (2 studies) B,D</td>
</tr>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⊕⊕⊕ low3</td>
<td>The mean quality of sleep in the ramelteon groups was 0.04 points lower5 (0.13 lower to 0.05 higher)</td>
<td>805 (3 studies) B,C,D</td>
</tr>
<tr>
<td>Sleep Efficiency (PSG)</td>
<td>⊕⊕⊕ low4</td>
<td>The mean sleep efficiency in the ramelteon groups was 1.93 percent higher (1.00 to 2.87 higher)</td>
<td>592 (3 studies) A,C,D</td>
</tr>
<tr>
<td>Number of Awakenings (Subjective)</td>
<td>⊕⊕⊕ moderate8</td>
<td>The mean number of awakenings in the ramelteon group was 0.12 awakenings higher (0.08 to 0.15 higher)</td>
<td>335 (1 study) B</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence
1 Heterogeneity (I² = 98%) is greater than allowance (75%)
2 95% CI (-12.75, -6.38) crosses Clinical Significance (10 min)
3 All studies funded by industry
4 Heterogeneity (I² = 93%) greater than allowance (75%)
5 7-point Likert scale (1=excellent, 7=very poor)
6 Heterogeneity (I² =100%) greater than allowance (75%)
7 Heterogeneity (I² =99%) greater than allowance (75%)
8 95% CI (-21.45, 2.90) crosses Clinical Significance (20 min)

Doxepin - Meta-Analyses and Summary of Findings Tables

Figure S4952 – Meta-analysis of data for PSG-determined sleep latency in response to doxepin 3 mg

Figure S53 – Meta-analysis of data for subjectively-determined sleep latency in response to doxepin 3 mg
Figure S54 – Meta-analysis of data for PSG-determined total sleep time in response to doxepin 3 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI [min]</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krystal 2010</td>
<td>35.7</td>
<td>4.2</td>
<td>74</td>
<td>34.2</td>
<td>5.7</td>
<td>70</td>
<td>21.3%</td>
<td>38.00 [13.41, 62.59]</td>
<td>-2.09</td>
</tr>
<tr>
<td>Krystal 2011</td>
<td>40.8</td>
<td>5.3</td>
<td>66</td>
<td>39.4</td>
<td>4.9</td>
<td>67</td>
<td>19.0%</td>
<td>19.50 [-0.70, 39.70]</td>
<td>2.00</td>
</tr>
<tr>
<td>Roth 2007</td>
<td>41.5</td>
<td>3.5</td>
<td>66</td>
<td>39.6</td>
<td>4.6</td>
<td>68</td>
<td>20.1%</td>
<td>25.88 [11.37, 40.39]</td>
<td>2.92</td>
</tr>
<tr>
<td>Scheff 2008</td>
<td>39.0</td>
<td>4.1</td>
<td>74</td>
<td>38.0</td>
<td>4.9</td>
<td>73</td>
<td>31.0%</td>
<td>29.90 [16.16, 43.65]</td>
<td>-0.04</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>392.7</td>
<td>100.0%</td>
<td></td>
<td>382.6</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>28.14 [18.48, 37.79]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.06, Chi² = 1.89, df = 3 (P = 0.64), I² = 0%
Test for overall effect: Z = 0.69 (P < 0.00001)

Figure S55 – Meta-analysis of data for subjectively-determined total sleep time in response to doxepin 3 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI [min]</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krystal 2010</td>
<td>39.4</td>
<td>5.9</td>
<td>74</td>
<td>33.6</td>
<td>7.7</td>
<td>70</td>
<td>48.4%</td>
<td>34.25 [19.77, 58.73]</td>
<td>14.68</td>
</tr>
<tr>
<td>Krystal 2011</td>
<td>38.2</td>
<td>5.9</td>
<td>74</td>
<td>34.0</td>
<td>7.7</td>
<td>70</td>
<td>50.8%</td>
<td>24.20 [10.67, 37.73]</td>
<td>2.95</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>148.6</td>
<td>100.0%</td>
<td></td>
<td>142.4</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>43.57 [15.16, 81.98]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.31, Chi² = 6.09, df = 1 (P = 0.02), I² = 82%
Test for overall effect: Z = 2.22 (P = 0.03)

Figure S56 – Meta-analysis of data for PSG-determined wake after sleep onset in response to doxepin 3 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI [min]</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krystal 2010</td>
<td>75.7</td>
<td>37.6</td>
<td>74</td>
<td>103.2</td>
<td>50.8</td>
<td>70</td>
<td>20.8%</td>
<td>-28.58 [-48.16, -19.00]</td>
<td>-13.33</td>
</tr>
<tr>
<td>Krystal 2011</td>
<td>47.2</td>
<td>43.5</td>
<td>66</td>
<td>60.5</td>
<td>39.8</td>
<td>67</td>
<td>22.7%</td>
<td>-13.30 [-27.20, 0.60]</td>
<td>-13.30</td>
</tr>
<tr>
<td>Roth 2007</td>
<td>38.5</td>
<td>25.2</td>
<td>66</td>
<td>61.1</td>
<td>45.9</td>
<td>66</td>
<td>25.0%</td>
<td>-22.60 [-34.94, -0.46]</td>
<td>-22.60</td>
</tr>
<tr>
<td>Scheff 2008</td>
<td>64.8</td>
<td>31.6</td>
<td>74</td>
<td>83.8</td>
<td>38.3</td>
<td>73</td>
<td>30.5%</td>
<td>-21.60 [-32.54, -8.67]</td>
<td>-21.60</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>282.7</td>
<td>100.0%</td>
<td></td>
<td>276.4</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>-22.17 [-29.62, -14.72]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 13.34, Chi² = 3.90, df = 3 (P = 0.27), I² = 23%
Test for overall effect: Z = 5.03 (P < 0.00001)

Figure S57 – Meta-analysis of data for subjectively-determined quality of sleep in response to doxepin 3 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [Std]</th>
<th>SD [Std]</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI [Std]</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krystal 2010</td>
<td>0.3 [0.3]</td>
<td>1.1</td>
<td>74</td>
<td>70</td>
<td>0.73 [0.40, 1.07]</td>
<td>-0.07</td>
</tr>
<tr>
<td>Krystal 2011</td>
<td>0.9 [0.9]</td>
<td>0.9</td>
<td>74</td>
<td>70</td>
<td>0.41 [0.09, 0.74]</td>
<td>0.52</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>148.6</td>
<td>100.0%</td>
<td></td>
<td>142.4</td>
<td>0.57 [0.26, 0.88]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.02, Chi² = 1.78, df = 1 (P = 0.19), I² = 43%
Test for overall effect: Z = 3.53 (P < 0.0005)

Figure S58 – Meta-analysis of data for PSG-determined sleep efficiency in response to doxepin 3 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [%]</th>
<th>SD [%]</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI [%]</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krystal 2010</td>
<td>78.1</td>
<td>17.8</td>
<td>74</td>
<td>70</td>
<td>11.10 [3.84, 18.38]</td>
<td>-11.10</td>
</tr>
<tr>
<td>Roth 2007</td>
<td>80.5</td>
<td>7.1</td>
<td>66</td>
<td>66</td>
<td>4.30 [2.29, 6.31]</td>
<td>4.30</td>
</tr>
<tr>
<td>Scheff 2008</td>
<td>81.4</td>
<td>5.5</td>
<td>74</td>
<td>73</td>
<td>7.30 [4.44, 10.16]</td>
<td>7.30</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>214.5</td>
<td>100.0%</td>
<td></td>
<td>209.7</td>
<td>5.78 [4.50, 7.07]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.78, Chi² = 2.41, df = 2 (P = 0.30), I² = 17%
Test for overall effect: Z = 5.02 (P < 0.00001)

Figure S59 – Meta-analysis of data for PSG-determined number of awakenings in response to doxepin 3 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI [min]</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krystal 2010</td>
<td>12.9</td>
<td>5.6</td>
<td>74</td>
<td>73</td>
<td>1.99 [0.37, 3.62]</td>
<td>-1.99</td>
</tr>
<tr>
<td>Roth 2007</td>
<td>9.9</td>
<td>4.1</td>
<td>66</td>
<td>66</td>
<td>0.20 [1.18, 0.59]</td>
<td>0.20</td>
</tr>
<tr>
<td>Scheff 2008</td>
<td>12.5</td>
<td>5.3</td>
<td>74</td>
<td>73</td>
<td>0.68 [0.50, 1.12]</td>
<td>0.68</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>214.0</td>
<td>100.0%</td>
<td></td>
<td>209.7</td>
<td>0.53 [0.37, 0.71]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00, Chi² = 0.53, df = 2 (P = 0.76), I² = 0%
Test for overall effect: Z = 1.16 (P = 0.25)
Figure S60 – Meta-analysis of data for the occurrence of headache in response to doxepin 3 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Doxepin 3 mg</th>
<th>Placebo</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krystal 2010</td>
<td>4</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>Krystal 2011</td>
<td>3</td>
<td>68</td>
<td>7</td>
</tr>
<tr>
<td>Roth 2007</td>
<td>0</td>
<td>66</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>203</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>7</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.61; df = 2 (P = 0.74); I² = 0%  
Test for overall effect: Z = 2.68 (P = 0.001)

Figure S61 – Meta-analysis of data for the occurrence of somnolence in response to doxepin 3 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Doxepin 3 mg</th>
<th>Placebo</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krystal 2010</td>
<td>1</td>
<td>70</td>
<td>3</td>
</tr>
<tr>
<td>Krystal 2011</td>
<td>6</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>Roth 2007</td>
<td>1</td>
<td>66</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>204</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>8</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.03; Chi² = 2.55, df = 2 (P = 0.28); I² = 21%  
Test for overall effect: Z = 0.29 (P = 0.77)

Figure S62 – Meta-analysis of data for the occurrence of diarrhea in response to doxepin 3 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Doxepin 3 mg</th>
<th>Placebo</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krystal 2010</td>
<td>0</td>
<td>70</td>
<td>1</td>
</tr>
<tr>
<td>Krystal 2011</td>
<td>1</td>
<td>68</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>138</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.04, df = 1 (P = 0.31); I² = 4%  
Test for overall effect: Z = 0.02 (P = 0.99)

Figure S63 – Meta-analysis of data for the occurrence of upper respiratory tract infection in response to doxepin 3 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Doxepin 3 mg</th>
<th>Placebo</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krystal 2010</td>
<td>1</td>
<td>70</td>
<td>1</td>
</tr>
<tr>
<td>Krystal 2011</td>
<td>2</td>
<td>68</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>138</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%  
Test for overall effect: Z = 0.36 (P = 0.72)
Table S15 – Summary of Findings table for doxepin 3 mg for the treatment of chronic insomnia

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 3 mg Doxepin vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (PSG)</td>
<td>⊕⊕⊕ moderate¹</td>
<td>The mean sleep latency in the doxepin groups was 2.3 minutes lower (6.22 lower to 1.62 higher)</td>
<td>558 (4 studies)ABC,D</td>
</tr>
<tr>
<td>Sleep Latency (Subjective)</td>
<td>⊕⊕ low¹</td>
<td>The mean sleep latency in the doxepin groups was 9.35 minutes lower (21.89 lower to 3.19 higher)</td>
<td>291 (2 studies)AD</td>
</tr>
<tr>
<td>Total Sleep Time* (PSG)</td>
<td>⊕⊕ low¹</td>
<td>The mean total sleep time in the doxepin groups was 26.14 minutes higher (18.49 to 33.79 higher)</td>
<td>558 (4 studies)ABC,D</td>
</tr>
<tr>
<td>Total Sleep Time (Subjective)</td>
<td>⊕⊕ very low¹,7,8</td>
<td>The mean total sleep time in the doxepin groups was 43.57 minutes higher (5.16 to 81.98 higher)</td>
<td>291 (2 studies)AD</td>
</tr>
<tr>
<td>Wake After Sleep Onset* (PSG)</td>
<td>⊕⊕ low²</td>
<td>The mean wake after sleep onset in the doxepin groups was 22.17 minutes lower (29.62 to 14.72 lower)</td>
<td>558 (4 studies)ABC,D</td>
</tr>
<tr>
<td>Wake After Sleep Onset (Subjective)</td>
<td>⊕⊕ low¹</td>
<td>The mean wake after sleep onset in the doxepin groups was 20.0 minutes lower (39.07 to 0.92 lower)</td>
<td>147 (1 study)D</td>
</tr>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⊕⊕ low¹</td>
<td>The mean quality of sleep in the doxepin groups was 0.57 standard deviations higher (0.26 to 0.88 higher)</td>
<td>291 (2 studies)AD</td>
</tr>
<tr>
<td>Sleep Efficiency (PSG)</td>
<td>⊕⊕ low¹</td>
<td>The mean sleep efficiency in the doxepin groups was 6.78 percent higher (4.5 to 9.07 higher)</td>
<td>423 (3 studies)ACD</td>
</tr>
<tr>
<td>Number of Awakenings (PSG)</td>
<td>⊕⊕ moderate¹</td>
<td>The mean number of awakenings in the doxepin groups was 0.53 awakenings higher (0.37 lower to 1.42 higher)</td>
<td>423 (3 studies)ACD</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence
¹ All studies funded by Industry
² 95% CI (-29.62, -14.72) crosses Clinical Significance (20 min)
³ 95% CI (18.49, 33.79) crosses Clinical Significance (20 min)
⁴ 95% CI (4.50, 9.07) crosses Clinical Significance (5%)
⁵ 95% CI (0.26, 0.88) crosses Clinical Significance (SMD 0.5)
⁶ 95% CI (-21.89, 3.19) crosses Clinical Significance (20 min)
⁷ Heterogeneity (I² = 82%) greater than allowance (75%)
⁸ 95% CI (5.16, 81.98) crosses Clinical Significance (30 min)
⁹ 95% CI (-39.07, -0.92) crosses Clinical Significance (30 min)

Figure S64 – Meta-analysis of data for PSG-determined sleep latency in response to doxepin 6 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>8 mg Doxepin</th>
<th>Mean [min] SD</th>
<th>Total</th>
<th>Mean [min] SD</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krystal 2011</td>
<td>24.6</td>
<td>21.1</td>
<td>68</td>
<td>32</td>
<td>35.3</td>
<td>67</td>
<td>16.2%</td>
<td>-7.40 [-17.73, 2.93]</td>
</tr>
<tr>
<td>Roth 2007</td>
<td>27.3</td>
<td>19.44</td>
<td>67</td>
<td>33</td>
<td>22.02</td>
<td>68</td>
<td>31.3%</td>
<td>-5.70 [-12.76, 1.36]</td>
</tr>
<tr>
<td>Scharf 2008</td>
<td>22.4</td>
<td>14.84</td>
<td>74</td>
<td>28.8</td>
<td>19.28</td>
<td>73</td>
<td>52.9%</td>
<td>-4.40 [-9.86, 1.06]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>209</td>
<td>206</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>-5.29 [-9.25, -1.34]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.008; Chi² = 0.29, df = 2 (P = 0.88); I² = 0%
Test for overall effect: Z = 2.62 (P = 0.009)

Figure S65 – Meta-analysis of data for PSG-determined total sleep time in response to doxepin 6 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>8 mg Doxepin</th>
<th>Mean [min] SD</th>
<th>Total</th>
<th>Mean [min] SD</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krystal 2011</td>
<td>415.5</td>
<td>44.2</td>
<td>68</td>
<td>391.5</td>
<td>48.9</td>
<td>67</td>
<td>26.1%</td>
<td>28.88 [1.27, 53.3]</td>
</tr>
<tr>
<td>Roth 2007</td>
<td>418.4</td>
<td>32.63</td>
<td>67</td>
<td>306.6</td>
<td>40.86</td>
<td>66</td>
<td>32.6%</td>
<td>29.60 [1.47, 42.86]</td>
</tr>
<tr>
<td>Scharf 2008</td>
<td>388.4</td>
<td>32.28</td>
<td>74</td>
<td>360.7</td>
<td>43.98</td>
<td>73</td>
<td>41.4%</td>
<td>37.70 [25.21, 50.19]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>209</td>
<td>206</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>32.27 [24.24, 40.30]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.008; Chi² = 1.24, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 7.88 (P < 0.00001)
Figure S66 – Meta-analysis of data for subjectively-determined total sleep time in response to doxepin 6 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lankford 2012</td>
<td>334.1</td>
<td>66.4</td>
<td>130</td>
<td>335.4</td>
<td>64.7</td>
<td>124</td>
<td>56.7%</td>
<td>8.96 [6.42, 25.62]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scharf 2008</td>
<td>370.0</td>
<td>64.9</td>
<td>74</td>
<td>340</td>
<td>71.9</td>
<td>73</td>
<td>43.4%</td>
<td>38.00 [8.71, 62.00]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong> (95% CI)</td>
<td>264</td>
<td>197</td>
<td>100.0%</td>
<td>188.4 [1.65, 39.34]</td>
<td></td>
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</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Tau^2 = 125.28, Ch^2 = 2.29, df = 1 (P = 0.13), P = 0.56%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 1.88 (P = 0.062)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Figure S67 – Meta-analysis of data for PSG-determined wake after sleep onset in response to doxepin 6 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krystal 2011</td>
<td>40.7</td>
<td>37.3</td>
<td>68</td>
<td>38.8</td>
<td>38.8</td>
<td>67</td>
<td>23.2%</td>
<td>-19.06 [9.37, -7.64]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roth 2007</td>
<td>38.1</td>
<td>25.1</td>
<td>67</td>
<td>45.79</td>
<td>66</td>
<td>66</td>
<td>20.4%</td>
<td>-23.00 [16.50, -10.42]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scharf 2008</td>
<td>56.6</td>
<td>28.3</td>
<td>74</td>
<td>38.33</td>
<td>73</td>
<td>73</td>
<td>40.4%</td>
<td>-29.29 [71.21, -16.33]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong> (95% CI)</td>
<td>269</td>
<td>206</td>
<td>100.0%</td>
<td>-23.40 [-30.34, -16.46]</td>
<td></td>
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</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Tau^2 = 0.88, Ch^2 = 0.50, df = 2 (P = 0.75%), P = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 0.81 (P = 0.416)</td>
<td></td>
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</tr>
</tbody>
</table>

Figure S68 – Meta-analysis of data for subjectively-determined wake after sleep onset in response to doxepin 6 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Mean [min]</th>
<th>SD [min]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lankford 2012</td>
<td>88.5</td>
<td>43.9</td>
<td>130</td>
<td>78.9</td>
<td>68.6</td>
<td>124</td>
<td>70.3%</td>
<td>-12.48 [-24.88, 0.06]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scharf 2008</td>
<td>10.2</td>
<td>57.0</td>
<td>74</td>
<td>89.3</td>
<td>81.56</td>
<td>73</td>
<td>29.7%</td>
<td>-19.10 [-30.30, 0.10]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong> (95% CI)</td>
<td>197</td>
<td>100.0%</td>
<td>143.9 [-24.86, 3.93]</td>
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<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Tau^2 = 0.00, Ch^2 = 0.33, df = 1 (P = 0.57%), P = 0%</td>
<td></td>
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<td></td>
<td>Test for overall effect: Z = 1.70 (P = 0.092)</td>
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</table>

Figure S69 – Meta-analysis of data for subjectively-determined quality of sleep in response to doxepin 6 mg

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Lankford 2012</td>
<td>0.4</td>
<td>1</td>
<td>130</td>
<td>0.2</td>
<td>1</td>
<td>127</td>
<td>61.9%</td>
<td>0.19 [-0.09, 0.47]</td>
<td></td>
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</tr>
<tr>
<td>Scharf 2008</td>
<td>0.9</td>
<td>0.92</td>
<td>74</td>
<td>0.5</td>
<td>0.99</td>
<td>73</td>
<td>38.1%</td>
<td>0.42 [0.09, 0.74]</td>
<td></td>
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</tr>
<tr>
<td><strong>Total</strong> (95% CI)</td>
<td>204</td>
<td>100.0%</td>
<td>0.29 [0.06, 0.49]</td>
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<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Tau^2 = 0.00, Ch^2 = 1.18, df = 1 (P = 0.29%), P = 15%</td>
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<td></td>
<td>Test for overall effect: Z = 2.51 (P = 0.01)</td>
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</table>

Figure S70 – Meta-analysis of data for PSG-determined sleep efficiency in response to doxepin 6 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean [%]</th>
<th>SD [%]</th>
<th>Total</th>
<th>Mean [%]</th>
<th>SD [%]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth 2007</td>
<td>87.2</td>
<td>6.67</td>
<td>67</td>
<td>81.2</td>
<td>10.18</td>
<td>66</td>
<td>44.1%</td>
<td>6.00 [8.07, 8.93]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scharf 2008</td>
<td>63.3</td>
<td>6.73</td>
<td>74</td>
<td>75.1</td>
<td>9.16</td>
<td>73</td>
<td>55.3%</td>
<td>7.90 [8.30, 10.50]</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Total</strong> (95% CI)</td>
<td>141</td>
<td>100.0%</td>
<td>7.06 [5.12, 9.01]</td>
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<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Tau^2 = 0.00, Ch^2 = 0.80, df = 1 (P = 0.34%), P = 0%</td>
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<td></td>
<td>Test for overall effect: Z = 7.12 (P &lt; 0.00001)</td>
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</tbody>
</table>

Figure S71 – Meta-analysis of data for PSG-determined number of awakenings in response to doxepin 6 mg

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth 2007</td>
<td>9.1</td>
<td>4.1</td>
<td>67</td>
<td>3.86</td>
<td>66</td>
<td>66</td>
<td>54.6%</td>
<td>0.30 [-1.06, 1.65]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scharf 2008</td>
<td>12.6</td>
<td>4.76</td>
<td>74</td>
<td>11.4</td>
<td>4.45</td>
<td>73</td>
<td>45.2%</td>
<td>0.60 [-0.09, 2.09]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong> (95% CI)</td>
<td>141</td>
<td>100.0%</td>
<td>0.44 [-0.57, 1.44]</td>
<td></td>
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</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Tau^2 = 0.00, Ch^2 = 0.00, df = 1 (P = 0.77%), P = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>Test for overall effect: Z = 0.05 (P = 0.39)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Table S16 – Summary of Findings table for doxepin 6 mg for the treatment of chronic insomnia

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Absolute Difference 6 mg Doxepin vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (PSG)</td>
<td>⊕⊕⊕⊕ ⊖ moderate</td>
<td>The mean sleep latency in the doxepin groups was 5.29 minutes lower (9.25 to 1.34 lower)</td>
<td>415</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total events 19</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.86$; $df = 2$ $P = 0.40$, $I^2 = 0$%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Test for overall effect: $Z = 3.09$ ($P = 0.002$)</td>
<td></td>
</tr>
<tr>
<td>Total Sleep Time* (PSG)</td>
<td>⊕⊕⊕⊕ ⊖ moderate</td>
<td>The mean total sleep time in the doxepin groups was 32.27 minutes higher (24.24 to 40.3 higher)</td>
<td>415</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total events 19</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 7.33$; $df = 2$ $P = 0.09$, $I^2 = 0$%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Test for overall effect: $Z = 2.30$ ($P = 0.02$)</td>
<td></td>
</tr>
<tr>
<td>Total Sleep Time (Subjective)</td>
<td>⊕⊕⊕⊕ low</td>
<td>The mean total sleep time in the doxepin groups was 18.84 minutes higher (1.65 lower to 39.34 higher)</td>
<td>401</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total events 19</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.86$; $df = 2$ $P = 0.40$, $I^2 = 0$%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Test for overall effect: $Z = 3.09$ ($P = 0.002$)</td>
<td></td>
</tr>
<tr>
<td>Wake After Sleep Onset* (PSG)</td>
<td>⊕⊕⊕⊕ low</td>
<td>The mean wake after sleep onset in the doxepin groups was 23.4 minutes lower (30.34 to 16.46 lower)</td>
<td>415</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total events 19</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.86$; $df = 2$ $P = 0.40$, $I^2 = 0$%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Test for overall effect: $Z = 3.09$ ($P = 0.002$)</td>
<td></td>
</tr>
<tr>
<td>Wake After Sleep Onset (Subjective)</td>
<td>⊕⊕⊕⊕ moderate</td>
<td>The mean wake after sleep onset in the doxepin groups was 14.39 minutes lower (24.86 to 3.93 lower)</td>
<td>401</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total events 19</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.86$; $df = 2$ $P = 0.40$, $I^2 = 0$%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Test for overall effect: $Z = 3.09$ ($P = 0.002$)</td>
<td></td>
</tr>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⊕⊕⊕⊕ moderate</td>
<td>The mean quality of sleep in the doxepin groups was 0.28 standard deviations higher (0.06 to 0.49 higher)</td>
<td>404</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total events 19</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.86$; $df = 2$ $P = 0.40$, $I^2 = 0$%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Test for overall effect: $Z = 3.09$ ($P = 0.002$)</td>
<td></td>
</tr>
<tr>
<td>Sleep Efficiency (PSG)</td>
<td>⊕⊕⊕⊕ moderate</td>
<td>The mean sleep efficiency in the doxepin groups was 7.06 percent higher (5.12 to 9.01 higher)</td>
<td>280</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total events 19</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.86$; $df = 2$ $P = 0.40$, $I^2 = 0$%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Test for overall effect: $Z = 3.09$ ($P = 0.002$)</td>
<td></td>
</tr>
<tr>
<td>Number of Awakenings (PSG)</td>
<td>⊕⊕⊕⊕ moderate</td>
<td>The mean number of awakenings in the doxepin groups was 0.44 awakenings higher (0.57 lower to 1.44 higher)</td>
<td>280</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total events 19</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.86$; $df = 2$ $P = 0.40$, $I^2 = 0$%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Test for overall effect: $Z = 3.09$ ($P = 0.002$)</td>
<td></td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence
1 All studies funded by industry
2 95% CI (-30.34, -16.46) crosses Clinical Significance (20 min)
3 95% CI (-1.65, 39.34) crosses Clinical Significance (30 min)
### Trazadone - Summary of Findings Table

**Table S17 – Summary of Findings table for trazodone 50 mg for the treatment of chronic insomnia**

**References:** Walsh 1998(A)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 50 mg Trazodone vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (Subjective)</td>
<td>⊕⊕⊕⊕⊕ moderate ¹</td>
<td>The mean sleep latency in the trazadone group was 10.20 minutes lower (11.44 to 8.95 lower)</td>
<td>187 (1 study)²</td>
</tr>
<tr>
<td>Total Sleep Time* (Subjective)</td>
<td>⊕⊕⊕⊕⊕ moderate ¹</td>
<td>The mean total sleep time in the trazadone group was 21.80 minutes higher (20.10 to 23.49 higher)</td>
<td>187 (1 study)²</td>
</tr>
<tr>
<td>Wake After Sleep Onset* (Subjective)</td>
<td>⊕⊕⊕⊕⊕ moderate ¹</td>
<td>The mean wake after sleep onset in the trazadone group was 7.70 minutes lower (8.89 to 6.5 lower)</td>
<td>187 (1 study)²</td>
</tr>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⊕⊕⊕⊕⊕ moderate ¹</td>
<td>The mean quality of sleep in the trazadone group was 0.13 points² lower (0.14 to 0.11 lower)</td>
<td>187 (1 study)²</td>
</tr>
<tr>
<td>Number of Awakenings (Subjective)</td>
<td>⊕⊕⊕⊕⊕ moderate ¹</td>
<td>The mean number of awakenings in the trazadone group was 0.40 awakenings lower (0.42 to 0.37 lower)</td>
<td>187 (1 study)²</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence

1 Study funded by industry

2 4-point scale (1=Excellent, 4=Poor)

### Tiagabine - Meta-Analyses and Summary of Findings Tables

**Figure S74 – Meta-analysis of data for PSG-determined sleep latency in response to tiagabine 4 mg**

**Figure S75 – Meta-analysis of data for subjectively-determined sleep latency in response to tiagabine 4 mg**

**Figure S76 – Meta-analysis of data for PSG-determined total sleep time in response to tiagabine 4 mg**

**Figure S77 – Meta-analysis of data for subjectively-determined total sleep time in response to tiagabine 4 mg**
Figure S84 – Meta-analysis of data for the occurrence of headache in response to tiagabine 4 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Tiagabine 4 mg</th>
<th>Placebo</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth 2006</td>
<td>1</td>
<td>33</td>
<td>43.8%</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>1</td>
<td>0.03 [0.07, 0.07]</td>
</tr>
<tr>
<td>Walsh JCSM 2006</td>
<td>4</td>
<td>46</td>
<td>22.7%</td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>2</td>
<td>0.04 [0.06, 0.14]</td>
</tr>
<tr>
<td>Walsh SLEEP 2006</td>
<td>2</td>
<td>51</td>
<td>33.7%</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>3</td>
<td>-0.02 [-0.10, 0.08]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>135</td>
<td>138</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>0.00 [-0.04, 0.05]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00, Ch² = 0.93, df = 2 (P = 0.63); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.17 (P = 0.86)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure S85 – Meta-analysis of data for the occurrence of nausea in response to tiagabine 4 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Tiagabine 4 mg</th>
<th>Placebo</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth 2006</td>
<td>1</td>
<td>38</td>
<td>16.5%</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>0</td>
<td>0.03 [0.04, 0.10]</td>
</tr>
<tr>
<td>Walsh JCSM 2006</td>
<td>1</td>
<td>46</td>
<td>24.1%</td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>0</td>
<td>0.02 [0.04, 0.08]</td>
</tr>
<tr>
<td>Walsh SLEEP 2006</td>
<td>0</td>
<td>51</td>
<td>59.4%</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>0</td>
<td>0.00 [0.04, 0.04]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>135</td>
<td>138</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>0.01 [0.02, 0.04]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00, Ch² = 0.73, df = 2 (P = 0.68); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.66 (P = 0.51)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Quality of the evidence (GRADE)</td>
<td>Absolute Difference 4 mg Tiagabine vs Placebo</td>
<td>No of Participants (studies)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Sleep Latency (PSG)</td>
<td>⊕⊕⊕⊕ low1,2,3</td>
<td>The mean sleep latency in the tiagabine groups was 3.65 minutes higher (8 lower to 15.31 higher)</td>
<td>269 (3 studies) AB, C</td>
</tr>
<tr>
<td>Sleep Latency (Subjective)</td>
<td>⊕⊕⊕ moderate2</td>
<td>The mean sleep latency in the tiagabine groups was 13.31 minutes higher (7.54 to 19.07 higher)</td>
<td>139 (2 studies) A, C</td>
</tr>
<tr>
<td>Total Sleep Time* (PSG)</td>
<td>⊕⊕⊕ low3</td>
<td>The mean total sleep time in the tiagabine groups was 1.21 minutes lower (7.44 lower to 5.02 higher)</td>
<td>269 (3 studies) A, B, C</td>
</tr>
<tr>
<td>Total Sleep Time (Subjective)</td>
<td>⊕⊕⊕ moderate3</td>
<td>The mean total sleep time in the tiagabine groups was 19.95 minutes lower (25.35 to 14.54 lower)</td>
<td>169 (2 studies) A, C</td>
</tr>
<tr>
<td>Wake After Sleep Onset* (PSG)</td>
<td>⊕⊕⊕ low4</td>
<td>The mean wake after sleep onset in the tiagabine groups was 0.56 minutes lower (6.77 lower to 5.65 higher)</td>
<td>269 (3 studies) A, B, C</td>
</tr>
<tr>
<td>Wake After Sleep Onset (Subjective)</td>
<td>⊕⊕⊕ moderate5</td>
<td>The mean wake after sleep onset in the tiagabine groups was 4.29 minutes higher (0.22 lower to 8.79 higher)</td>
<td>169 (2 studies) A, C</td>
</tr>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⊕⊕⊕ very low6,7,8</td>
<td>The mean quality of sleep in the tiagabine groups was 0.48 standard deviations higher (0.5 lower to 1.46 higher)</td>
<td>169 (2 studies) A, C</td>
</tr>
<tr>
<td>Sleep Efficiency (PSG)</td>
<td>⊕⊕⊕ moderate5</td>
<td>The mean sleep efficiency in the tiagabine groups was 0.53 percent lower (1.05 to 0.02 lower)</td>
<td>269 (3 studies) A, B, C</td>
</tr>
<tr>
<td>Number of Awakenings (PSG)</td>
<td>⊕⊕⊕ low8</td>
<td>The mean number of awakenings in the tiagabine groups was 0.5 awakenings higher (1.29 lower to 2.29 higher)</td>
<td>193 (2 studies) B, C</td>
</tr>
<tr>
<td>Number of Awakenings (Subjective)</td>
<td>⊕⊕⊕ low9</td>
<td>The mean number of awakenings in the tiagabine groups was 0.21 awakenings lower (0.9 lower to 0.48 higher)</td>
<td>169 (2 studies) A, C</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence
1 Heterogeneity (I² = 99%) greater than allowance (75%)
2 95% CI (-8.0, 15.31) crosses Clinical Significance (10 min)
3 All studies funded by industry
4 Heterogeneity (I² = 89%) greater than allowance (75%)
5 Heterogeneity (I² = 85%) greater than allowance (75%)
6 95% CI (-1.29, 2.29) crosses Clinical Significance (2 awakenings)
7 Heterogeneity (I² = 90%) greater than allowance (75%)
8 95% CI (-0.90, 0.48) crosses zero standard mean difference
9 95% CI (-0.90, 0.48) crosses Clinical Significance (0.5 awakenings)
### Table S19 – Summary of Findings table for tiagabine 6 mg for the treatment of chronic insomnia

**References:** Roth 2006(A); Walsh 2006 JCSM(B)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 6 mg Tiagabine vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency (PSG)</td>
<td>⊕⊕⊕⊕ low</td>
<td>The mean sleep latency in the tiagabine groups was 6.9 minutes higher (2.22 to 11.58 higher)</td>
<td>175 (2 studies) A,B</td>
</tr>
<tr>
<td>Sleep Latency (Subjective)</td>
<td>⊕⊕⊕ moderate³</td>
<td>The mean sleep latency in the tiagabine groups was 5.68 minutes higher (3.05 to 8.3 higher)</td>
<td>175 (2 studies) A,B</td>
</tr>
<tr>
<td>Total Sleep Time* (PSG)</td>
<td>⊕⊕⊕⊕ moderate³</td>
<td>The mean total sleep time in the tiagabine groups was 7.17 minutes higher (0.26 lower to 14.59 higher)</td>
<td>175 (2 studies) A,B</td>
</tr>
<tr>
<td>Total Sleep Time (Subjective)</td>
<td>⊕⊕⊕ moderate³</td>
<td>The mean total sleep time in the tiagabine groups was 9.65 minutes lower (14.05 to 5.25 lower)</td>
<td>175 (2 studies) A,B</td>
</tr>
<tr>
<td>Wake After Sleep Onset* (PSG)</td>
<td>⊕⊕⊕ very low¹,²,³</td>
<td>The mean wake after sleep onset in the tiagabine groups was 9.24 minutes lower (24.78 lower to 6.3 higher)</td>
<td>175 (2 studies) A,B</td>
</tr>
<tr>
<td>Wake After Sleep Onset (Subjective)</td>
<td>⊕⊕⊕ moderate³</td>
<td>The mean wake after sleep onset in the tiagabine groups was 5.68 minutes higher (3.05 to 8.3 higher)</td>
<td>175 (2 studies) A,B</td>
</tr>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⊕⊕⊕ low</td>
<td>The mean quality of sleep in the tiagabine groups was 0.01 standard deviations higher (0.28 lower to 0.31 higher)</td>
<td>175 (2 studies) A,B</td>
</tr>
<tr>
<td>Sleep Efficiency (PSG)</td>
<td>⊕⊕⊕ moderate³</td>
<td>The mean sleep efficiency in the tiagabine groups was 1.46 percent higher (0.15 lower to 3.06 higher)</td>
<td>175 (2 studies) A,B</td>
</tr>
<tr>
<td>Number of Awakenings (Subjective)</td>
<td>⊕⊕⊕⊕ very low²,⁵,⁶</td>
<td>The mean number of awakenings in the tiagabine groups was 0.49 awakenings lower (1.84 lower to 0.87 higher)</td>
<td>175 (2 studies) A,B</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence
  1 Heterogeneity (I² = 81%) crosses threshold (75%)
  2 95% CI (-24.78, 6.30) crosses Clinical Significance (20 min)
  3 All studies funded by industry
  4 95% CI (-0.28, 0.31) crosses zero standard mean difference
  5 Heterogeneity (I² = 83%) crosses threshold (75%)
  6 95% CI (-1.84, 0.87) crosses Clinical Significance (0.5 awakenings)
  7 95% CI (2.22, 11.58) crosses Clinical Significance (10 min)
### Table S20 – Summary of Findings table for tiagabine 8 mg for the treatment of chronic insomnia

**References:** Roth 2006(A); Walsh 2006(B); Walsh 2006 JCSM(C)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 6 mg Tiagabine vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency (PSG)</td>
<td>⊕⊕⊕⊕ moderate</td>
<td>The mean sleep latency in the tiagabine groups was 1.22 minutes lower (2.66 lower to 0.22 higher)</td>
<td>271 (3 studies) A,B,C</td>
</tr>
<tr>
<td>Sleep Latency (Subjective)</td>
<td>⊕⊕⊕⊕ moderate</td>
<td>The mean sleep latency in the tiagabine groups was 2.12 minutes lower (3.48 to 0.76 lower)</td>
<td>171 (2 studies) A,C</td>
</tr>
<tr>
<td>Total Sleep Time* (PSG)</td>
<td>⊕⊕⊕ low</td>
<td>The mean total sleep time in the tiagabine groups was 3.49 minutes higher (6.43 lower to 13.42 higher)</td>
<td>271 (3 studies) A,B,C</td>
</tr>
<tr>
<td>Total Sleep Time (Subjective)</td>
<td>⊕⊕⊕ low</td>
<td>The mean total sleep time in the tiagabine groups was 16.09 minutes lower (44.97 lower to 12.79 higher)</td>
<td>171 (2 studies) A,C</td>
</tr>
<tr>
<td>Wake After Sleep Onset* (PSG)</td>
<td>⊕⊕⊕ low</td>
<td>The mean wake after sleep onset in the tiagabine groups was 2.42 minutes lower (10.35 lower to 5.51 higher)</td>
<td>271 (3 studies) A,B,C</td>
</tr>
<tr>
<td>Wake After Sleep Onset (Subjective)</td>
<td>⊕⊕⊕ moderate</td>
<td>The mean wake after sleep onset in the tiagabine groups was 9.71 minutes higher (5.7 to 13.72 higher)</td>
<td>171 (2 studies) A,C</td>
</tr>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⊕⊕⊕ very low</td>
<td>The mean quality of sleep in the tiagabine groups was 0.37 standard deviations higher (0.65 lower to 1.39 higher)</td>
<td>171 (2 studies) A,C</td>
</tr>
<tr>
<td>Sleep Efficiency (PSG)</td>
<td>⊕⊕⊕ low</td>
<td>The mean sleep efficiency in the tiagabine groups was 0.68 percent higher (1.41 lower to 2.76 higher)</td>
<td>271 (3 studies) A,B,C</td>
</tr>
<tr>
<td>Number of Awakenings (PSG)</td>
<td>⊕⊕⊕ low</td>
<td>The mean number of awakenings in the tiagabine groups was 0.88 awakenings lower (3.7 lower to 1.95 higher)</td>
<td>192 (2 studies) R,C</td>
</tr>
<tr>
<td>Number of Awakenings (Subjective)</td>
<td>⊕⊕⊕ low</td>
<td>The mean number of awakenings in the tiagabine groups was 0.3 awakenings higher (0.38 lower to 0.98 higher)</td>
<td>171 (2 studies) A,C</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence
1. All studies funded by industry
2. Heterogeneity (I² = 93%) greater than allowance (75%)
3. Heterogeneity (I² = 94%) greater than allowance (75%)
4. 95% CI (-3.70, 1.95) crosses Clinical Significance (2 awakenings)
5. Heterogeneity (I² = 91%) greater than allowance (75%)
6. 95% CI (-0.65, 1.39) crosses zero standard mean difference
7. Heterogeneity (I² = 89%) greater than allowance (75%)
8. 95% CI (-44.97, 12.79) crosses Clinical Significance
9. 95% CI (-0.38, 0.98) crosses Clinical Significance (0.5 awakenings)
Figure S86 – Meta-analysis of data for subjectively-determined sleep latency in response to diphenhydramine 50 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean (min)</th>
<th>SD (min)</th>
<th>Total</th>
<th>Mean (min)</th>
<th>SD (min)</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI (min)</th>
<th>IV, Random, 95% CI (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass 2008</td>
<td>32.4</td>
<td>22.7</td>
<td>19</td>
<td>36.9</td>
<td>24.9</td>
<td>19</td>
<td>14.2%</td>
<td>-4.60 (-10.52, 1.32)</td>
<td>0.29 (-3.31, 3.90)</td>
</tr>
<tr>
<td>Morin 2005</td>
<td>21.62</td>
<td>12.67</td>
<td>60</td>
<td>32.77</td>
<td>21.49</td>
<td>65</td>
<td>95.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>78</td>
<td></td>
<td>84</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td>-2.47 (-5.17, 3.32)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tukey's HSD, p = 0.69, Chisquare = 0.07, df = 1, p = 0.75, I² = 0%.
Test for overall effect Z = 1.62 (p = 0.11)

Figure S87 – Meta-analysis of data for subjectively-determined total sleep time in response to diphenhydramine 50 mg

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean (min)</th>
<th>SD (min)</th>
<th>Total</th>
<th>Mean (min)</th>
<th>SD (min)</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI (min)</th>
<th>IV, Random, 95% CI (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass 2008</td>
<td>396</td>
<td>78</td>
<td>19</td>
<td>378</td>
<td>79</td>
<td>19</td>
<td>100.0%</td>
<td>10.00 (-7.50, 37.50)</td>
<td>17.83 (-6.22, 41.90)</td>
</tr>
<tr>
<td>Morin 2005</td>
<td>410.58</td>
<td>60.62</td>
<td>56</td>
<td>461.76</td>
<td>72.32</td>
<td>65</td>
<td>91.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>77</td>
<td></td>
<td>84</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td>17.86 [3.79, 39.51]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tukey's HSD, p = 0.00, Chisquare = 0.00, df = 1, p = 1.00, I² = 0%
Test for overall effect Z = 1.62 (p = 0.11)

Table S21 – Summary of Findings table for diphenhydramine 50 mg for the treatment of chronic insomnia

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 50 mg Diphenhydramine vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (PSG)</td>
<td>⊕⊕⊕⊕ low^1,7</td>
<td>The mean sleep latency in the diphenhydramine group was 7.89 minutes lower (17.40 lower to 1.62 higher)</td>
<td>52 (1 study)^A</td>
</tr>
<tr>
<td>Sleep Latency (Subjective)</td>
<td>⊕⊕⊕⊕ low^1,2</td>
<td>The mean sleep latency in the diphenhydramine groups was 2.47 minutes lower (8.17 lower to 3.23 higher)</td>
<td>163 (2 studies)^AB</td>
</tr>
<tr>
<td>Total Sleep Time* (PSG)</td>
<td>⊕⊕⊕⊕ low^1,8</td>
<td>The mean total sleep time in the diphenhydramine group was 12.37 minutes higher (13.38 lower to 38.12 higher)</td>
<td>52 (1 study)^A</td>
</tr>
<tr>
<td>Total Sleep Time (Subjective)</td>
<td>⊕⊕⊕⊕ low^1,2</td>
<td>The mean total sleep time in the diphenhydramine groups was 17.86 minutes higher (3.79 lower to 39.51 higher)</td>
<td>161 (2 studies)^AB</td>
</tr>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⊕⊕⊕ moderate^5</td>
<td>The mean quality of sleep in the diphenhydramine group was 0.1 points^6 higher (0.45 lower to 0.65 higher)</td>
<td>38 (1 study)^A</td>
</tr>
<tr>
<td>Sleep Efficiency (PSG)</td>
<td>⊕⊕⊕⊕ low^1,5</td>
<td>The mean sleep efficiency in the diphenhydramine group was 2.59 percent higher (3.25 lower to 8.43 higher)</td>
<td>52 (1 study)^B</td>
</tr>
<tr>
<td>Sleep Efficiency (Subjective)</td>
<td>⊕⊕⊕ moderate^5</td>
<td>The mean sleep efficiency in the diphenhydramine group was 4.61 percent higher (1.33 to 7.88 higher)</td>
<td>123 (1 study)^A</td>
</tr>
<tr>
<td>Number of Awakenings (Subjective)</td>
<td>⊕⊕⊕ moderate^3</td>
<td>The mean number of awakenings in the diphenhydramine group was 0.3 awakenings lower (1.03 lower to 0.43 higher)</td>
<td>38 (1 study)^A</td>
</tr>
</tbody>
</table>

^1 Critical Outcome, used to determine Quality of Evidence
^2 1 of 2 studies funded by industry
^3 95% CI (-1.03, 0.43) crosses Clinical Significance (0.5 awakenings)
^4 95% CI (-3.25, 8.43) crosses Clinical Significance (5%)
^5 Study funded by industry
^6 95% CI (-0.45, 0.65) crosses zero standard mean difference
^7 95% CI (-17.4, 1.62) crosses Clinical Significance (10 minutes)
^8 95% CI (-13.38, 38.12) crosses Clinical Significance (20 minutes)
^9 5-point scale (higher score indicates better sleep quality)
Melatonin - Meta-Analyses and Summary of Findings Tables

Figure S88 – Meta-analysis of data for subjectively-determined quality of sleep in response to melatonin 2 mg

Table S22 – Summary of Findings table for melatonin 2 mg for the treatment of chronic insomnia

References: Lemoine 2007(A); Luthringer 2009(B); Wade 2007(C)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 2 mg Melatonin vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency* (PSG)</td>
<td>⬤⬤⬤⬤ low</td>
<td>The mean sleep latency in the melatonin group was 8.9 minutes lower (15.45 to 2.35 lower)</td>
<td>40 (1 study)</td>
</tr>
<tr>
<td>Total Sleep Time (PSG)</td>
<td>⬤⬤⬤⬤ very low</td>
<td>The mean total sleep time in the melatonin group was 2.2 minutes higher (19.13 lower to 23.53 higher)</td>
<td>40 (1 study)</td>
</tr>
<tr>
<td>Wake After Sleep Onset (PSG)</td>
<td>⬤⬤⬤ low</td>
<td>The mean wake after sleep onset in the melatonin group was 8.5 minutes higher (11.75 lower to 28.75 higher)</td>
<td>40 (1 study)</td>
</tr>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⬤⬤⬤⬤ very low</td>
<td>The mean quality of sleep in the melatonin group was 0.21 standard deviations higher (0.36 lower to 0.77 higher)</td>
<td>461 (3 studies)</td>
</tr>
<tr>
<td>Number of Awakenings (PSG)</td>
<td>⬤⬤⬤⬤ very low</td>
<td>The mean number of awakenings in the melatonin group was 1.4 awakenings higher (4.59 lower to 7.39 higher)</td>
<td>40 (1 study)</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence

1 Heterogeneity ($I^2 = 83\%$) greater than allowance (75%)
2 95% CI (-0.36, 0.77) crosses zero standard mean difference
3 All studies funded by industry
4 95% CI (-15.45, -2.35) crosses Clinical Significance (10 min)
5 95% CI (-11.75, 28.75) crosses Clinical Significance (20 min)
6 95% CI (-19.13, 23.53) crosses Clinical Significance (20 min)
7 95% CI (-4.59, 7.39) crosses Clinical Significance

L-tryptophan - Summary of Findings Table

Table S23 – Summary of Findings table for L-tryptophan 250 mg for the treatment of chronic insomnia

Reference: Hudson 2005

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference 250 mg Tryptophan vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wake After Sleep Onset* (Subjective)</td>
<td>⬤⬤ high</td>
<td>The mean wake after sleep onset in the Tryptophan groups was 9.70 minutes lower (15.21 to 4.18 lower)</td>
<td>31 (1 study)</td>
</tr>
<tr>
<td>Total Sleep Time (Subjective)</td>
<td>⬤⬤ moderate</td>
<td>The mean total sleep time in the Tryptophan groups was 20.00 minutes lower (31.29 to 8.7 lower)</td>
<td>32 (1 study)</td>
</tr>
<tr>
<td>Quality of Sleep* (Subjective)</td>
<td>⬤⬤ high</td>
<td>The mean quality of sleep in the Tryptophan groups was 0.30 points higher (0.22 to 0.37 higher)</td>
<td>32 (1 study)</td>
</tr>
<tr>
<td>Sleep Efficiency (Subjective)</td>
<td>⬤⬤ high</td>
<td>The mean sleep efficiency in the Tryptophan groups was 2.20 percent lower (4.27 to 0.12 lower)</td>
<td>32 (1 study)</td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence

1 95% CI (8.7, 31.29) crosses Clinical Significance (30 min)
2 3-point scale (Sleep Quality index: 1=low, 3=high)
## Valerian - Summary of Findings Table

**Table S24 – Summary of Findings table for valerian for the treatment of chronic insomnia**

**References:** Morin 2005(A)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Absolute Difference Valerian-hops vs Placebo</th>
<th>No of Participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep Latency</strong></td>
<td>low</td>
<td>The mean sleep latency in the Valerian-hops groups was 9.29 minutes lower (18.3 to 0.27 lower)</td>
<td>48 (1 study)³</td>
</tr>
<tr>
<td>(PSG)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sleep Latency</strong></td>
<td>moderate</td>
<td>The mean sleep latency in the Valerian-hops groups was 3.77 minutes higher (4.47 lower to 12.01 higher)</td>
<td>124 (1 study)³</td>
</tr>
<tr>
<td>(Subjective)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Sleep Time</strong></td>
<td>very low</td>
<td>The mean total sleep time in the Valerian-hops groups was 10.96 minutes higher (21.67 lower to 43.59 higher)</td>
<td>48 (1 study)³</td>
</tr>
<tr>
<td>(PSG)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Sleep Time</strong></td>
<td>moderate</td>
<td>The mean total sleep time in the Valerian-hops groups was 3.12 minutes higher (22.08 lower to 28.32 higher)</td>
<td>123 (1 study)³</td>
</tr>
<tr>
<td>(Subjective)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sleep Efficiency</strong></td>
<td>very low</td>
<td>The mean sleep efficiency in the Valerian-hops groups was 0.96 percent higher (5.02 lower to 6.94 higher)</td>
<td>48 (1 study)³</td>
</tr>
<tr>
<td>(PSG)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sleep Efficiency</strong></td>
<td>moderate</td>
<td>The mean sleep efficiency in the Valerian-hops groups was 1.85 percent higher (1.9 lower to 5.6 higher)</td>
<td>123 (1 study)³</td>
</tr>
<tr>
<td>(Subjective)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Critical Outcome, used to determine Quality of Evidence

¹ 95% CI (-18.3, -0.27) crosses Clinical Significance (10 min)
² Study funded by industry
³ 95% CI (-21.67, 43.59) crosses Clinical Significance (20 min)
⁴ 95% CI (-5.02, 6.94) crosses Clinical Significance (5%)