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

References: Herring 2012(A)

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 10 mg Suvorexant vs Placebo	No of Participants (studies)
Sleep Latency* (PSG)	⊕⊕⊖⊖ **low**[1,2]	The mean sleep latency in the suvorexant group was **2.3 minutes lower** (13.68 lower to 9.08 higher)	175 (1 study)[A]
Wake After Sleep Onset* (PSG)	⊕⊕⊖⊖ **low**[2,3]	The mean wake after sleep onset in the suvorexant group was **21.5 minutes lower** (36.34 to 6.66 lower)	175 (1 study)[A]
Sleep Efficiency (PSG)	⊕⊕⊖⊖ **low**[2,4]	The mean sleep efficiency in the suvorexant group was **4.7 percent higher** (0.97 to 8.43 higher)	175 (1 study)[A]

* 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

References: Herring 2016(A)

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 15/20 mg Suvorexant vs Placebo	No of Participants (studies)
Sleep Latency* (PSG)	⊕⊕⊖⊖ **low**[1,2]	The mean sleep latency in the suvorexant group was **8.1 minutes lower** (13.85 to 2.35 lower)	423 (1 study)[A]
Sleep Latency (Subjective)	⊕⊕⊕⊖ **moderate**[2]	The mean sleep latency in the suvorexant group was **5.2 minutes lower** (10.1 to 0.3 lower)	567 (1 study)[A]
Total Sleep Time* (Subjective)	⊕⊕⊕⊖ **moderate**[2]	The mean total sleep time in the suvorexant group was **10.6 minutes higher** (1.79 to 19.41 higher)	567 (1 study)[A]
Wake After Sleep Onset* (PSG)	⊕⊕⊖⊖ **low**[2,3]	The mean wake after sleep onset in the suvorexant group was **16.60 minutes lower** (24.87 to 8.33 lower)	567 (1 study)[A]

* Critical Outcome, used to determine Quality of Evidence
[1] 95% CI (-13.85 to -2.35) crosses Clinical Significance Threshold (10 min)
[2] Study funded by industry
[3] 95% CI (-24.87 to -8.33) crosses Clinical Significance Threshold (20 min)

Table S3 – Summary of Findings table for suvorexant 20 mg for the treatment of chronic insomnia

References: Herring 2012(A)

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 20 mg Suvorexant vs Placebo	No of Participants (studies)
Sleep Latency* (PSG)	⊕⊕⊕⊖ **moderate**[2]	The mean sleep latency in the suvorexant group was **22.3 minutes lower** (33.77 to 10.83 lower)	173 (1 study)[A]
Wake After Sleep Onset* (PSG)	⊕⊕⊖⊖ **low**[1,2]	The mean wake after sleep onset in the suvorexant group was **28.1 minutes lower** (43.07 to 13.13 lower)	173 (1 study)[A]
Sleep Efficiency (PSG)	⊕⊕⊕⊖ **moderate**[2]	The mean sleep efficiency in the suvorexant group was **10.4 percent higher** (6.65 to 14.15 higher)	173 (1 study)[A]

* Critical Outcome, used to determine Quality of Evidence
[1] 95% CI (-43.07 to -13.13) crosses Clinical Significance Threshold (20 min)
[2] 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

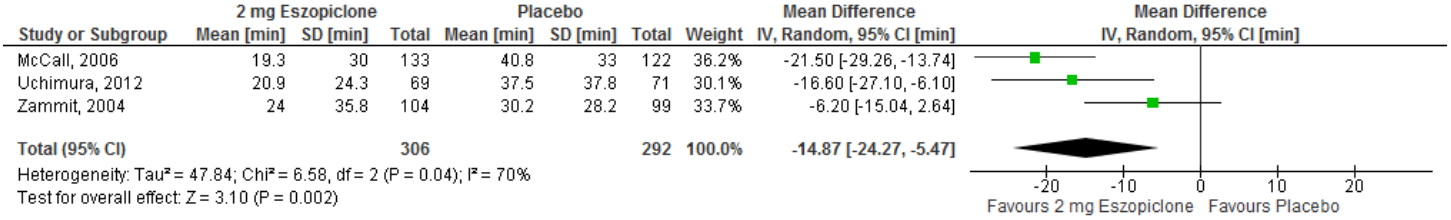

Figure S2 – Meta-analysis of data for subjectively-determined sleep latency in response to eszopiclone 2 mg

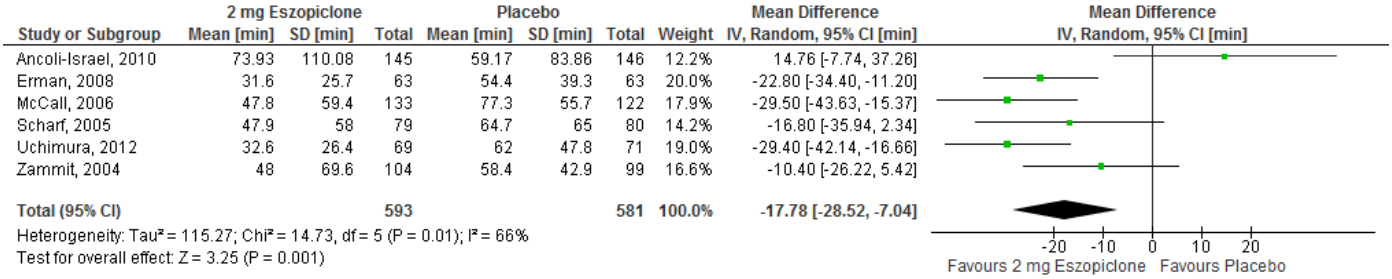

Figure S3 – Meta-analysis of data for subjectively-determined total sleep time in response to eszopiclone 2 mg

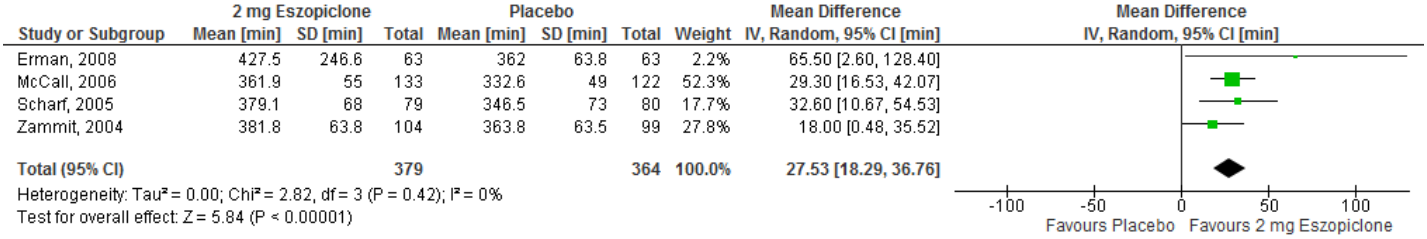

Figure S4 – Meta-analysis of data for PSG-determined wake after sleep onset in response to eszopiclone 2 mg

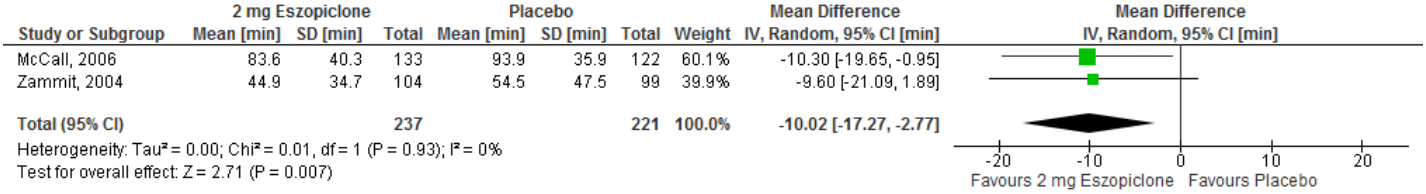

Figure S5 – Meta-analysis of data for subjectively-determined wake after sleep onset in response to eszopiclone 2 mg

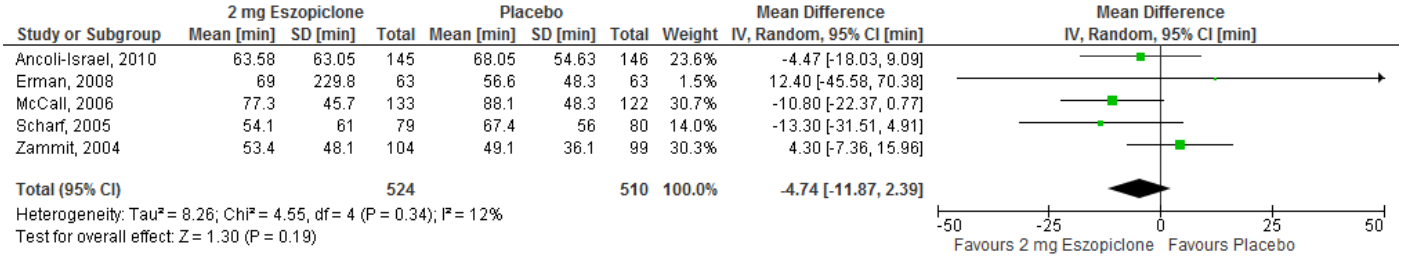

Figure S6 – Meta-analysis of data for subjectively-determined quality of sleep in response to eszopiclone 2 mg

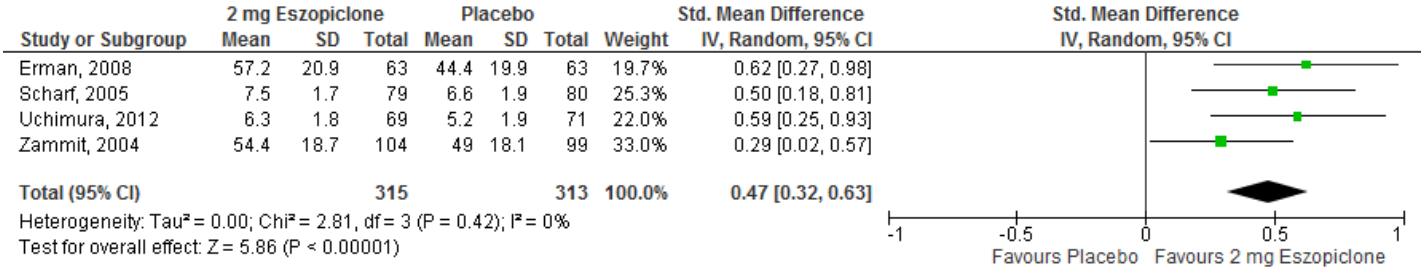

Figure S7 – Meta-analysis of data for PSG-determined sleep efficiency in response to eszopiclone 2 mg

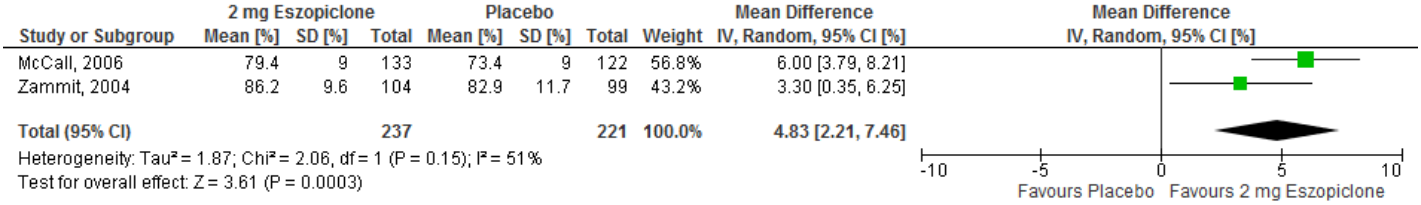

Figure S8 – Meta-analysis of data for PSG-determined number of awakenings in response to eszopiclone 2 mg

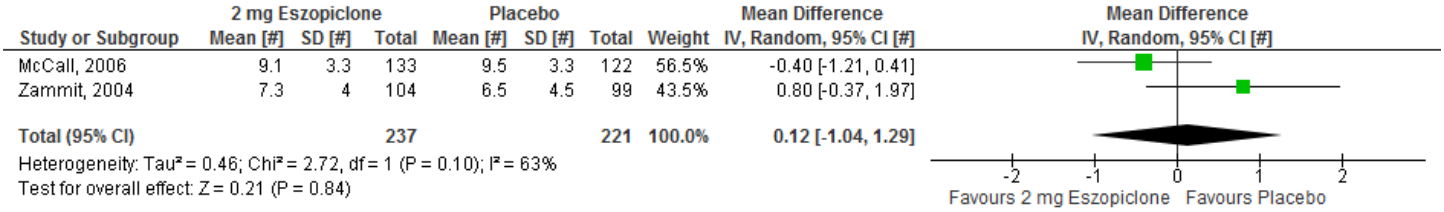

Figure S9 – Meta-analysis of data for subjectively-determined number of awakenings in response to eszopiclone 2 mg

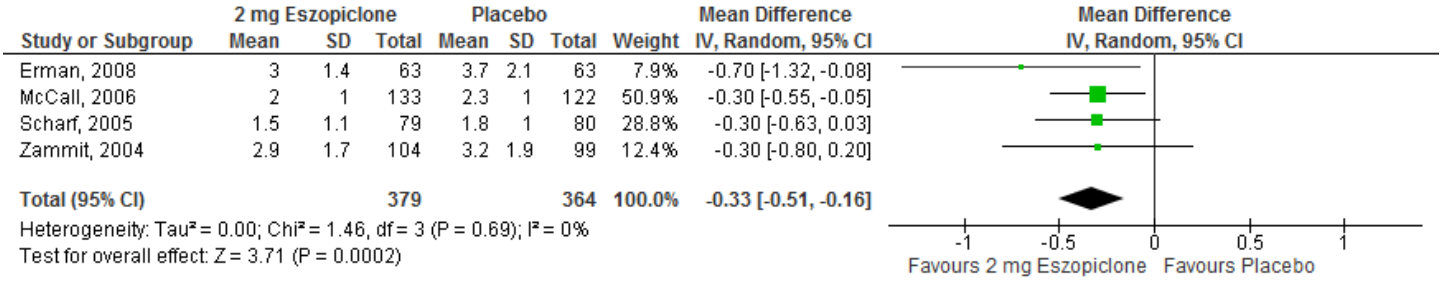

Figure S10– Meta-analysis of data for the occurrence of dizziness in response to eszopiclone 2 mg

Study or Subgroup	Eszopiclone 2 mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Erman 2008	0	63	3	63	21.5%	-0.05 [-0.11, 0.01]
McCall 2006	12	133	2	122	23.2%	0.07 [0.02, 0.13]
Uchimura 2012	3	104	4	99	24.2%	-0.01 [-0.06, 0.04]
Zammit 1971	0	69	0	71	31.1%	0.00 [-0.03, 0.03]
Total (95% CI)		**369**		**355**	**100.0%**	**0.00 [-0.04, 0.05]**
Total events	15		9			

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

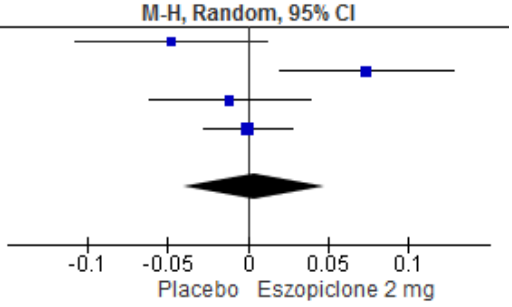

Figure S11– Meta-analysis of data for the occurrence of dry mouth in response to eszopiclone 2 mg

Study or Subgroup	Eszopiclone 2 mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
McCall 2006	16	133	2	122	47.7%	0.10 [0.04, 0.16]
Zammit 1971	5	104	2	99	52.3%	0.03 [-0.02, 0.08]
Total (95% CI)		**237**		**221**	**100.0%**	**0.06 [-0.01, 0.14]**
Total events	21		4			

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

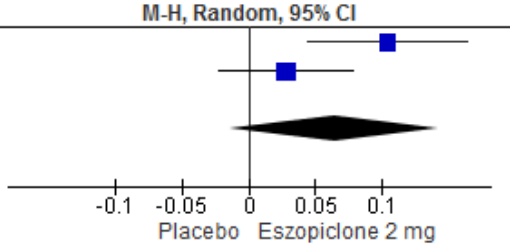

Figure S12– Meta-analysis of data for the occurrence of headache in response to eszopiclone 2 mg

Study or Subgroup	Eszopiclone 2 mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Ancoli-Israel 2010	20	145	18	146	33.4%	0.01 [-0.06, 0.09]
Erman 2008	4	63	6	63	22.6%	-0.03 [-0.13, 0.06]
Scharf 2005	12	79	12	80	16.2%	0.00 [-0.11, 0.11]
Zammit 1971	14	104	8	99	27.9%	0.05 [-0.03, 0.14]
Total (95% CI)		**391**		**388**	**100.0%**	**0.01 [-0.03, 0.06]**
Total events	50		44			

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

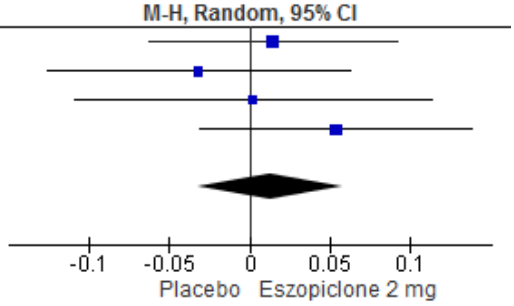

Figure S13– Meta-analysis of data for the occurrence of somnolence in response to eszopiclone 2 mg

Study or Subgroup	Eszopiclone 2 mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Erman 2008	2	63	2	63	19.6%	0.00 [-0.06, 0.06]
McCall 2006	12	133	9	122	16.2%	0.02 [-0.05, 0.08]
Scharf 2005	3	79	7	80	13.1%	-0.05 [-0.12, 0.03]
Uchimura 2012	8	104	3	99	19.5%	0.05 [-0.01, 0.11]
Zammit 1971	2	69	1	71	31.6%	0.01 [-0.03, 0.06]
Total (95% CI)		**448**		**435**	**100.0%**	**0.01 [-0.02, 0.04]**
Total events	27		22			

Heterogeneity: Tau² = 0.00; Chi² = 3.98, df = 4 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)

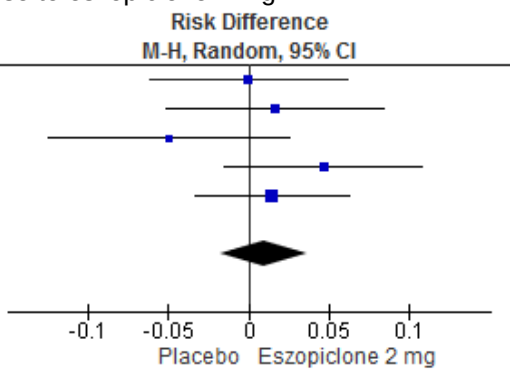

Figure S14– Meta-analysis of data for the occurrence of unpleasant taste in response to eszopiclone 2 mg

Study or Subgroup	Eszopiclone 2 mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Ancoli-Israel 2010	18	145	2	146	21.2%	0.11 [0.05, 0.17]
Erman 2008	3	63	1	63	20.6%	0.03 [-0.03, 0.09]
McCall 2006	16	133	0	122	21.2%	0.12 [0.06, 0.18]
Scharf 2005	3	79	7	80	18.9%	-0.05 [-0.12, 0.03]
Zammit 1971	18	104	3	99	18.2%	0.14 [0.06, 0.22]
Total (95% CI)		**524**		**510**	**100.0%**	**0.07 [0.01, 0.14]**
Total events	58		13			

Heterogeneity: Tau² = 0.00; Chi² = 19.57, df = 4 (P = 0.0006); I² = 80%
Test for overall effect: Z = 2.20 (P = 0.03)

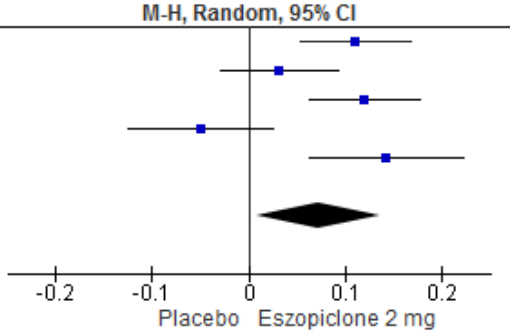

Table S4 – Summary of Findings table for eszopiclone 2 mg for the treatment of chronic insomnia

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

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

* Critical Outcome, used to determine Quality of Evidence
[1] 95% CI (-24.27, -5.47) crosses Clinical Signficance (10 min)
[2] All studies funded by industry
[3] 95% CI (-33.81, -6.35) crosses Clinical Signficance (20 min)
[4] 95% CI (18.29, 36.76) crosses Clinical Signficance (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)

Figure S15 – Meta-analysis of data for PSG-determined sleep latency in response to eszopiclone 3 mg

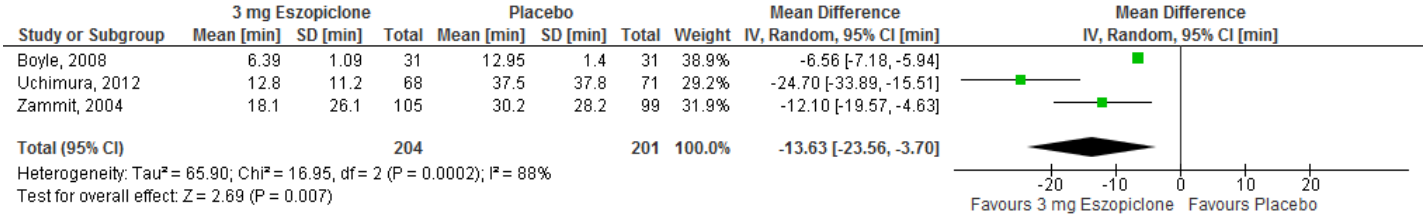

Figure S16 – Meta-analysis of data for subjectively-determined sleep latency in response to eszopiclone 3 mg

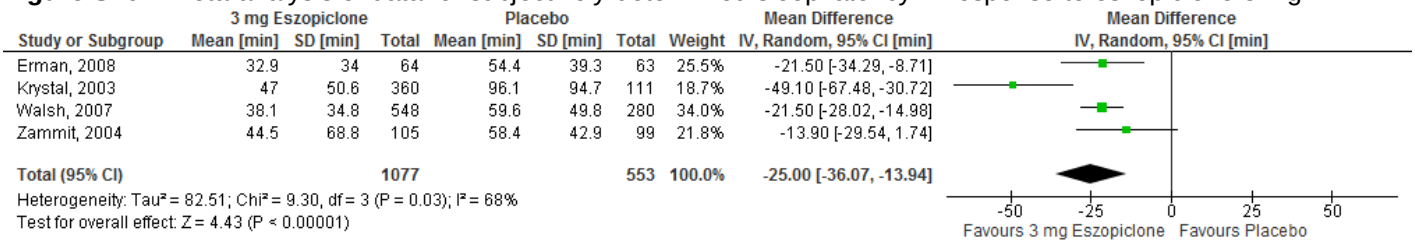

Figure S17 – Meta-analysis of data for subjectively-determined total sleep time in response to eszopiclone 3 mg

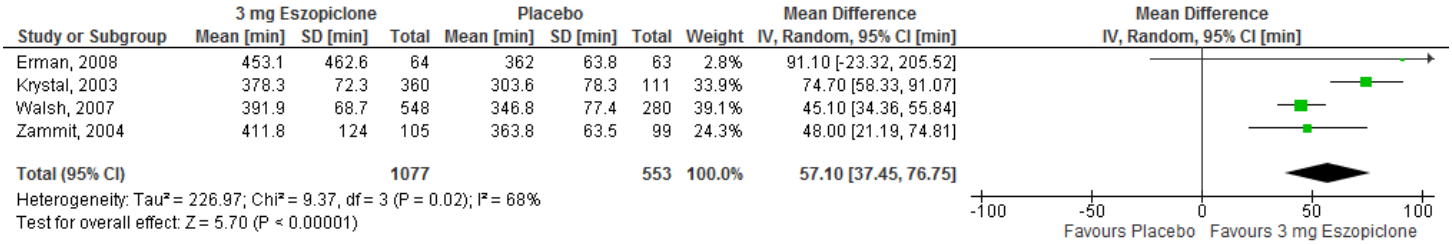

Figure S18 – Meta-analysis of data for PSG-determined wake after sleep onset in response to eszopiclone 3 mg

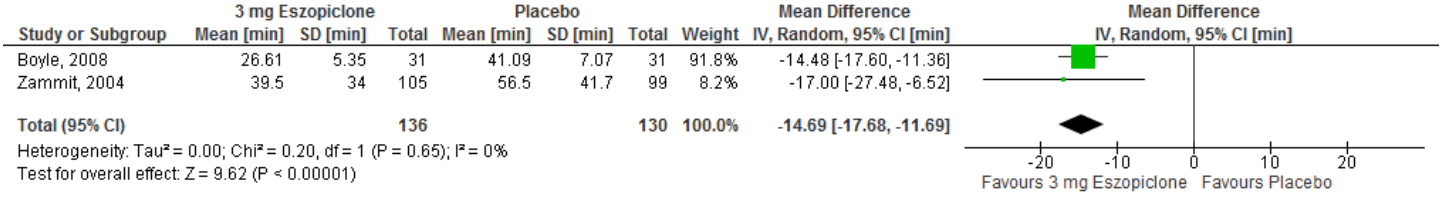

Figure S19 – Meta-analysis of data for subjectively-determined wake after sleep onset in response to eszopiclone 3 mg

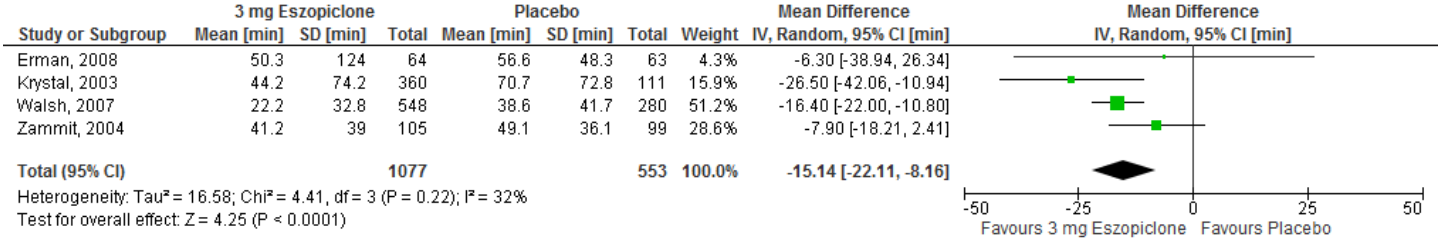

Figure S20 – Meta-analysis of data for subjectively-determined quality of sleep in response to eszopiclone 3 mg

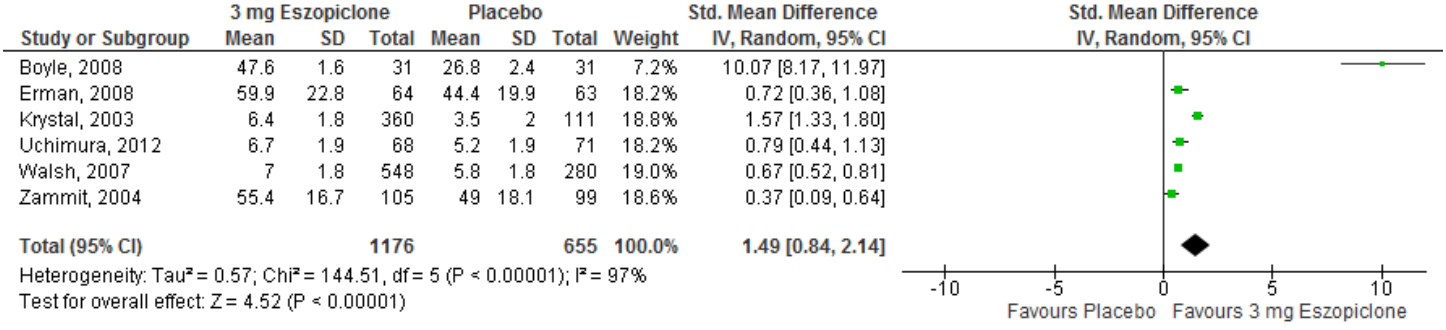

Figure S21 – Meta-analysis of data for PSG-determined sleep efficiency in response to eszopiclone 3 mg

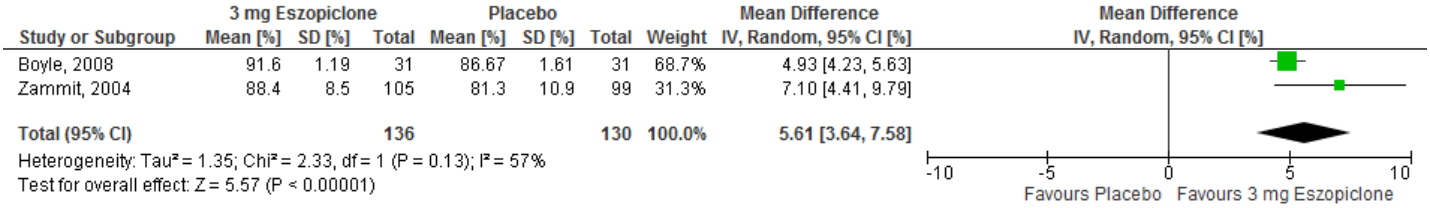

Figure S22 – Meta-analysis of data for subjectively-determined number of awakenings in response to eszopiclone 3 mg

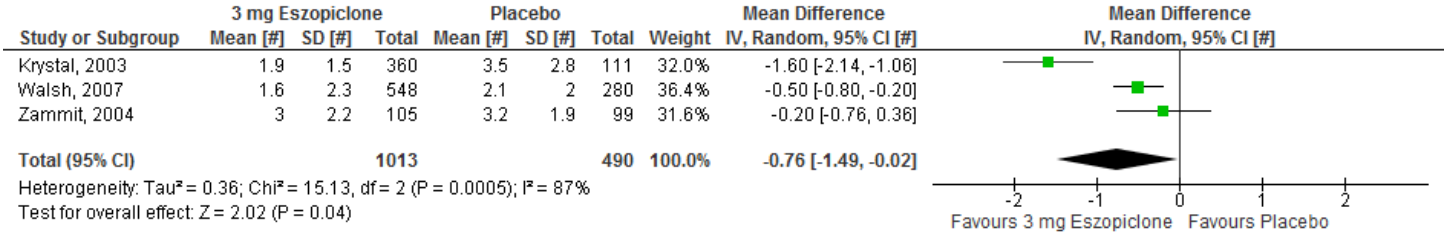

Table S5 – Summary of Findings table for eszopiclone 3 mg for the treatment of chronic insomnia

References: Boyle 2008(A); Erman 2008(B); Krystal 2003(C); Uchimura 2012(D); Walsh 2007(E); Zammit 2004(F)

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 3 mg Eszopiclone vs Placebo	No of Participants (studies)
Sleep Latency* (PSG)	⊕⊖⊖⊖ **very low**[1,2,3]	The mean sleep latency in the eszopiclone groups was **13.63 minutes lower** (23.56 to 3.7 lower)	405 (3 studies)[A,D,F]
Sleep Latency (Subjective)	⊕⊕⊖⊖ **low**[3,4]	The mean sleep latency in the eszopiclone groups was **25.00 minutes lower** (36.07 to 13.94 lower)	1630 (4 studies)[B,C,E,F]
Total Sleep Time* (Subjective)	⊕⊕⊕⊖ **moderate**[3]	The mean total sleep time in the eszopiclone groups was **57.10 minutes higher** (37.45 to 76.75 higher)	1630 (4 studies)[B,C,E,F]
Wake After Sleep Onset* (PSG)	⊕⊕⊕⊖ **moderate**[3]	The mean wake after sleep onset in the eszopiclone groups was **14.69 minutes lower** (17.68 to 11.69 lower)	266 (2 studies)[A,F]
Wake After Sleep Onset (Subjective)	⊕⊕⊖⊖ **low**[3,5]	The mean wake after sleep onset in the eszopiclone groups was **15.14 minutes lower** (22.11 to 8.16 lower)	1630 (4 studies)[B,C,E,F]
Quality of Sleep* (Subjective)	⊕⊕⊖⊖ **low**[3,9]	The mean quality of sleep in the eszopiclone groups was **1.49 standard deviations higher** (0.84 to 2.14 higher)	1769 (6 studies)[A,B,C,D,E,F]
Sleep Efficiency (PSG)	⊕⊕⊖⊖ **low**[3,6]	The mean sleep efficiency in the eszopiclone groups was **5.61 percent higher** (3.64 to 7.58 higher)	266 (2 studies)[A,F]
Number of Awakenings (Subjective)	⊕⊖⊖⊖ **very low**[3,6,7]	The mean number awakenings in the eszopiclone groups was **0.76 awakenings lower** (1.49 to 0.02 lower)	1503 (3 studies)[C,E,F]

* 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] 95% CI (-22.11, -8.16) crossess Clinical Significance (20 min)
[6] Heterogeneity (I^2 = 87%) greater than allowance (75%)
[7] 95% CI (-1.49, -0.02) crosses Clinical Significance (0.5 awakenings)
[8] 95% CI (3.64, 7.58) crosses Clinical Significance
[9] 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)

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 5 mg Zaleplon vs Placebo	No of Participants (studies)
Quality of Sleep* (Subjective)	⊕⊕⊕⊖ **moderate**[1]	The mean quality of sleep in the zaleplon group was **0.10 points**[2] **lower** (0.27 lower to 0.07 higher)	277 (1 study)[A]

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

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

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

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 10 mg Zaleplon vs Placebo	No of Participants (studies)
Sleep Latency* (PSG)	⊕⊕⊖⊖ **low**[1,3]	The mean sleep latency in the zaleplon group was **9.50 minutes lower** (18.80 to 0.19 lower)	94 (1 study)[B]
Sleep Latency (Subjective)	⊕⊕⊖⊖ **low**[2,3]	The mean sleep latency in the zaleplon group was **11.40 minutes lower** (27.36 lower to 4.56 higher)	92 (1 study)[B]
Total Sleep Time* (Subjective)	⊕⊕⊖⊖ **low**[3,4]	The mean total sleep time in the zaleplon group was **21.50 minutes higher** (5.60 lower to 48.6 higher)	93 (1 study)[B]
Wake After Sleep Onset (PSG)	⊕⊕⊕⊖ **moderate**[3]	The mean wake after sleep onset in the zaleplon group was **2.10 minutes lower** (10.23 lower to 6.03 higher)	92 (1 study)[B]
Quality of Sleep* (Subjective)	⊕⊕⊕⊖ **moderate**[3]	The mean quality of sleep in the zaleplon group was **0.10 points**[5] **lower** (0.27 lower to 0.07 higher)	283 (1 study)[A]

* Critical Outcome, used to determine Quality of Evidence
[1] 95% CI (-18.8, -0.19) crosses Clinical Significance (10 min)
[2] 95% CI (-27.36, 4.56) crosses Clinical Significance (20 min)
[3] Study funded by Industry
[4] 95% CI (-5.60, 48.60) crosses Clinical Significance (30 min)
[5] 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

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 6.25 mg Zolpidem vs Placebo	No of Participants (studies)
Sleep Latency* (PSG)	⊕⊕⊖⊖ **low**[1,2]	The mean sleep latency in the zolpidem group was **5.27 minutes lower** (11.47 lower to 0.93 higher)	199 (1 study)
Wake After Sleep Onset* (PSG)	⊕⊕⊖⊖ **low**[1,3]	The mean wake after sleep onset in the zolpidem group was **13.03 minutes lower** (22.5 to 3.55 lower)	199 (1 study)
Sleep Efficiency (PSG)	⊕⊕⊕⊖ **moderate**[1]	The mean sleep efficiency in the zolpidem group was **1.60 percent higher** (1.4 lower to 4.6 higher)	199 (1 study)

* 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

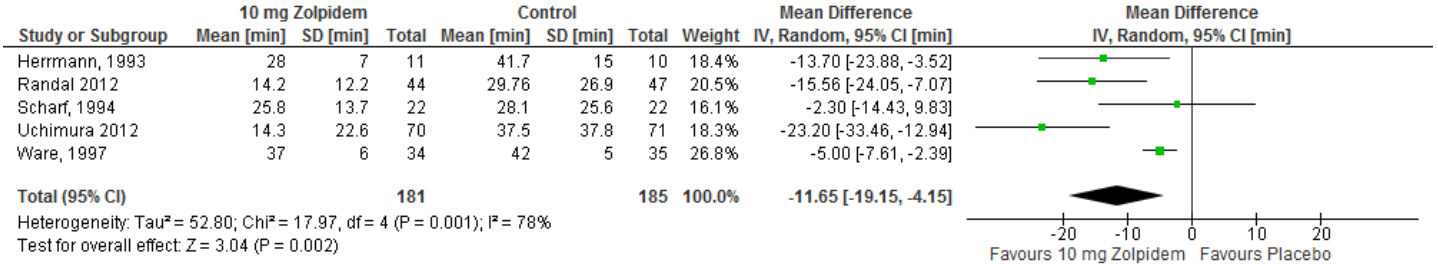

Figure S24 – Meta-analysis of data for subjectively-determined sleep latency in response to zolpidem 10 mg

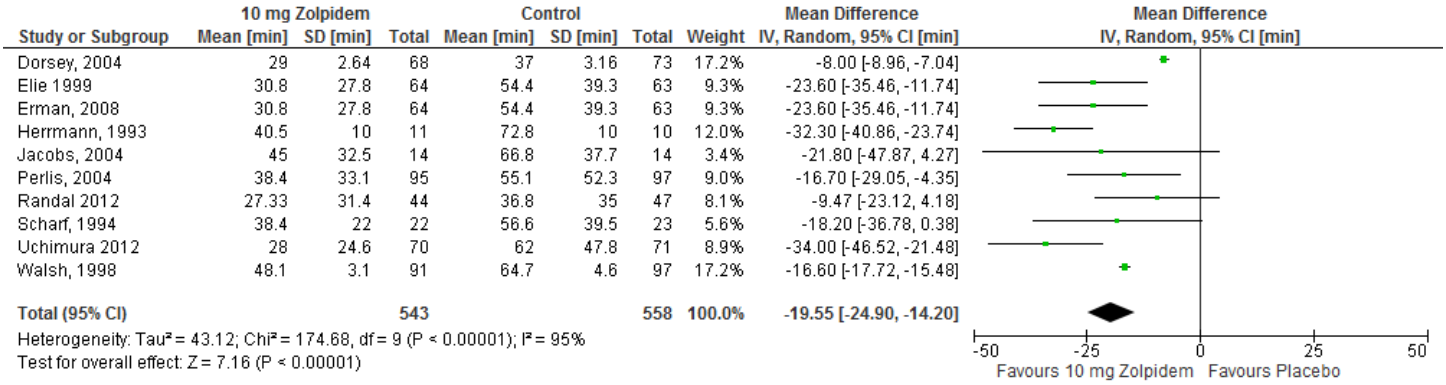

Figure S25 – Meta-analysis of data for PSG-determined total sleep time in response to zolpidem 10 mg

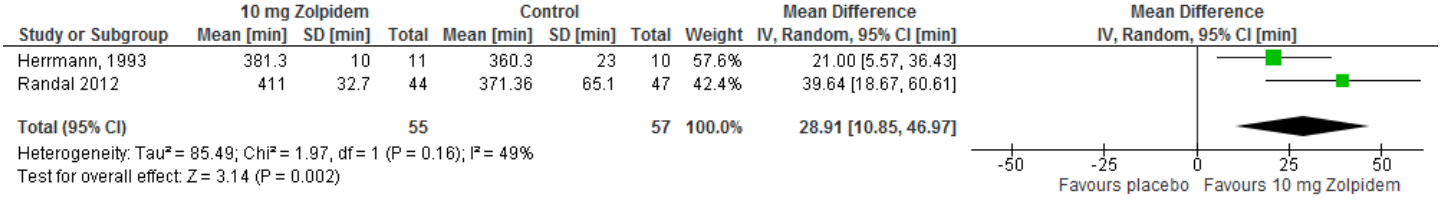

Figure S26 – Meta-analysis of data for subjectively-determined total sleep time in response to zolpidem 10 mg

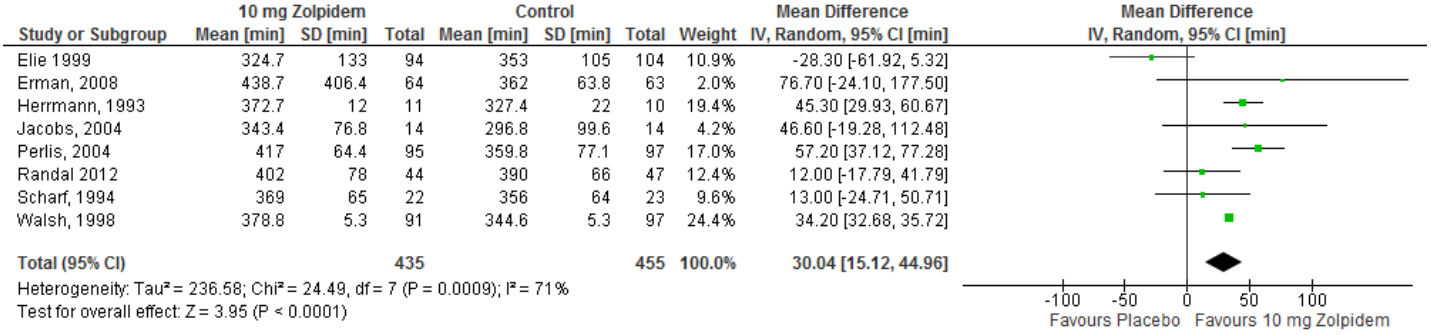

Figure S27 – Meta-analysis of data for PSG-determined wake after sleep onset in response to zolpidem 10 mg

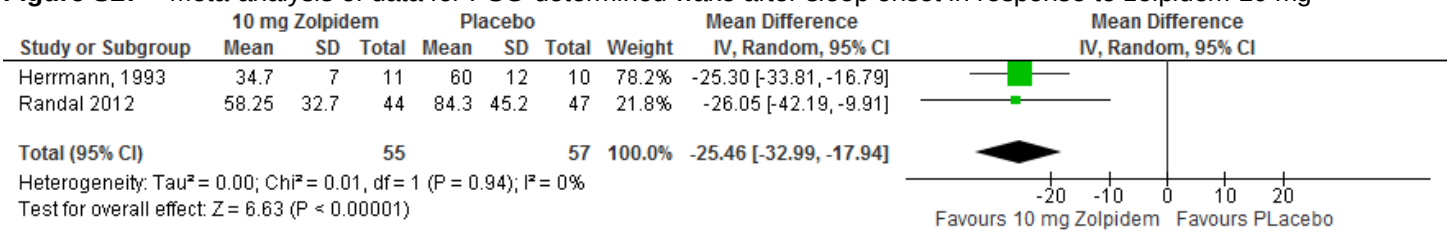

Figure S28 – Meta-analysis of data for subjectively-determined wake after sleep onset in response to zolpidem 10 mg

Study or Subgroup	10 mg Zolpidem Mean [min]	SD [min]	Total	Control Mean [min]	SD [min]	Total	Weight	Mean Difference IV, Random, 95% CI [min]
Dorsey, 2004	29	5.3	68	47	4.72	73	35.3%	-18.00 [-19.66, -16.34]
Erman, 2008	74.7	226.6	64	56.6	48.3	63	1.2%	18.10 [-38.68, 74.88]
Perlis, 2004	32.6	43.5	95	55.4	56.1	97	12.7%	-22.80 [-36.98, -8.62]
Randal 2012	52.3	58.3	44	59.62	52.4	47	6.2%	-7.32 [-30.15, 15.51]
Scharf, 1994	32.7	30.2	22	37.2	32.5	23	8.8%	-4.50 [-22.82, 13.82]
Walsh, 1998	39.5	3.6	91	49.8	4	97	35.8%	-10.30 [-11.39, -9.21]
Total (95% CI)			**384**			**400**	**100.0%**	**-13.57 [-19.84, -7.30]**

Heterogeneity: Tau² = 28.27; Chi² = 61.87, df = 5 (P < 0.00001); I² = 92%
Test for overall effect: Z = 4.24 (P < 0.0001)

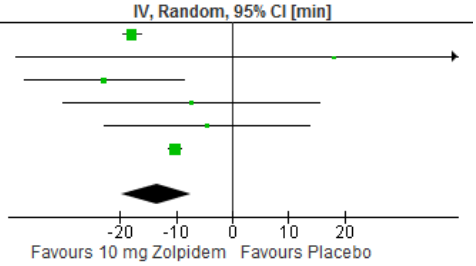

Figure S29 – Meta-analysis of data for subjectively-determined quality of sleep in response to zolpidem 10 mg

Study or Subgroup	10 mg Zolpidem Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Erman, 2008	55.6	21.1	64	44.4	19.9	63	17.2%	0.54 [0.19, 0.90]
Randal 2012	1.4	0.7	44	1.38	0.6	47	16.9%	0.03 [-0.38, 0.44]
Scharf, 1994	1.5	0.7	22	1.4	0.5	23	15.7%	0.16 [-0.42, 0.75]
Staner, 2005	68.8	21.5	23	61.1	21.6	23	15.7%	0.35 [-0.23, 0.93]
Uchimura 2012	6.6	2	70	5.2	1.9	71	17.3%	0.71 [0.37, 1.05]
Walsh, 1998	1.55	0.05	91	1.44	0.06	97	17.2%	1.98 [1.63, 2.33]
Total (95% CI)			**314**			**324**	**100.0%**	**0.64 [0.03, 1.26]**

Heterogeneity: Tau² = 0.54; Chi² = 65.94, df = 5 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.05 (P = 0.04)

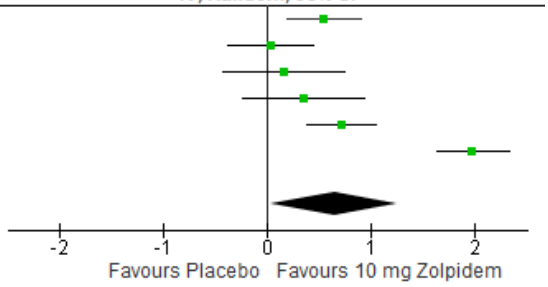

Figure S30 – Meta-analysis of data for PSG-determined sleep efficiency in response to zolpidem 10 mg

Study or Subgroup	10 mg Zolpidem Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Herrmann, 1993	86.6	2	11	78.3	5	10	19.4%	8.30 [4.98, 11.62]
Randal 2012	85.71	6.5	44	78.88	10.4	47	17.6%	6.83 [3.29, 10.37]
Scharf, 1994	87.9	6.4	22	80.7	13.4	23	7.2%	7.20 [1.11, 13.29]
Ware, 1997	79	2	34	74	2	35	55.8%	5.00 [4.06, 5.94]
Total (95% CI)			**111**			**115**	**100.0%**	**6.12 [4.39, 7.85]**

Heterogeneity: Tau² = 1.17; Chi² = 4.59, df = 3 (P = 0.20); I² = 35%
Test for overall effect: Z = 6.93 (P < 0.00001)

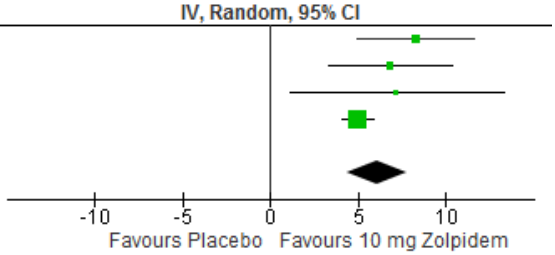

Figure S31 – Meta-analysis of data for PSG-determined number of awakenings in response to zolpidem 10 mg

Study or Subgroup	10 mg Zolpidem Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Scharf, 1994	6.7	3.2	22	6.7	3.5	22	5.4%	0.00 [-1.98, 1.98]
Ware, 1997	6	1	34	7	1	35	94.6%	-1.00 [-1.47, -0.53]
Total (95% CI)			**56**			**57**	**100.0%**	**-0.95 [-1.41, -0.49]**

Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 4.04 (P < 0.0001)

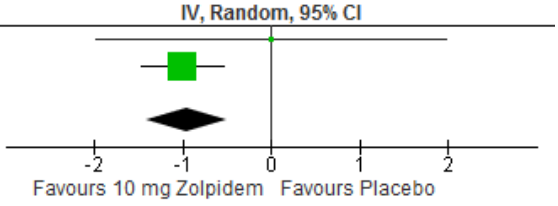

Figure S32 – Meta-analysis of data for subjectively-determined number of awakenings in response to zolpidem 10 mg

Study or Subgroup	10 mg Zolpidem Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Dorsey, 2004	1.4	0.12	68	1.8	0.12	73	34.1%	-0.40 [-0.44, -0.36]
Elie 1999	2.6	1.7	63	1.8	1	70	6.8%	0.80 [0.32, 1.28]
Herrmann, 1993	1.8	0.4	11	2.3	0.4	10	11.2%	-0.50 [-0.84, -0.16]
Perlis, 2004	1.03	0.92	95	1.64	1.33	97	12.1%	-0.61 [-0.93, -0.29]
Scharf, 1994	2.7	2.1	22	2.5	1	23	1.9%	0.20 [-0.77, 1.17]
Walsh, 1998	1.5	0.2	91	1.8	0.1	97	33.8%	-0.30 [-0.35, -0.25]
Total (95% CI)			**350**			**370**	**100.0%**	**-0.31 [-0.45, -0.17]**

Heterogeneity: Tau² = 0.01; Chi² = 37.05, df = 5 (P < 0.00001); I² = 87%
Test for overall effect: Z = 4.37 (P < 0.0001)

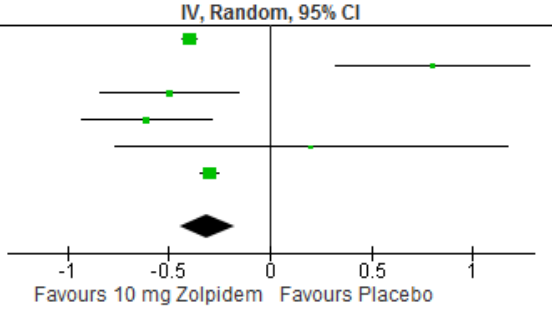

Figure S33 – Meta-analysis of data for the occurrence of amnesia in response to zolpidem 10 mg

Study or Subgroup	Zolpidem 10mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Elie 1999	6	122	3	126	40.0%	0.03 [-0.02, 0.07]
Scharf 1994	5	122	0	126	60.0%	0.04 [0.00, 0.08]
Total (95% CI)		**244**		**252**	**100.0%**	**0.03 [0.01, 0.06]**
Total events	11		3			

Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 2.31 (P = 0.02)

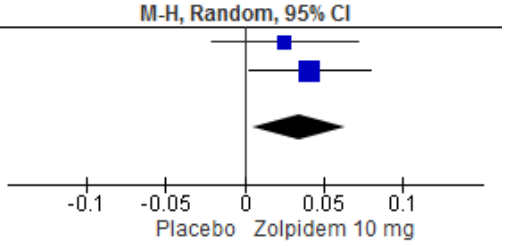

Figure S34 – Meta-analysis of data for the occurrence of dizziness in response to zolpidem 10 mg

Study or Subgroup	Zolpidem 10mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Dorsey 2004	6	68	0	73	27.2%	0.09 [0.02, 0.16]
Erman JCSM 2008	6	64	3	63	17.7%	0.05 [-0.04, 0.13]
Scharf 1994	3	26	0	24	7.3%	0.12 [-0.02, 0.25]
Uchimura 2012	3	70	0	71	47.8%	0.04 [-0.01, 0.10]
Total (95% CI)		**228**		**231**	**100.0%**	**0.06 [0.02, 0.10]**
Total events	18		3			

Heterogeneity: Tau² = 0.00; Chi² = 1.75, df = 3 (P = 0.62); I² = 0%
Test for overall effect: Z = 3.21 (P = 0.001)

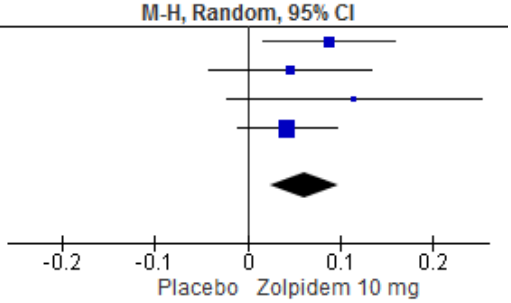

Figure S35 – Meta-analysis of data for the occurrence of headache in response to zolpidem 10 mg

Study or Subgroup	Zolpidem 10mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Dorsey 2004	36	68	24	73	26.4%	0.20 [0.04, 0.36]
Erman JCSM 2008	6	64	6	63	38.6%	-0.00 [-0.10, 0.10]
Walsh 1998	22	91	18	97	35.0%	0.06 [-0.06, 0.17]
Total (95% CI)		**223**		**233**	**100.0%**	**0.07 [-0.04, 0.19]**
Total events	64		48			

Heterogeneity: Tau² = 0.01; Chi² = 5.00, df = 2 (P = 0.08); I² = 60%
Test for overall effect: Z = 1.25 (P = 0.21)

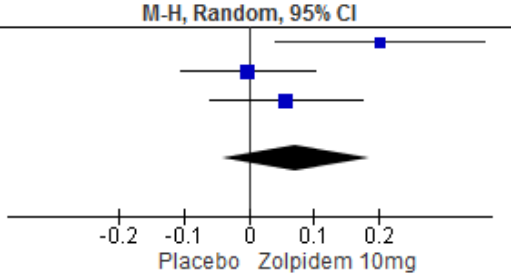

Figure S36 – Meta-analysis of data for the occurrence of nausea in response to zolpidem 10 mg

Study or Subgroup	Zolpidem 10mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Erman JCSM 2008	4	64	2	63	68.7%	0.03 [-0.04, 0.10]
Scharf 1994	1	26	1	24	31.3%	-0.00 [-0.11, 0.11]
Total (95% CI)		**90**		**87**	**100.0%**	**0.02 [-0.04, 0.08]**
Total events	5		3			

Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)

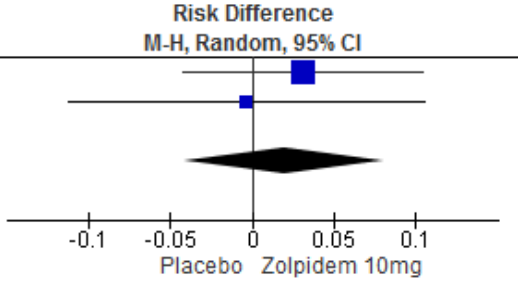

Figure S37 – Meta-analysis of data for the occurrence of somnolence in response to zolpidem 10 mg

Study or Subgroup	Zolpidem 10mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Dorsey 2004	7	68	1	73	14.0%	0.09 [0.01, 0.17]
Elie 1999	6	122	3	126	37.9%	0.03 [-0.02, 0.07]
Erman JCSM 2008	6	64	2	63	11.9%	0.06 [-0.02, 0.15]
Scharf 1994	3	26	0	24	4.3%	0.12 [-0.02, 0.25]
Uchimura 2012	3	70	2	71	22.2%	0.01 [-0.05, 0.08]
Walsh 1998	14	91	8	97	9.7%	0.07 [-0.02, 0.16]
Total (95% CI)		**441**		**454**	**100.0%**	**0.04 [0.02, 0.07]**
Total events	39		16			

Heterogeneity: Tau² = 0.00; Chi² = 4.74, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 3.04 (P = 0.002)

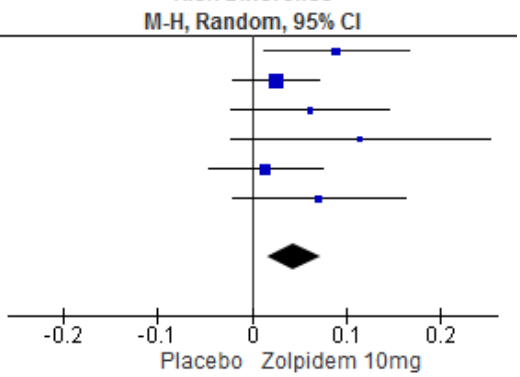

Figure S38 – Meta-analysis of data for the occurrence of taste perversion in response to zolpidem 10 mg

Study or Subgroup	Zolpidem 10mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Elie 1999	3	122	1	126	60.5%	0.02 [-0.01, 0.05]
Uchimura 2012	1	70	1	71	39.5%	0.00 [-0.04, 0.04]
Total (95% CI)		**192**		**197**	**100.0%**	**0.01 [-0.01, 0.03]**
Total events	4		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)

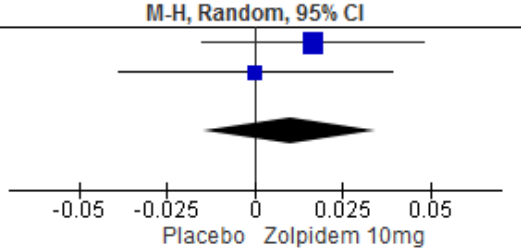

Table S9 – Summary of Findings table for zolpidem 10 mg for the treatment of chronic insomnia

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)

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 10 mg Zolpidem vs Placebo	No of Participants (studies)
Sleep Latency* (PSG)	⊕⊖⊖⊖ **very low**[1,2,3]	The mean sleep latency in the zolpidem groups was **11.65 minutes lower** (19.15 to 4.15 lower)	366 (5 studies)[D,G,H,J,L]
Sleep Latency (Subjective)	⊕⊖⊖⊖ **very low**[3,4,5]	The mean sleep latency in the zolpidem groups was **19.55 minutes lower** (24.90 to 14.20 lower)	1101 (10 studies)[A,B,C,D,E,FG,H,J,K]
Total Sleep Time* (PSG)	⊕⊕⊖⊖ **low**[3,12]	The mean total sleep time in the zolpidem groups was **28.91 minutes higher** (10.85 to 46.97 higher)	112 (2 studies)[D,G]
Total Sleep Time* (Subjective)	⊕⊕⊖⊖ **low**[3,7]	The mean total sleep time in the zolpidem groups was **30.04 minutes higher** (15.12 to 44.96 higher)	890 (8 studies)[B,C,D,E,F,G,H,K]
Wake After Sleep Onset* (PSG)	⊕⊕⊖⊖ **low**[3,13]	The mean wake after sleep onset in the zolpidem groups was **25.46 minutes lower** (32.99 to 17.94 lower)	112 (2 studies)[D,G]
Wake After Sleep Onset (Subjective)	⊕⊕⊖⊖ **low**[3,6]	The mean wake after sleep onset in the zolpidem groups was **13.57 minutes lower** (19.84 to 7.30 lower)	784 (6 studies)[A,C,F,G,H,K]
Quality of Sleep* (Subjective)	⊕⊖⊖⊖ **very low**[3,10,11]	The mean quality of sleep in the zolpidem groups was **0.64 standard deviations higher** (0.03 to 1.26 higher)	638 (6 studies)[C,G,H,I,J,K]
Sleep Efficiency (PSG)	⊕⊕⊖⊖ **low**[3,9]	The mean sleep efficiency in the zolpidem groups was **6.12 percent higher** (4.39 to 7.85 higher)	226 (4 studies)[D,G,H,L]
Number of Awakenings (PSG)	⊕⊕⊕⊖ **moderate**[3]	The mean number of awakenings in the zolpidem groups was **0.95 awakenings lower** (1.41 to 0.49 lower)	113 (2 studies)[H,L]
Number of Awakenings (Subjective)	⊕⊕⊖⊖ **low**[3,8]	The mean number of awakenings in the zolpidem groups was **0.31 awakenings lower** (0.45 to 0.17 lower)	720 (6 studies)[A,B,D,F,H,K]

* Critical Outcome, used to determine Quality of Evidence
[1] Heterogeneity (I^2 = 78%) greater than allowance (75%)
[2] 95% CI (-19.15, -4.15) crosses Clinical Significance (10 min)
[3] Studies funded by industry
[4] Heterogeneity (I^2 = 95%) greater than allowance (75%)
[5] 95% CI (-24.90, -14.20) crosses Clinical Significance (20 min)
[6] Heterogeneity (I^2 = 92%) greater than allowance (75%)
[7] 95% CI (15.12, 44.96) crosses Clinical Significance (30 min)
[8] Heterogeneity (I^2 = 87%) greater than allowance (75%)
[9] 95% CI (4.39, 7.85) crosses Clinical Significance (5%)
[10] Heterogeneity (I^2 = 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

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 12.5 Zolpidem vs Placebo	No of Participants (studies)
Sleep Latency* (PSG)	⊕⊕⊖⊖ **low**[1,2]	The mean sleep latency in the zolpidem group was **8.19 minutes lower** (15.22 to 1.15 lower)	212 (1 study)
Wake After Sleep Onset* (PSG)	⊕⊕⊖⊖ **low**[1,3]	The mean wake after sleep onset in the zolpidem group was **19.99 minutes lower** (27.33 to 12.64 lower)	212 (1 study)
Sleep Efficiency (PSG)	⊕⊕⊕⊖ **moderate**[1]	The mean sleep efficiency in the zolpidem group was **3.9 percent higher** (1.38 to 6.41 higher)	212 (1 study)

* 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

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 0.25 mg Triazolam vs Placebo	No of Participants (studies)
Sleep Latency* (Subjective)	⊕⊕⊕⊕ **high**	The mean sleep latency in the triazolam group was **9.20 minutes lower** (22.3 lower to 3.9 higher)	64 (1 study)
Total Sleep Time (Subjective)	⊕⊕⊕⊖ **moderate**[1]	The mean total sleep time in the triazolam group was **25.20 minutes higher** (9.12 lower to 59.52 higher)	64 (1 study)
Quality of Sleep* (Subjective)	⊕⊕⊕⊕ **high**	The mean quality of sleep in the triazolam group was **0.37 points**[3] **lower** (0.66 to 0.07 lower)	64 (1 study)
Number of Awakenings (Subjective)	⊕⊕⊖⊖ **low**[2]	The mean number of awakenings in the triazolam group was **0.37 awakenings lower** (1.7 lower to 0.96 higher)	64 (1 study)

* 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

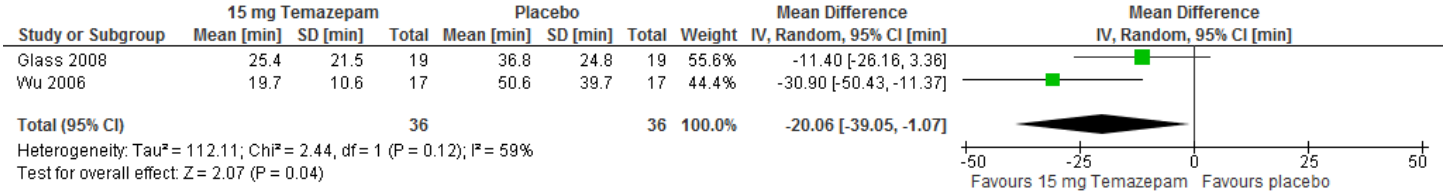

Figure S40 – Meta-analysis of data for subjectively-determined total sleep time in response to temazepam 15 mg

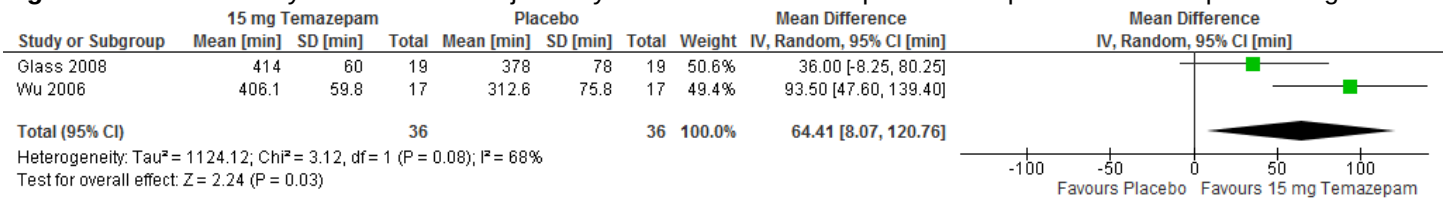

Figure S41 – Meta-analysis of data for subjectively-determined quality of sleep in response to temazepam 15 mg

Study or Subgroup	15 mg Temazepam Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Glass 2008	3.3	0.86	19	2.9	0.77	19	47.9%	0.48 [-0.17, 1.13]
Hindmarch 1979	4.67	0.94	20	4.62	1.43	20	52.1%	0.04 [-0.58, 0.66]
Total (95% CI)			**39**			**39**	**100.0%**	**0.25 [-0.20, 0.70]**

Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 1.10 (P = 0.27)

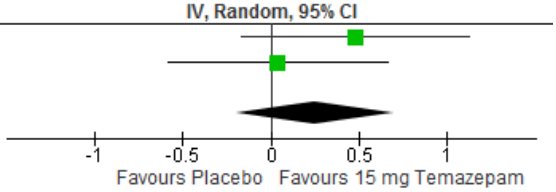

Table S12 – Summary of Findings table for temazepam 15 mg for the treatment of chronic insomnia

Reference: Glass 2008(A); Hindmarch 1979(B); Wu 2006 (C)

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 15 mg Temazepam vs Placebo	No of Participants (studies)
Sleep Latency* (PSG)	⊕⊕⊕⊕ **high**	The mean sleep latency in the temazepam group was **37.1 minutes lower** (52.8 to 21.31 lower)	34 (1 study)[C]
Sleep Latency (Subjective)	⊕⊕⊕⊖ **moderate**[2]	The mean sleep latency in the temazepam group was **20.06 minutes lower** (39.05 to 1.07 lower)	72 (2 studies)[A,C]
Total Sleep Time* (PSG)	⊕⊕⊕⊕ **high**	The mean total sleep time in the temazepam group was **99.1 minutes higher** (63.4 to 134.7 lower)	34 (1 study)[C]
Total Sleep Time (Subjective)	⊕⊕⊕⊖ **moderate**[3]	The mean total sleep time in the temazepam groups was **64.41 minutes higher** (8.07 to 120.76 higher)	72 (2 studies)[A,C]
Quality of Sleep* (Subjective)	⊕⊕⊕⊖ **moderate**[1]	The mean quality of sleep in the temazepam group was **0.25 standard deviations higher** (0.2 lower to 0.7 higher)	39 (2 studies)[A,B]
Sleep Efficiency (PSG)	⊕⊕⊕⊖ **moderate**[5]	The mean sleep efficiency in the temazepam group was **13.3 percent higher** (3.9 to 22.6 higher)	34 (1 study)[C]
Sleep Efficiency (Subjective)	⊕⊕⊕⊖ **moderate**[6]	The mean sleep efficiency in the temazepam group was **14.1 percent higher** (5.8 to 22.3 higher)	34 (1 study)[C]
Number of Awakenings (Subjective)	⊕⊕⊕⊖ **moderate**[4]	The mean number of awakenings in the temazepam group was **0.5 awakenings lower** (1.29 lower to 0.29 higher)	38 (1 study)[A]

* 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 (8.07,120.76) crosses Clinical Significance (30 min)
[4] 95% CI (-1.29, 0.29) crosses Clinical Significance (0.5 awakenings)
[5] 95% CI (3.9, 22.6) crosses Clinical Significance (5%)
[6] 95% CI (5.8, 22.3) crosses Clinical Significance (10%)

Table S13 – Summary of Findings table for temazepam 30 mg for the treatment of chronic insomnia

References: Hindmarch 1979

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 30 mg Temazepam vs Placebo	No of Participants (studies)
Quality of Sleep* (Subjective)	⊕⊕⊕⊖ **moderate**[1]	The mean quality of sleep in the temazepam group was **0.69 cm² higher** (0.28 lower to 1.66 higher)	40 (1 study)

* Critical Outcome, used to determine Quality of Evidence
[1] 95% CI (-0.28, 1.66) crosses Clinical Significance (1.0 cm)
[2] 10 cm line analogue rating scale

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

Study or Subgroup	8 mg Ramelteon Mean [min]	SD [min]	Total	Placebo Mean [min]	SD [min]	Total	Weight	Mean Difference IV, Random, 95% CI [min]
Kohsaka, 2011	22.12	18.16	61	35.27	40.68	61	6.9%	-13.15 [-24.33, -1.97]
Roth, 2007	30.8	2.52	100	38.4	2.49	100	46.5%	-7.60 [-8.29, -6.91]
Zammit, 2007	31.5	2.91	139	42.5	2.97	131	46.5%	-11.00 [-11.70, -10.30]
Total (95% CI)			**300**			**292**	**100.0%**	**-9.57 [-12.75, -6.38]**

Heterogeneity: Tau² = 5.55; Chi² = 46.01, df = 2 (P < 0.00001); I² = 96%
Test for overall effect: Z = 5.89 (P < 0.00001)

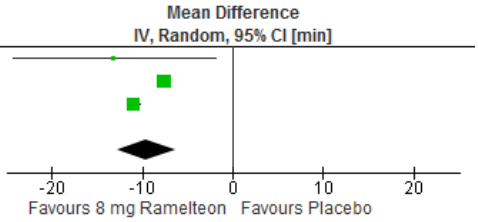

Figure S43 – Meta-analysis of data for subjectively-determined sleep latency in response to ramelteon 8 mg

Study or Subgroup	8 mg Ramelteon Mean [min]	SD [min]	Total	Placebo Mean [min]	SD [min]	Total	Weight	Mean Difference IV, Random, 95% CI [min]
Kohsaka, 2011	37.8	25.51	61	47.07	41.27	61	21.0%	-9.27 [-21.45, 2.91]
Roth, 2007	50.9	4.46	100	58.2	4.53	100	39.4%	-7.30 [-8.55, -6.05]
Zammit, 2007	44.8	3.6	139	61.5	3.7	131	39.6%	-16.70 [-17.57, -15.83]
Total (95% CI)			**300**			**292**	**100.0%**	**-11.44 [-19.56, -3.31]**

Heterogeneity: Tau² = 43.20; Chi² = 147.30, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 2.76 (P = 0.006)

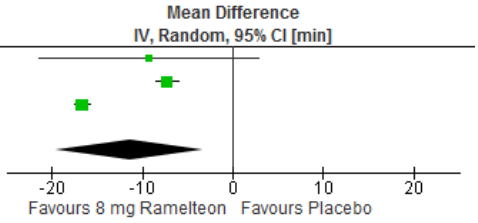

Figure S44 – Meta-analysis of data for PSG-determined total sleep time in response to ramelteon 8 mg

Study or Subgroup	8 mg Ramelteon Mean [min]	SD [min]	Total	Placebo Mean [min]	SD [min]	Total	Weight	Mean Difference IV, Random, 95% CI [min]
Kohsaka, 2011	407.2	45.33	61	394.7	52.35	61	7.0%	12.50 [-4.88, 29.88]
Mayer, 2009	381.39	3.233	159	380.11	3.255	176	31.2%	1.28 [0.58, 1.98]
Roth, 2007	362	5.03	100	350.4	5.04	100	30.7%	11.60 [10.20, 13.00]
Zammit, 2007	391.5	4.04	139	385.9	4.12	131	31.1%	5.60 [4.63, 6.57]
Total (95% CI)			**459**			**468**	**100.0%**	**6.58 [1.36, 11.80]**

Heterogeneity: Tau² = 22.59; Chi² = 183.95, df = 3 (P < 0.00001); I² = 98%
Test for overall effect: Z = 2.47 (P = 0.01)

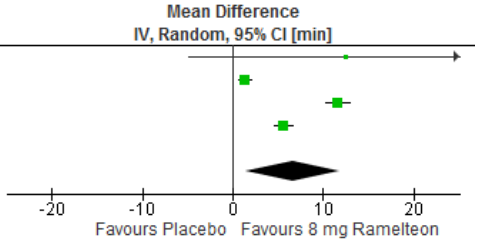

Figure S45 – Meta-analysis of data for subjectively-determined total sleep time in response to ramelteon 8 mg

Study or Subgroup	8 mg Ramelteon Mean [min]	SD [min]	Total	Placebo Mean [min]	SD [min]	Total	Weight	Mean Difference IV, Random, 95% CI [min]
Kohsaka, 2011	377.01	70.92	61	371.68	61.06	61	15.1%	5.33 [-18.15, 28.81]
Mayer, 2009	345.39	4.336	159	349.49	4.346	176	28.3%	-4.10 [-5.03, -3.17]
Roth, 2007	337	6.62	100	333.9	6.69	100	28.2%	3.10 [1.26, 4.94]
Zammit, 2007	365.4	5.6	139	347.1	5.7	131	28.3%	18.30 [16.95, 19.65]
Total (95% CI)			**459**			**468**	**100.0%**	**5.70 [-7.65, 19.04]**

Heterogeneity: Tau² = 163.34; Chi² = 717.67, df = 3 (P < 0.00001); I² = 100%
Test for overall effect: Z = 0.84 (P = 0.40)

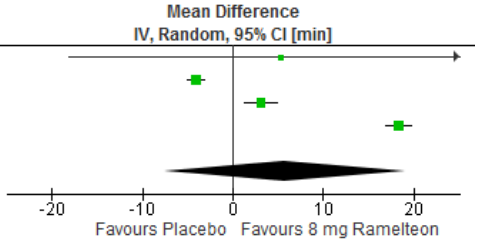

Figure S46 – Meta-analysis of data for PSG-determined wake after sleep onset in response to ramelteon 8 mg

Study or Subgroup	8 mg Ramelteon Mean [min]	SD [min]	Total	Placebo Mean [min]	SD [min]	Total	Weight	Mean Difference IV, Random, 95% CI [min]
Kohsaka, 2011	49.78	39.1	61	46.42	33.49	61	0.3%	3.36 [-9.56, 16.28]
Zammit, 2007	59.9	3.04	139	56.4	3.11	131	99.7%	3.50 [2.77, 4.23]
Total (95% CI)			**200**			**192**	**100.0%**	**3.50 [2.77, 4.23]**

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 9.36 (P < 0.00001)

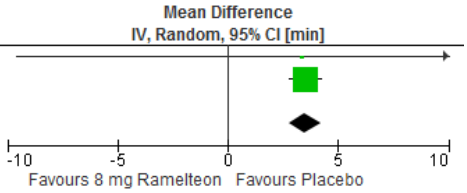

Figure S47 – Meta-analysis of data for subjectively-determined wake after sleep onset in response to ramelteon 8 mg

Study or Subgroup	8 mg Ramelteon Mean [min]	SD [min]	Total	Placebo Mean [min]	SD [min]	Total	Weight	Mean Difference IV, Random, 95% CI [min]
Mayer, 2009	90.89	3.796	159	79.54	3.822	176	50.1%	11.35 [10.53, 12.17]
Zammit, 2007	70.3	4.7	139	71.2	4.8	131	49.9%	-0.90 [-2.03, 0.23]
Total (95% CI)			**298**			**307**	**100.0%**	**5.23 [-6.77, 17.24]**

Heterogeneity: Tau² = 74.78; Chi² = 295.15, df = 1 (P < 0.00001); I² = 100%
Test for overall effect: Z = 0.85 (P = 0.39)

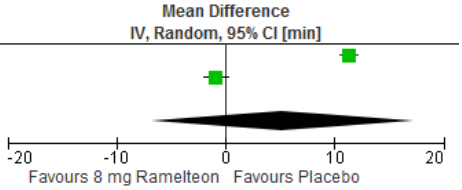

Figure S48 – Meta-analysis of data for PSG-determined quality of sleep in response to ramelteon 8 mg

Study or Subgroup	8 mg Ramelteon Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mayer, 2009	4.01	0.065	159	4.01	0.065	176	43.0%	0.00 [-0.01, 0.01]
Roth, 2007	3.8	0.1	100	3.8	1	100	14.1%	0.00 [-0.20, 0.20]
Zammit, 2007	3.6	0.06	139	3.7	0.06	131	42.9%	-0.10 [-0.11, -0.09]
Total (95% CI)			**398**			**407**	**100.0%**	**-0.04 [-0.13, 0.05]**

Heterogeneity: Tau² = 0.00; Chi² = 96.43, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.93 (P = 0.35)

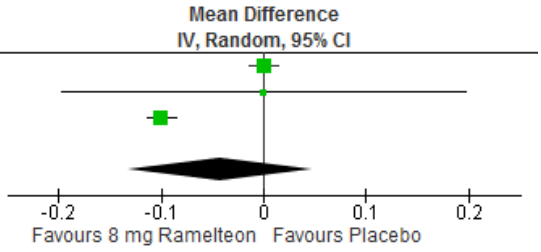

Figure S49 – Meta-analysis of data for PSG-determined sleep efficiency in response to ramelteon 8 mg

Study or Subgroup	8 mg Ramelteon Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kohsaka, 2011	84.83	9.44	61	82.26	10.9	61	5.9%	2.57 [-1.05, 6.19]
Roth, 2007	75.5	1.05	100	73.1	1.05	100	46.5%	2.40 [2.11, 2.69]
Zammit, 2007	81.8	0.84	139	80.4	0.86	131	47.6%	1.40 [1.20, 1.60]
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 = 93%
Test for overall effect: Z = 4.05 (P < 0.0001)

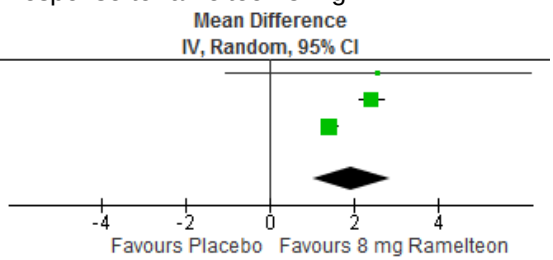

Figure S50 – Meta-analysis of data for the occurrence of headache in response to ramelteon 8 mg

Study or Subgroup	Ramelteon 8 mg Events	Total	placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Mayer 2009	18	228	18	223	33.8%	-0.00 [-0.05, 0.05]
Roth 2007	3	100	1	100	56.5%	0.02 [-0.02, 0.06]
Zammit 2007	27	139	24	131	9.7%	0.01 [-0.08, 0.10]
Total (95% CI)		**467**		**454**	**100.0%**	**0.01 [-0.02, 0.04]**
Total events	48		43			

Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.79 (P = 0.43)

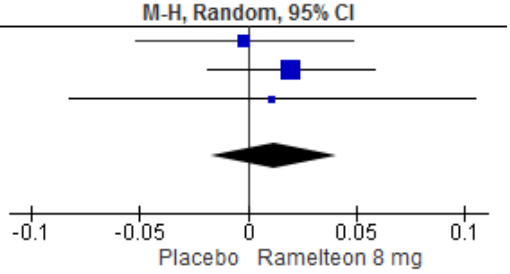

Figure S51 – Meta-analysis of data for the occurrence of upper respiratory tract infection in response to ramelteon 8 mg

Study or Subgroup	Ramelteon 8 mg Events	Total	placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Mayer 2009	18	228	18	223	44.5%	-0.00 [-0.05, 0.05]
Zammit 2007	6	139	4	131	55.5%	0.01 [-0.03, 0.06]
Total (95% CI)		**367**		**354**	**100.0%**	**0.01 [-0.03, 0.04]**
Total events	24		22			

Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.72)

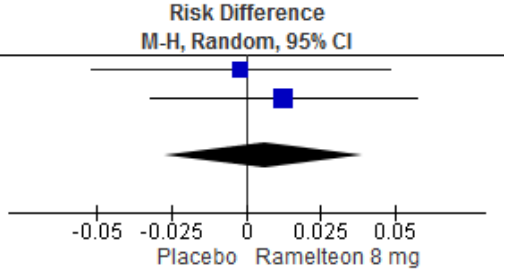

Table S14 – Summary of Findings table for ramelteon 8 mg for the treatment of chronic insomnia

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

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 8 mg Ramelteon vs Placebo	No of Participants (studies)
Sleep Latency* (PSG)	⊕⊖⊖⊖ **very low**[1,2,3]	The mean sleep latency in the ramelteon groups was **9.57 minutes lower** (12.75 to 6.38 lower)	592 (3 studies) [A,C,D]
Sleep Latency (Subjective)	⊕⊕⊖⊖ **low**[3,7,8]	The mean sleep latency in the ramelteon groups was **11.44 minutes lower** (19.56 to 3.31 lower)	592 (3 studies) [A,C,D]
Total Sleep Time (PSG)	⊕⊕⊖⊖ **low**[1,3]	The mean total sleep time in the ramelteon groups was **6.58 minutes higher** (1.36 to 11.80 higher)	927 (4 studies) [A,B,C,D]
Total Sleep Time (Subjective)	⊕⊕⊖⊖ **low**[3,6]	The mean total sleep time in the ramelteon groups was **5.70 minutes higher** (7.65 lower to 19.04 higher)	927 (4 studies) [A,B,C,D]
Wake After Sleep Onset (PSG)	⊕⊕⊕⊖ **moderate**[3]	The mean wake after sleep onset in the ramelteon groups was **3.50 minutes higher** (2.77 to 4.23 higher)	392 (2 study) [A,D]
Wake After Sleep Onset (Subjective)	⊕⊕⊖⊖ **low**[3,6]	The mean wake after sleep onset in the ramelteon groups was **5.23 minutes higher** (6.77 lower to 17.24 higher)	605 (2 studies) [B,D]
Quality of Sleep* (Subjective)	⊕⊕⊖⊖ **low**[1,3]	The mean quality of sleep in the ramelteon groups was **0.04 points lower**[5] (0.13 lower to 0.05 higher)	805 (3 studies) [B,C,D]
Sleep Efficiency (PSG)	⊕⊕⊖⊖ **low**[3,4]	The mean sleep efficiency in the ramelteon groups was **1.93 percent higher** (1.00 to 2.87 higher)	592 (3 studies) [A,C,D]
Number of Awakenings (Subjective)	⊕⊕⊕⊖ **moderate**[3]	The mean number of awakenings in the ramelteon group was **0.12 awakenings higher** (0.08 to 0.15 higher)	335 (1 study) [B]

* Critical Outcome, used to determine Quality of Evidence
[1] Heterogeneity (I^2 = 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 (I^2 = 93%) greater than allowance (75%)
[5] 7-point Likert scale (1=excellent, 7=very poor)
[6] Heterogeneity (I^2 =100%) greater than allowance (75%)
[7] Heterogeneity (I^2 =99%) greater than allowance (75%)
[8] 95% CI (-21.45, 2.90) crossses 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

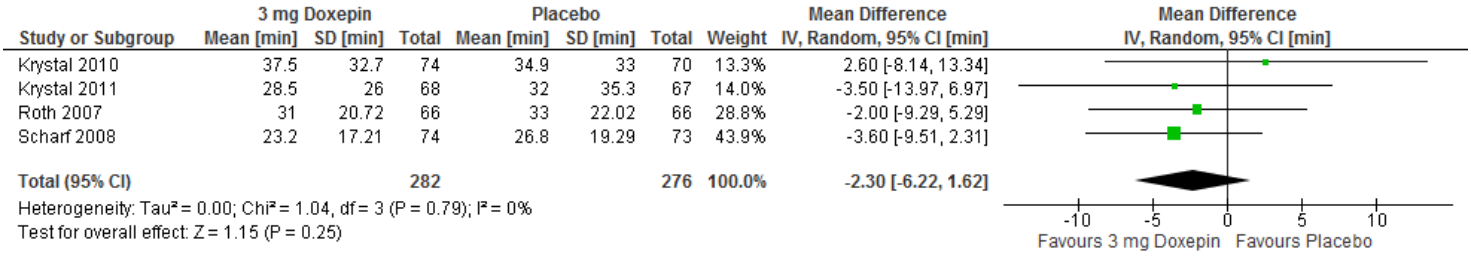

Figure S53 – Meta-analysis of data for subjectively-determined sleep latency in response to doxepin 3 mg

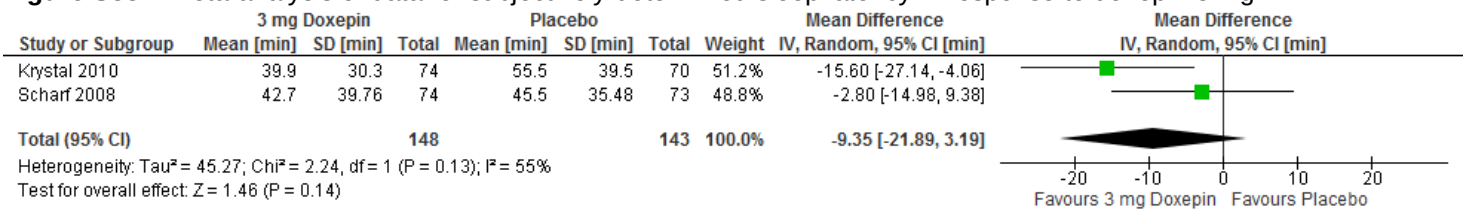

Figure S54 – Meta-analysis of data for PSG-determined total sleep time in response to doxepin 3 mg

Study or Subgroup	3 mg Doxepin Mean [min]	SD [min]	Total	Placebo Mean [min]	SD [min]	Total	Weight	Mean Difference IV, Random, 95% CI [min]
Krystal 2010	373.7	42.2	74	343.7	57.7	70	21.3%	30.00 [13.41, 46.59]
Krystal 2011	408	53.5	68	391.5	48.9	67	19.6%	16.50 [-0.79, 33.79]
Roth 2007	415.4	34.5	66	389.6	48.86	66	28.1%	25.80 [11.37, 40.23]
Scharf 2008	390.6	41.02	74	360.7	43.98	73	31.0%	29.90 [16.15, 43.65]
Total (95% CI)			**282**			**276**	**100.0%**	**26.14 [18.49, 33.79]**

Heterogeneity: Tau² = 0.00; Chi² = 1.69, df = 3 (P = 0.64); I² = 0%
Test for overall effect: Z = 6.69 (P < 0.00001)

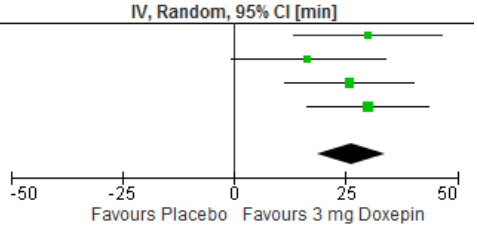

Figure S55 – Meta-analysis of data for subjectively-determined total sleep time in response to doxepin 3 mg

Study or Subgroup	3 mg Doxepin Mean [min]	SD [min]	Total	Placebo Mean [min]	SD [min]	Total	Weight	Mean Difference IV, Random, 95% CI [min]
Krystal 2010	389.4	65.9	74	326	77.9	70	49.4%	63.40 [39.77, 87.03]
Scharf 2008	364.2	64.9	74	340	71.79	73	50.6%	24.20 [2.07, 46.33]
Total (95% CI)			**148**			**143**	**100.0%**	**43.57 [5.16, 81.98]**

Heterogeneity: Tau² = 631.87; Chi² = 5.63, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 2.22 (P = 0.03)

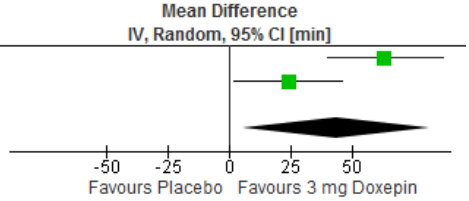

Figure S56 – Meta-analysis of data for PSG-determined wake after sleep onset in response to doxepin 3 mg

Study or Subgroup	3 mg Doxepin Mean [min]	SD [min]	Total	Placebo Mean [min]	SD [min]	Total	Weight	Mean Difference IV, Random, 95% CI [min]
Krystal 2010	75.7	37.6	74	109.2	50.8	70	20.8%	-33.50 [-48.16, -18.84]
Krystal 2011	47.2	43.5	68	60.5	38.8	67	22.7%	-13.30 [-27.20, 0.60]
Roth 2007	38.9	26.29	66	61.1	45.79	66	26.0%	-22.20 [-34.94, -9.46]
Scharf 2008	64.8	31.96	74	85.8	38.39	73	30.5%	-21.00 [-32.43, -9.57]
Total (95% CI)			**282**			**276**	**100.0%**	**-22.17 [-29.62, -14.72]**

Heterogeneity: Tau² = 13.34; Chi² = 3.90, df = 3 (P = 0.27); I² = 23%
Test for overall effect: Z = 5.83 (P < 0.00001)

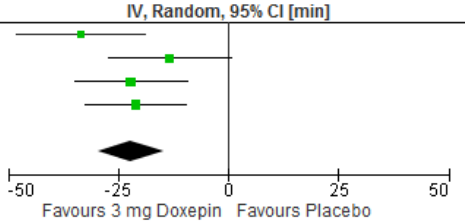

Figure S57 – Meta-analysis of data for subjectively-determined quality of sleep in response to doxepin 3 mg

Study or Subgroup	3 mg Doxepin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Krystal 2010	0.9	0.9	74	0.2	1	70	49.1%	0.73 [0.40, 1.07]
Scharf 2008	0.9	0.93	74	0.5	0.99	73	50.9%	0.41 [0.09, 0.74]
Total (95% CI)			**148**			**143**	**100.0%**	**0.57 [0.26, 0.88]**

Heterogeneity: Tau² = 0.02; Chi² = 1.76, df = 1 (P = 0.18); I² = 43%
Test for overall effect: Z = 3.58 (P = 0.0003)

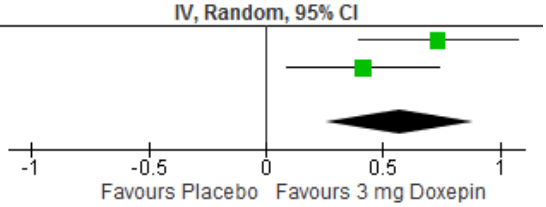

Figure S58 – Meta-analysis of data for PSG-determined sleep efficiency in response to doxepin 3 mg

Study or Subgroup	3 mg Doxepin Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Random, 95% CI [%]
Krystal 2010	76.1	17.8	74	65	25.7	70	9.4%	11.10 [3.84, 18.36]
Roth 2007	86.5	7.19	66	81.2	10.18	66	43.7%	5.30 [2.29, 8.31]
Scharf 2008	81.4	8.54	74	74.1	9.16	73	47.0%	7.30 [4.44, 10.16]
Total (95% CI)			**214**			**209**	**100.0%**	**6.78 [4.50, 9.07]**

Heterogeneity: Tau² = 0.75; Chi² = 2.41, df = 2 (P = 0.30); I² = 17%
Test for overall effect: Z = 5.82 (P < 0.00001)

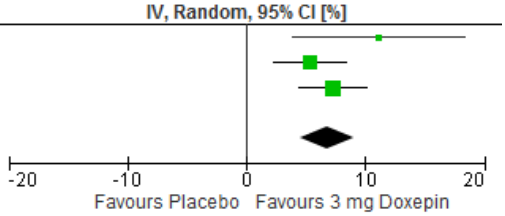

Figure S59 – Meta-analysis of data for PSG-determined number of awakenings in response to doxepin 3 mg

Study or Subgroup	3 mg Doxepin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Krystal 2010	12.9	5.6	74	11.9	5.3	70	25.2%	1.00 [-0.78, 2.78]
Roth 2007	8.9	4.1	66	8.7	3.86	66	43.2%	0.20 [-1.16, 1.56]
Scharf 2008	12.5	5.34	74	11.9	4.45	73	31.6%	0.60 [-0.99, 2.19]
Total (95% CI)			**214**			**209**	**100.0%**	**0.53 [-0.37, 1.42]**

Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 1.16 (P = 0.25)

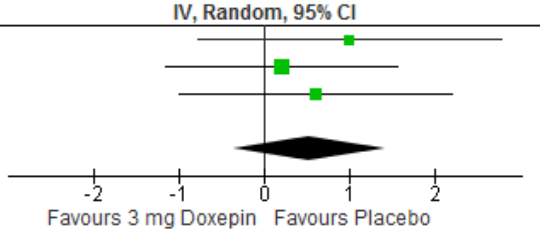

Figure S60 – Meta-analysis of data for the occurrence of headache in response to doxepin 3 mg

Study or Subgroup	Doxepin 3 mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Krystal 2010	4	70	10	70	19.2%	-0.09 [-0.18, 0.01]
Krystal 2011	3	68	7	67	24.0%	-0.06 [-0.15, 0.03]
Roth 2007	0	66	3	66	56.9%	-0.05 [-0.10, 0.01]
Total (95% CI)		**204**		**203**	**100.0%**	**-0.06 [-0.10, -0.01]**
Total events	7		20			

Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 2.58 (P = 0.010)

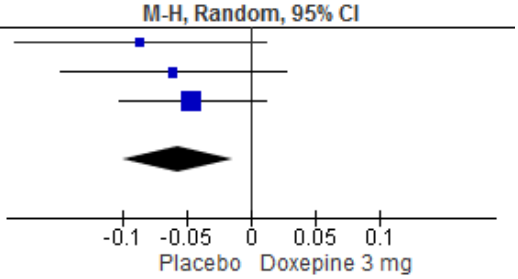

Figure S61 – Meta-analysis of data for the occurrence of somnolence in response to doxepin 3 mg

Study or Subgroup	Doxepin 3 mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Krystal 2010	1	70	3	70	33.1%	-0.03 [-0.08, 0.03]
Krystal 2011	6	68	3	67	16.4%	0.04 [-0.04, 0.13]
Roth 2007	1	66	0	66	50.5%	0.02 [-0.03, 0.06]
Total (95% CI)		**204**		**203**	**100.0%**	**0.01 [-0.03, 0.04]**
Total events	8		6			

Heterogeneity: Tau² = 0.00; Chi² = 2.55, df = 2 (P = 0.28); I² = 21%
Test for overall effect: Z = 0.29 (P = 0.77)

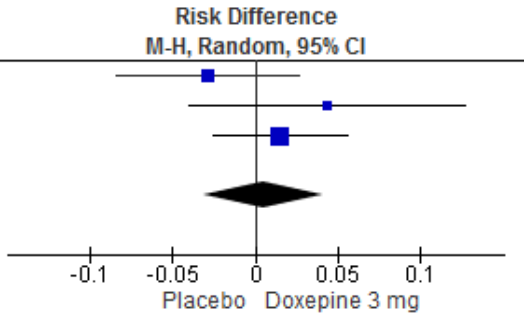

Figure S62 – Meta-analysis of data for the occurrence of diarrhea in response to doxepin 3 mg

Study or Subgroup	Doxepin 3 mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Krystal 2010	0	70	1	70	51.5%	-0.01 [-0.05, 0.02]
Krystal 2011	1	68	0	67	48.5%	0.01 [-0.03, 0.05]
Total (95% CI)		**138**		**137**	**100.0%**	**-0.00 [-0.03, 0.03]**
Total events	1		1			

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

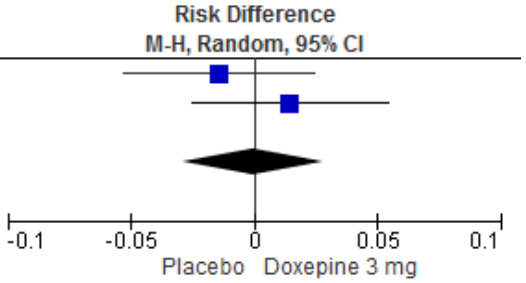

Figure S63 – Meta-analysis of data for the occurrence of upper respiratory tract infection in response to doxepin 3 mg

Study or Subgroup	Doxepin 3 mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Krystal 2010	1	70	1	70	61.4%	0.00 [-0.04, 0.04]
Krystal 2011	2	68	1	67	38.6%	0.01 [-0.04, 0.06]
Total (95% CI)		**138**		**137**	**100.0%**	**0.01 [-0.03, 0.04]**
Total events	3		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.36 (P = 0.72)

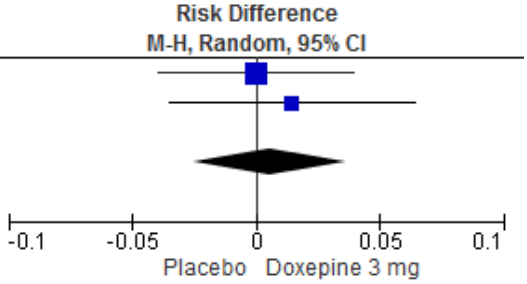

Table S15 – Summary of Findings table for doxepin 3 mg for the treatment of chronic insomnia

References: Krystal 2010(A); Krystal 2011(B); Roth 2007(C); Scharf 2008(D)

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 3 mg Doxepin vs Placebo	No of Participants (studies)
Sleep Latency* (PSG)	⊕⊕⊕⊖ **moderate**[1]	The mean sleep latency in the doxepin groups was **2.3 minutes lower** (6.22 lower to 1.62 higher)	558 (4 studies)[A,B,C,D]
Sleep Latency (Subjective)	⊕⊕⊖⊖ **low**[1,6]	The mean sleep latency in the doxepin groups was **9.35 minutes lower** (21.89 lower to 3.19 higher)	291 (2 studies)[A,D]
Total Sleep Time* (PSG)	⊕⊕⊖⊖ **low**[1,3]	The mean total sleep time in the doxepin groups was **26.14 minutes higher** (18.49 to 33.79 higher)	558 (4 studies)[A,B,C,D]
Total Sleep Time (Subjective)	⊕⊖⊖⊖ **very low**[1,7,8]	The mean total sleep time in the doxepin groups was **43.57 minutes higher** (5.16 to 81.98 higher)	291 (2 studies)[A,D]
Wake After Sleep Onset* (PSG)	⊕⊕⊖⊖ **low**[1,2]	The mean wake after sleep onset in the doxepin groups was **22.17 minutes lower** (29.62 to 14.72 lower)	558 (4 studies)[A,B,C,D]
Wake After Sleep Onset (Subjective)	⊕⊕⊖⊖ **low**[1,9]	The mean wake after sleep onset in the doxepin group was **20.0 minutes lower** (39.07 to 0.92 lower)	147 (1 study)[D]
Quality of Sleep* (Subjective)	⊕⊕⊖⊖ **low**[1,5]	The mean quality of sleep in the doxepin groups was **0.57 standard deviations higher** (0.26 to 0.88 higher)	291 (2 studies)[A,D]
Sleep Efficiency (PSG)	⊕⊕⊖⊖ **low**[1,4]	The mean sleep efficiency in the doxepin groups was **6.78 percent higher** (4.5 to 9.07 higher)	423 (3 studies)[A,C,D]
Number of Awakenings (PSG)	⊕⊕⊕⊖ **moderate**[1]	The mean number of awakenings in the doxepin groups was **0.53 awakenings higher** (0.37 lower to 1.42 higher)	423 (3 studies)[A,C,D]

* 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 (I^2 = 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

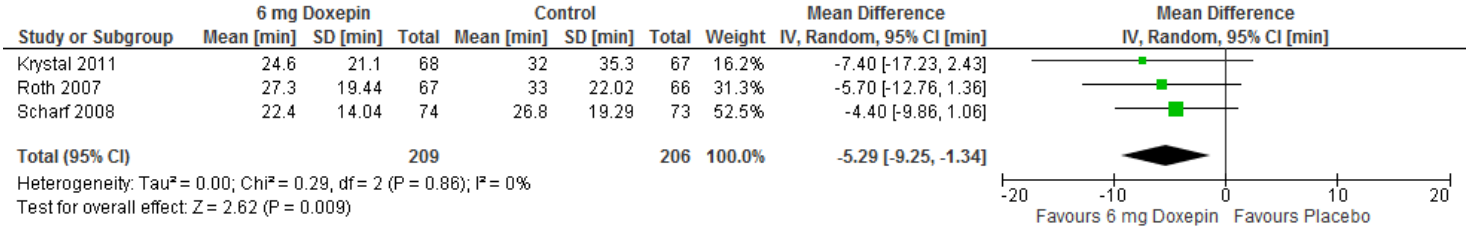

Figure S65 – Meta-analysis of data for PSG-determined total sleep time in response to doxepin 6 mg

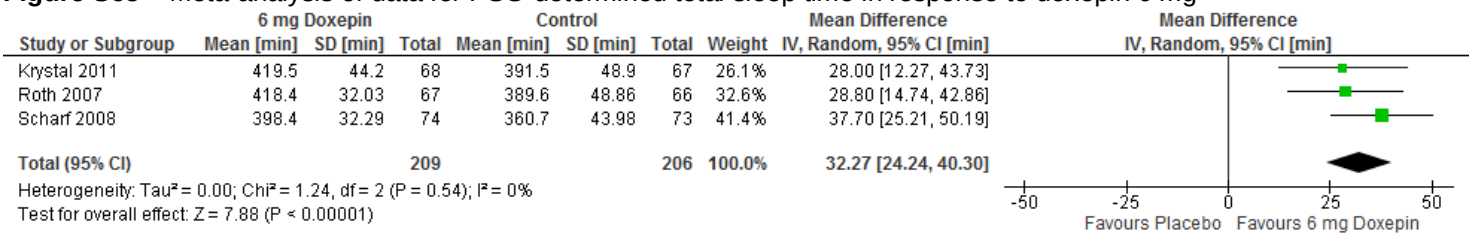

Figure S66 – Meta-analysis of data for subjectively-determined total sleep time in response to doxepin 6 mg

Study or Subgroup	6 mg Doxepin Mean [min]	SD [min]	Total	Control Mean [min]	SD [min]	Total	Weight	Mean Difference IV, Random, 95% CI [min]
Lankford 2012	346.1	66.4	130	336.4	64.7	124	56.7%	9.70 [-6.42, 25.82]
Scharf 2008	370.8	64.59	74	340	71.79	73	43.3%	30.80 [8.71, 52.89]
Total (95% CI)			**204**			**197**	**100.0%**	**18.84 [-1.65, 39.34]**

Heterogeneity: Tau² = 125.28; Chi² = 2.29, df = 1 (P = 0.13); I² = 56%
Test for overall effect: Z = 1.80 (P = 0.07)

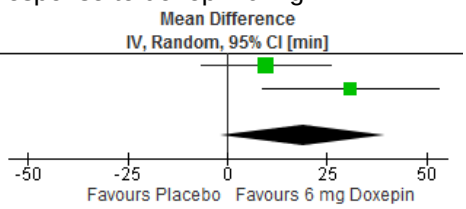

Figure S67 – Meta-analysis of data for PSG-determined wake after sleep onset in response to doxepin 6 mg

Study or Subgroup	6 mg Doxepin Mean [min]	SD [min]	Total	Control Mean [min]	SD [min]	Total	Weight	Mean Difference IV, Random, 95% CI [min]
Krystal 2011	40.7	37.3	68	60.5	38.8	67	29.2%	-19.80 [-32.64, -6.96]
Roth 2007	38.1	25.16	67	61.1	45.79	66	30.4%	-23.00 [-35.58, -10.42]
Scharf 2008	59.5	28.3	74	85.8	38.39	73	40.4%	-26.30 [-37.21, -15.39]
Total (95% CI)			**209**			**206**	**100.0%**	**-23.40 [-30.34, -16.46]**

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 6.61 (P < 0.00001)

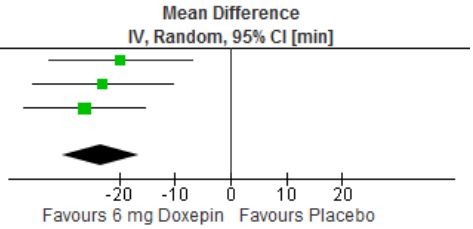

Figure S68 – Meta-analysis of data for subjectively-determined wake after sleep onset in response to doxepin 6 mg

Study or Subgroup	6 mg Doxepin Mean [min]	SD [min]	Total	Control Mean [min]	SD [min]	Total	Weight	Mean Difference IV, Random, 95% CI [min]
Lankford 2012	66.5	43.9	130	78.9	56.5	124	70.3%	-12.40 [-24.88, 0.08]
Scharf 2008	70.2	57.08	74	89.3	61.56	73	29.7%	-19.10 [-38.30, 0.10]
Total (95% CI)			**204**			**197**	**100.0%**	**-14.39 [-24.86, -3.93]**

Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 2.70 (P = 0.007)

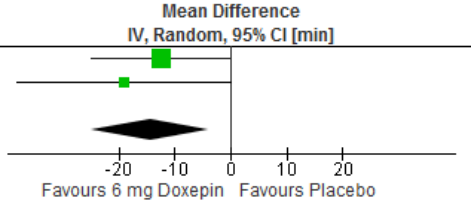

Figure S69 – Meta-analysis of data for subjectively-determined quality of sleep in response to doxepin 6 mg

Study or Subgroup	6 mg Doxepin Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Lankford 2012	0.4	1	130	0.2	1.1	127	61.9%	0.19 [-0.06, 0.43]
Scharf 2008	0.9	0.92	74	0.5	0.99	73	38.1%	0.42 [0.09, 0.74]
Total (95% CI)			**204**			**200**	**100.0%**	**0.28 [0.06, 0.49]**

Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 1 (P = 0.28); I² = 15%
Test for overall effect: Z = 2.51 (P = 0.01)

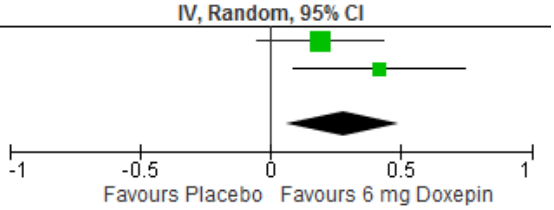

Figure S70 – Meta-analysis of data for PSG-determined sleep efficiency in response to doxepin 6 mg

Study or Subgroup	6 mg Doxepin Mean [%]	SD [%]	Total	Control Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Random, 95% CI [%]
Roth 2007	87.2	6.67	67	81.2	10.18	66	44.1%	6.00 [3.07, 8.93]
Scharf 2008	83	6.73	74	75.1	9.16	73	55.9%	7.90 [5.30, 10.50]
Total (95% CI)			**141**			**139**	**100.0%**	**7.06 [5.12, 9.01]**

Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 7.12 (P < 0.00001)

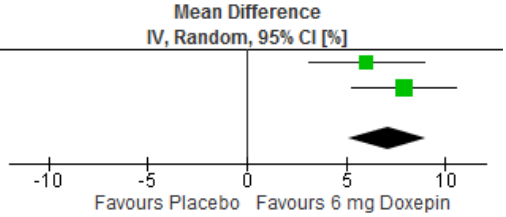

Figure S71 – Meta-analysis of data for PSG-determined number of awakenings in response to doxepin 6 mg

Study or Subgroup	6 mg Doxepin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Roth 2007	9	4.1	67	8.7	3.86	66	54.8%	0.30 [-1.05, 1.65]
Scharf 2008	12.5	4.76	74	11.9	4.45	73	45.2%	0.60 [-0.89, 2.09]
Total (95% CI)			**141**			**139**	**100.0%**	**0.44 [-0.57, 1.44]**

Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.39)

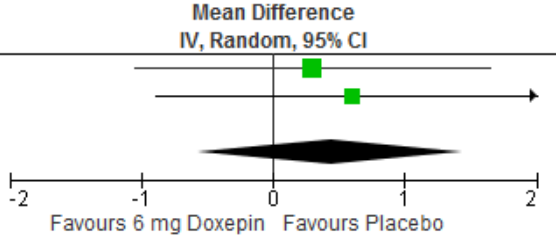

Figure S72 – Meta-analysis of data for the occurrence of headache in response to doxepin 6 mg

Study or Subgroup	Doxepin 6 mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Krystal 2011	0	68	6	67	15.8%	-0.09 [-0.16, -0.02]
Lankford 2012	0	130	5	124	59.5%	-0.04 [-0.08, -0.00]
Roth 2007	1	66	3	66	24.6%	-0.03 [-0.09, 0.03]
Total (95% CI)		**264**		**257**	**100.0%**	**-0.05 [-0.07, -0.02]**
Total events	1		14			

Heterogeneity: Tau² = 0.00; Chi² = 1.86, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 3.09 (P = 0.002)

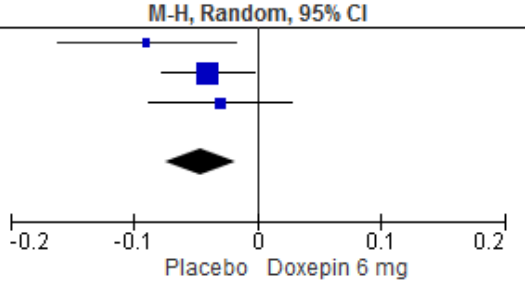

Figure S73 – Meta-analysis of data for the occurrence of somnolence in response to doxepin 6 mg

Study or Subgroup	Doxepin 6 mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Krystal 2011	5	68	3	67	18.6%	0.03 [-0.05, 0.11]
Lankford 2012	12	130	4	124	34.1%	0.06 [0.00, 0.12]
Roth 2007	2	66	0	66	47.3%	0.03 [-0.02, 0.08]
Total (95% CI)		**264**		**257**	**100.0%**	**0.04 [0.01, 0.07]**
Total events	19		7			

Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 2.30 (P = 0.02)

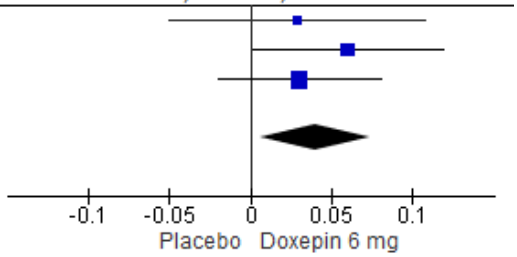

Table S16 – Summary of Findings table for doxepin 6 mg for the treatment of chronic insomnia

References: Krystal 2011(A); Roth 2007(B); Lankford 2012(C); Scharf 2008(D)

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 6 mg Doxepin vs Placebo	No of Participants (studies)
Sleep Latency* (PSG)	⊕⊕⊕⊖ **moderate**[1]	The mean sleep latency in the doxepin groups was **5.29 minutes lower** (9.25 to 1.34 lower)	415 (3 studies)[A,B,D]
Total Sleep Time* (PSG)	⊕⊕⊕⊖ **moderate**[1]	The mean total sleep time in the doxepin groups was **32.27 minutes higher** (24.24 to 40.3 higher)	415 (3 studies)[A,B,D]
Total Sleep Time (Subjective)	⊕⊕⊖⊖ **low**[1,3]	The mean total sleep time in the doxepin groups was **18.84 minutes higher** (1.65 lower to 39.34 higher)	401 (2 studies)[C,D]
Wake After Sleep Onset* (PSG)	⊕⊕⊖⊖ **low**[1,2]	The mean wake after sleep onset in the doxepin groups was **23.4 minutes lower** (30.34 to 16.46 lower)	415 (3 studies)[A,B,D]
Wake After Sleep Onset (Subjective)	⊕⊕⊕⊖ **moderate**[1]	The mean wake after sleep onset in the doxepin groups was **14.39 minutes lower** (24.86 to 3.93 lower)	401 (2 studies)[C,D]
Quality of Sleep* (Subjective)	⊕⊕⊕⊖ **moderate**[1]	The mean quality of sleep in the doxepin groups was **0.28 standard deviations higher** (0.06 to 0.49 higher)	404 (2 studies)[C,D]
Sleep Efficiency (PSG)	⊕⊕⊕⊖ **moderate**[1]	The mean sleep efficiency in the doxepin groups was **7.06 percent higher** (5.12 to 9.01 higher)	280 (2 studies)[B,D]
Number of Awakenings (PSG)	⊕⊕⊕⊖ **moderate**[1]	The mean number of awakenings in the doxepin groups was **0.44 awakenings higher** (0.57 lower to 1.44 higher)	280 (2 studies)[B,D]

* 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)

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

* 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

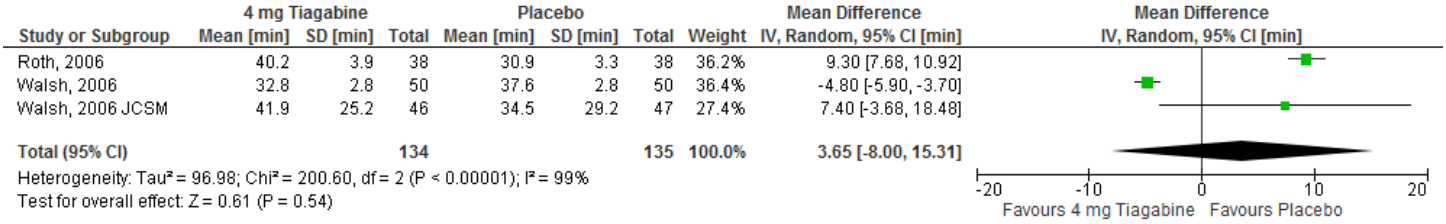

Figure S75 – Meta-analysis of data for subjectively-determined sleep latency in response to tiagabine 4 mg

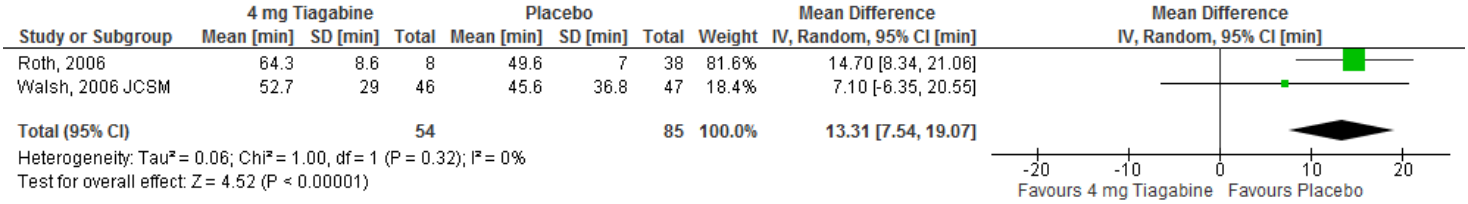

Figure S76 – Meta-analysis of data for PSG-determined total sleep time in response to tiagabine 4 mg

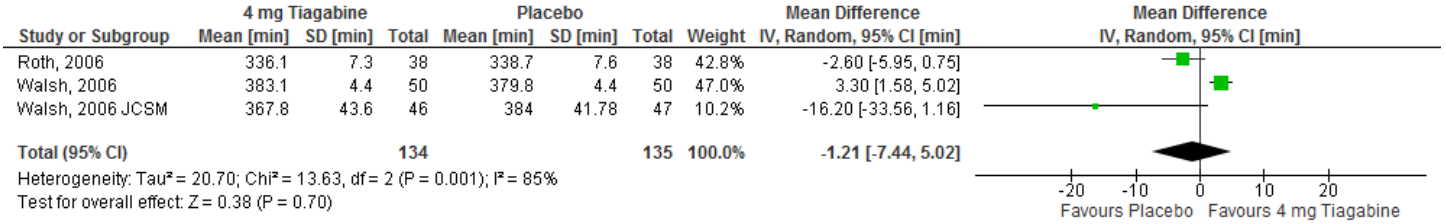

Figure S77 – Meta-analysis of data for subjectively-determined total sleep time in response to tiagabine 4 mg

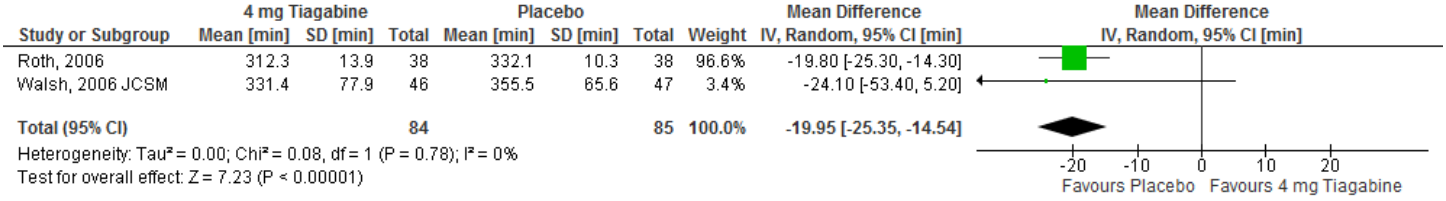

Figure S78 – Meta-analysis of data for PSG-determined wake after sleep onset in response to tiagabine 4 mg

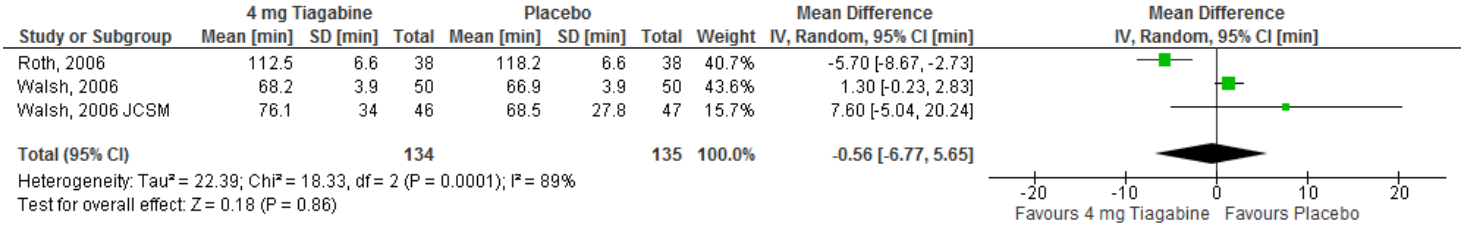

Figure S79 – Meta-analysis of data for subjectively-determined wake after sleep onset in response to tiagabine 4 mg

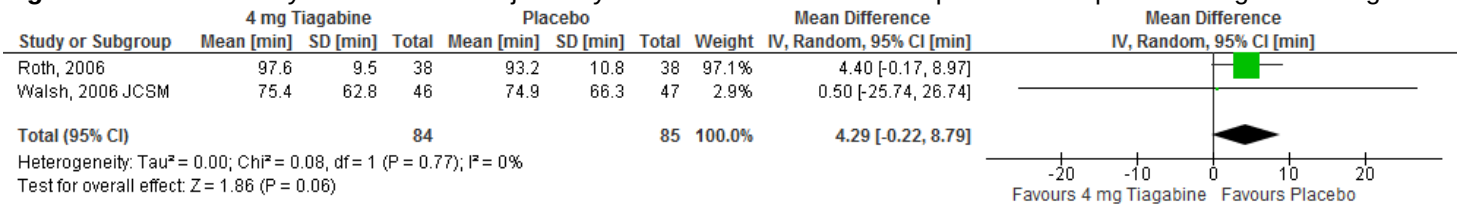

Figure S80 – Meta-analysis of data for subjectively-determined quality of sleep in response to tiagabine 4 mg

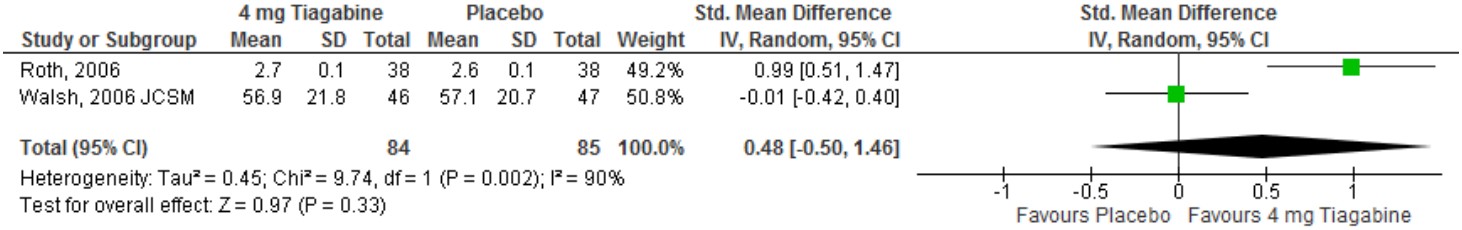

Figure S81 – Meta-analysis of data for PSG-determined sleep efficiency in response to tiagabine 4 mg

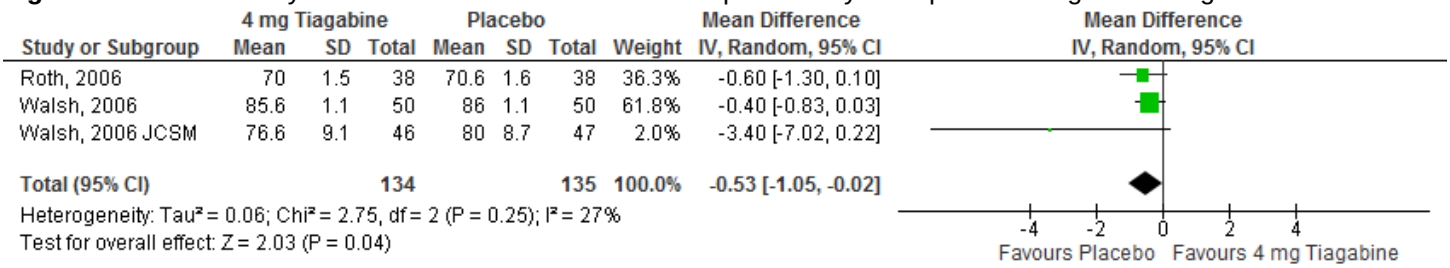

Figure S82 – Meta-analysis of data for PSG-determined number of awakenings in response to tiagabine 4 mg

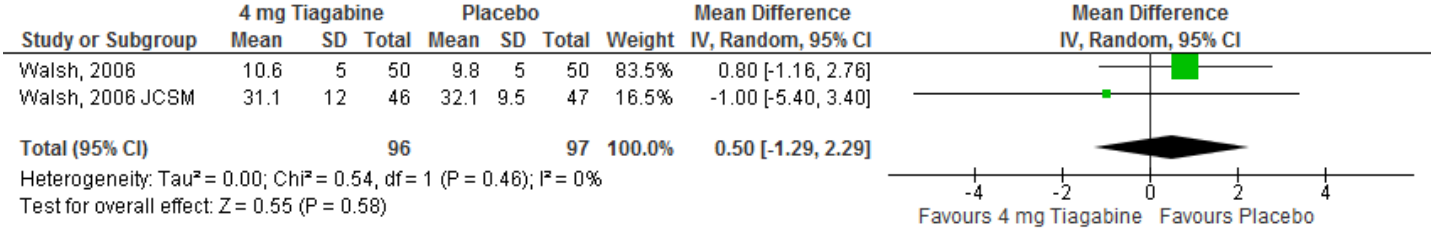

Figure S83 – Meta-analysis of data for subjectively-determined number of awakenings in response to tiagabine 4 mg

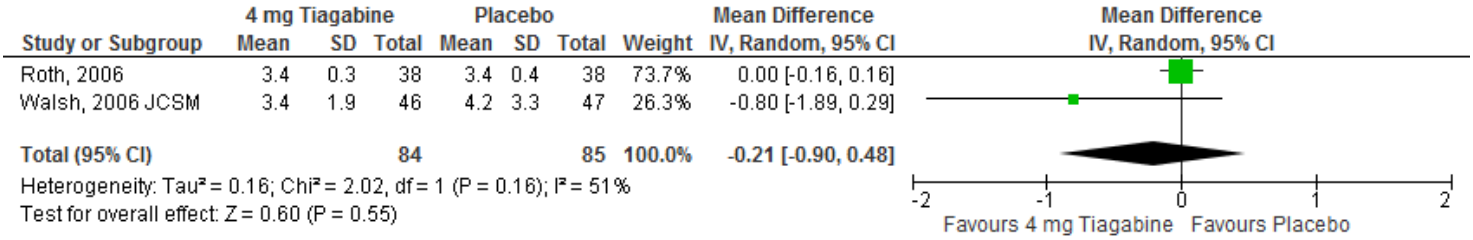

Figure S84 – Meta-analysis of data for the occurrence of headache in response to tiagabine 4 mg

Study or Subgroup	Tiagabine 4 mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Roth 2006	1	38	1	38	43.6%	0.00 [-0.07, 0.07]
Walsh JCSM 2006	4	46	2	47	22.7%	0.04 [-0.06, 0.14]
Walsh SLEEP 2006	2	51	3	53	33.7%	-0.02 [-0.10, 0.06]
Total (95% CI)		**135**		**138**	**100.0%**	**0.00 [-0.04, 0.05]**
Total events	7		6			

Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.86)

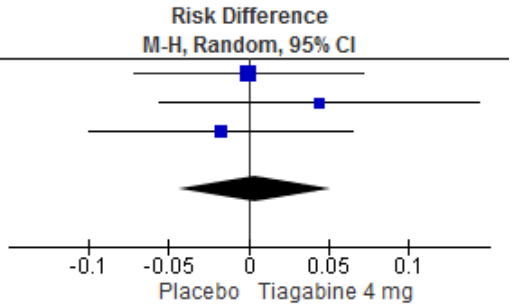

Figure S85 – Meta-analysis of data for the occurrence of nausea in response to tiagabine 4 mg

Study or Subgroup	Tiagabine 4 mg Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Roth 2006	1	38	0	38	16.5%	0.03 [-0.04, 0.10]
Walsh JCSM 2006	1	46	0	47	24.1%	0.02 [-0.04, 0.08]
Walsh SLEEP 2006	0	51	0	53	59.4%	0.00 [-0.04, 0.04]
Total (95% CI)		**135**		**138**	**100.0%**	**0.01 [-0.02, 0.04]**
Total events	2		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 2 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)

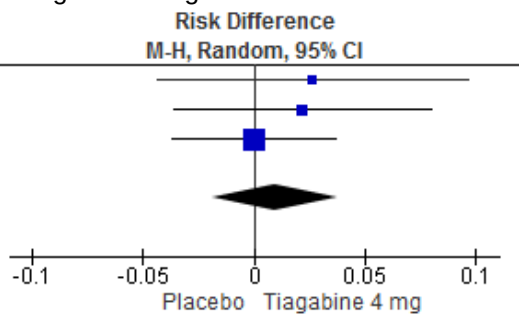

Table S18 – Summary of Findings table for tiagabine 4 mg for the treatment of chronic insomnia

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

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 4 mg Tiagabine vs Placebo	No of Participants (studies)
Sleep Latency (PSG)	⊕⊖⊖⊖ **very low**[1,2,3]	The mean sleep latency in the tiagabine groups was **3.65 minutes higher** (8 lower to 15.31 higher)	269 (3 studies)[A,B,C]
Sleep Latency (Subjective)	⊕⊕⊕⊖ **moderate**[3]	The mean sleep latency in the tiagabine groups was **13.31 minutes higher** (7.54 to 19.07 higher)	139 (2 studies)[A,C]
Total Sleep Time* (PSG)	⊕⊕⊖⊖ **low**[3,5]	The mean total sleep time in the tiagabine groups was **1.21 minutes lower** (7.44 lower to 5.02 higher)	269 (3 studies)[A,B,C]
Total Sleep Time (Subjective)	⊕⊕⊕⊖ **moderate**[3]	The mean total sleep time in the tiagabine groups was **19.95 minutes lower** (25.35 to 14.54 lower)	169 (2 studies)[A,C]
Wake After Sleep Onset* (PSG)	⊕⊕⊖⊖ **low**[3,4]	The mean wake after sleep onset in the tiagabine groups was **0.56 minutes lower** (6.77 lower to 5.65 higher)	269 (3 studies)[A,B,C]
Wake After Sleep Onset (Subjective)	⊕⊕⊕⊖ **moderate**[3]	The mean wake after sleep onset in the tiagabine groups was **4.29 minutes higher** (0.22 lower to 8.79 higher)	169 (2 studies)[A,C]
Quality of Sleep* (Subjective)	⊕⊖⊖⊖ **very low**[3,7,8]	The mean quality of sleep in the tiagabine groups was **0.48 standard deviations higher** (0.5 lower to 1.46 higher)	169 (2 studies)[A,C]
Sleep Efficiency (PSG)	⊕⊕⊕⊖ **moderate**[3]	The mean sleep efficiency in the tiagabine groups was **0.53 percent lower** (1.05 to 0.02 lower)	269 (3 studies)[A,B,C]
Number of Awakenings (PSG)	⊕⊕⊖⊖ **low**[3,6]	The mean number of awakenings in the tiagabine groups was **0.5 awakenings higher** (1.29 lower to 2.29 higher)	193 (2 studies)[B,C]
Number of Awakenings (Subjective)	⊕⊕⊖⊖ **low**[3,9]	The mean number of awakenings in the tiagabine groups was **0.21 awakenings lower** (0.9 lower to 0.48 higher)	169 (2 studies)[A,C]

* Critical Outcome, used to determine Quality of Evidence
[1] Heterogeneity (I^2 = 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 (I^2 = 89%) greater than allowance (75%)
[5] Heterogeneity (I^2 = 85%) greater than allowance (75%)
[6] 95% CI (-1.29, 2.29) crosses Clinical Significance (2 awakenings)
[7] Heterogeneity (I^2 = 90%) greater than allowance (75%)
[8] 95% CI (-0.50, 1.46) 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)

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 6 mg Tiagabine vs Placebo	No of Participants (studies)
Sleep Latency (PSG)	⊕⊕⊖⊖ **low**[3,7]	The mean sleep latency in the tiagabine groups was **6.9 minutes higher** (2.22 to 11.58 higher)	175 (2 studies) [A,B]
Sleep Latency (Subjective)	⊕⊕⊕⊖ **moderate**[3]	The mean sleep latency in the tiagabine groups was **5.68 minutes higher** (3.05 to 8.3 higher)	175 (2 studies) [A,B]
Total Sleep Time* (PSG)	⊕⊕⊕⊖ **moderate**[3]	The mean total sleep time in the tiagabine groups was **7.17 minutes higher** (0.26 lower to 14.59 higher)	175 (2 studies) [A,B]
Total Sleep Time (Subjective)	⊕⊕⊕⊖ **moderate**[3]	The mean total sleep time in the tiagabine groups was **9.65 minutes lower** (14.05 to 5.25 lower)	175 (2 studies) [A,B]
Wake After Sleep Onset* (PSG)	⊕⊖⊖⊖ **very low**[1,2,3]	The mean wake after sleep onset in the tiagabine groups was **9.24 minutes lower** (24.78 lower to 6.3 higher)	175 (2 studies) [A,B]
Wake After Sleep Onset (Subjective)	⊕⊕⊕⊖ **moderate**[3]	The mean wake after sleep onset in the tiagabine groups was **5.68 minutes higher** (3.05 to 8.3 higher)	175 (2 studies) [A,B]
Quality of Sleep* (Subjective)	⊕⊕⊖⊖ **low**[3,4]	The mean quality of sleep in the tiagabine groups was **0.01 standard deviations higher** (0.28 lower to 0.31 higher)	175 (2 studies) [A,B]
Sleep Efficiency (PSG)	⊕⊕⊕⊖ **moderate**[3]	The mean sleep efficiency in the tiagabine groups was **1.46 percent higher** (0.15 lower to 3.06 higher)	175 (2 studies) [A,B]
Number of Awakenings (Subjective)	⊕⊖⊖⊖ **very low**[3,5,6]	The mean number of awakenings in the tiagabine groups was **0.49 awakenings lower** (1.84 lower to 0.87 higher)	175 (2 studies) [A,B]

* Critical Outcome, used to determine Quality of Evidence
[1] Heterogeneity (I^2 = 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 (I^2 = 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)

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 6 mg Tiagabine vs Placebo	No of Participants (studies)
Sleep Latency (PSG)	⊕⊕⊕⊖ **moderate**[1]	The mean sleep latency in the tiagabine groups was **1.22 minutes lower** (2.66 lower to 0.22 higher)	271 (3 studies) [A,B,C]
Sleep Latency (Subjective)	⊕⊕⊕⊖ **moderate**[1]	The mean sleep latency in the tiagabine groups was **2.12 minutes lower** (3.48 to 0.76 lower)	171 (2 studies) [A,C]
Total Sleep Time* (PSG)	⊕⊕⊖⊖ **low**[1,3]	The mean total sleep time in the tiagabine groups was **3.49 minutes higher** (6.43 lower to 13.42 higher)	271 (3 studies) [A,B,C]
Total Sleep Time (Subjective)	⊕⊖⊖⊖ **very low**[1,7,8]	The mean total sleep time in the tiagabine groups was **16.09 minutes lower** (44.97 lower to 12.79 higher)	171 (2 studies) [A,C]
Wake After Sleep Onset* (PSG)	⊕⊕⊖⊖ **low**[1,2]	The mean wake after sleep onset in the tiagabine groups was **2.42 minutes lower** (10.35 lower to 5.51 higher)	271 (3 studies) [A,B,C]
Wake After Sleep Onset (Subjective)	⊕⊕⊕⊖ **moderate**[1]	The mean wake after sleep onset in the tiagabine groups was **9.71 minutes higher** (5.7 to 13.72 higher)	171 (2 studies) [A,C]
Quality of Sleep* (Subjective)	⊕⊖⊖⊖ **very low**[1,5,6]	The mean quality of sleep in the tiagabine groups was **0.37 standard deviations higher** (0.65 lower to 1.39 higher)	171 (2 studies) [A,C]
Sleep Efficiency (PSG)	⊕⊕⊖⊖ **low**[1,3]	The mean sleep efficiency in the tiagabine groups was **0.68 percent higher** (1.41 lower to 2.76 higher)	271 (3 studies) [A,B,C]
Number of Awakenings (PSG)	⊕⊕⊖⊖ **low**[1,4]	The mean number of awakenings in the tiagabine groups was **0.88 awakenings lower** (3.7 lower to 1.95 higher)	192 (2 studies) [B,C]
Number of Awakenings (Subjective)	⊕⊕⊖⊖ **low**[1,9]	The mean number of awakenings in the tiagabine groups was **0.3 awakenings higher** (0.38 lower to 0.98 higher)	171 (2 studies) [A,C]

* Critical Outcome, used to determine Quality of Evidence
[1] All studies funded by industry
[2] Heterogeneity (I^2 = 93%) greater than allowance (75%)
[3] Heterogeneity (I^2 = 94%) greater than allowance (75%)
[4] 95% CI (-3.70, 1.95) crosses Clinical Significance (2 awakenings)
[5] Heterogeneity (I^2 = 91%) greater than allowance (75%)
[6] 95% CI (-0.65, 1.39) crosses zero standard mean difference
[7] Heterogeneity (I^2 = 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)

Diphenhydramine - Meta-Analyses and Summary of Findings Table

Figure S86 – Meta-analysis of data for subjectively-determined sleep latency in response to diphenhydramine 50 mg

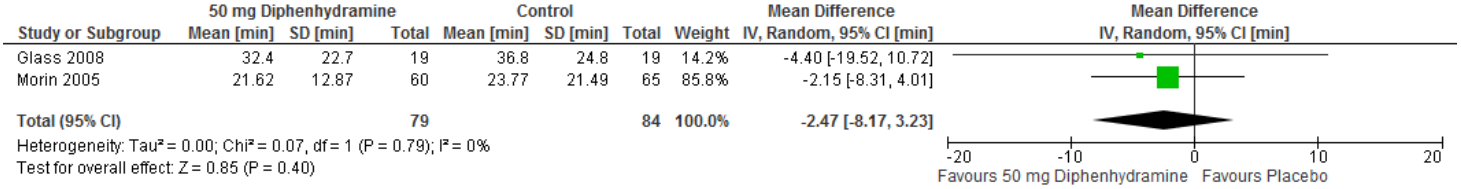

Figure S87 – Meta-analysis of data for subjectively-determined total sleep time in response to diphenhydramine 50 mg

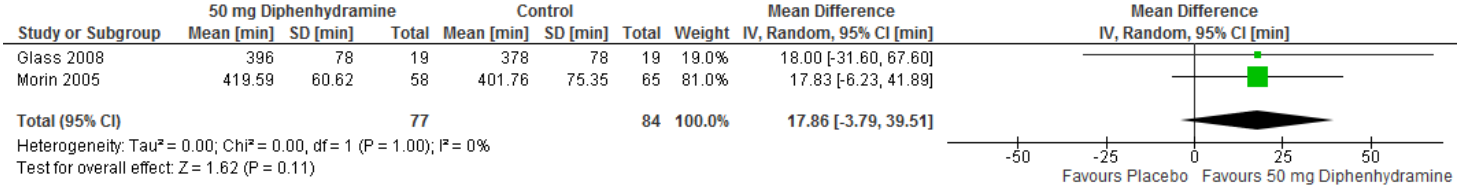

Table S21 – Summary of Findings table for diphenhydramine 50 mg for the treatment of chronic insomnia

References: Glass 2008(A); Morin 2005(B)

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 50 mg Diphenhydramine vs Placebo	No of Participants (studies)
Sleep Latency* (PSG)	⊕⊕⊖⊖ **low**[5,7]	The mean sleep latency in the diphenhydramine group was **7.89 minutes lower** (17.40 lower to 1.62 higher)	52 (1 study)[A]
Sleep Latency (Subjective)	⊕⊕⊖⊖ **low**[1,2]	The mean sleep latency in the diphenhydramine groups was **2.47 minutes lower** (8.17 lower to 3.23 higher)	163 (2 studies)[A,B]
Total Sleep Time* (PSG)	⊕⊕⊖⊖ **low**[5,8]	The mean total sleep time in the diphenhydramine group was **12.37 minutes higher** (13.38 lower to 38.12 higher)	52 (1 study)[A]
Total Sleep Time (Subjective)	⊕⊕⊖⊖ **low**[1,2]	The mean total sleep time in the diphenhydramine groups was **17.86 minutes higher** (3.79 lower to 39.51 higher)	161 (2 studies)[A,B]
Quality of Sleep* (Subjective)	⊕⊕⊕⊖ **moderate**[5]	The mean quality of sleep in the diphenhydramine group was **0.1 points**[9] **higher** (0.45 lower to 0.65 higher)	38 (1 study)[A]
Sleep Efficiency (PSG)	⊕⊕⊖⊖ **low**[4,5]	The mean sleep efficiency in the diphenhydramine group was **2.59 percent higher** (3.25 lower to 8.43 higher)	52 (1 study)[B]
Sleep Efficiency (Subjective)	⊕⊕⊕⊖ **moderate**[5]	The mean sleep efficiency in the diphenhydramine group was **4.61 percent higher** (1.33 to 7.88 higher)	123 (1 study)[A]
Number of Awakenings (Subjective)	⊕⊕⊕⊖ **moderate**[3]	The mean number of awakenings in the diphenhydramine group was **0.3 awakenings lower** (1.03 lower to 0.43 higher)	38 (1 study)[A]

* Critical Outcome, used to determine Quality of Evidence
[1] SL and TST 95% Ci cross Clinical Significance
[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

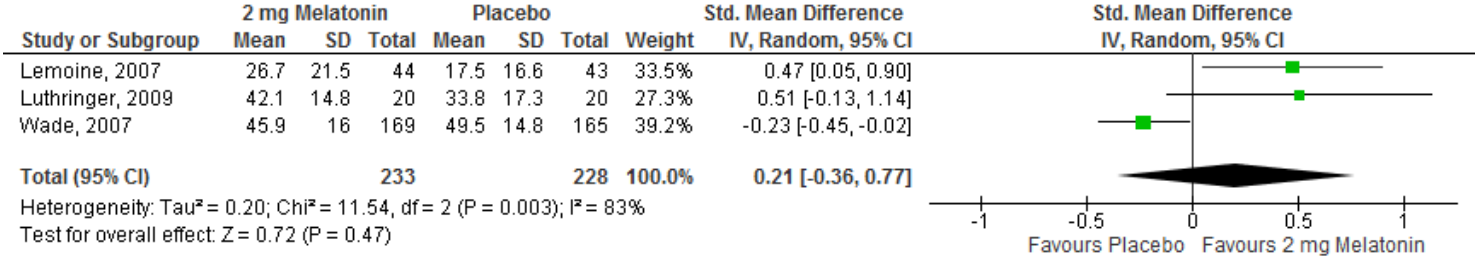

Table S22 – Summary of Findings table for melatonin 2 mg for the treatment of chronic insomnia

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

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 2 mg Melatonin vs Placebo	No of Participants (studies)
Sleep Latency* (PSG)	⊕⊕⊖⊖ **low**[3,4]	The mean sleep latency in the melatonin group was **8.9 minutes lower** (15.45 to 2.35 lower)	40 (1 study)[B]
Total Sleep Time (PSG)	⊕⊖⊖⊖ **very low**[3,6]	The mean total sleep time in the melatonin group was **2.2 minutes higher** (19.13 lower to 23.53 higher)	40 (1 study)[B]
Wake After Sleep Onset (PSG)	⊕⊕⊖⊖ **low**[3,5]	The mean wake after sleep onset in the melatonin group was **8.5 minutes higher** (11.75 lower to 28.75 higher)	40 (1 study)[B]
Quality of Sleep* (Subjective)	⊕⊖⊖⊖ **very low**[1,2,3]	The mean quality of sleep in the melatonin group was **0.21 standard deviations higher** (0.36 lower to 0.77 higher)	461 (3 studies)[A,B,C]
Number of Awakenings (PSG)	⊕⊖⊖⊖ **very low**[3,7]	The mean number of awakenings in the melatonin group was **1.4 awakenings higher** (4.59 lower to 7.39 higher)	40 (1 study)[B]

* 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

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 250 mg Tryptophan vs Placebo	No of Participants (studies)
Wake After Sleep Onset* (Subjective)	⊕⊕⊕⊕ **high**	The mean wake after sleep onset in the Tryptophan groups was **9.70 minutes lower** (15.21 to 4.18 lower)	31 (1 study)
Total Sleep Time (Subjective)	⊕⊕⊕⊖ **moderate**[1]	The mean total sleep time in the Tryptophan groups was **20.00 minutes lower** (31.29 to 8.7 lower)	32 (1 study)
Quality of Sleep* (Subjective)	⊕⊕⊕⊕ **high**	The mean quality of sleep in the Tryptophan groups was **0.30 points**[2] **higher** (0.22 to 0.37 higher)	32 (1 study)
Sleep Efficiency (Subjective)	⊕⊕⊕⊕ **high**	The mean sleep efficiency in the Tryptophan groups was **2.20 percent lower** (4.27 to 0.12 lower)	32 (1 study)

* 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)

Outcomes	Quality of the evidence (GRADE)	Absolute Difference Valerian-hops vs Placebo	No of Participants (studies)
Sleep Latency* (PSG)	⊕⊕⊖⊖ **low**[1,2]	The mean sleep latency in the Valerian-hops groups was **9.29 minutes lower** (18.3 to 0.27 lower)	48 (1 study) [A]
Sleep Latency (Subjective)	⊕⊕⊕⊖ **moderate**[2]	The mean sleep latency in the Valerian-hops groups was **3.77 minutes higher** (4.47 lower to 12.01 higher)	124 (1 study) [A]
Total Sleep Time (PSG)	⊕⊖⊖⊖ **very low**[2,3]	The mean total sleep time in the Valerian-hops groups was **10.96 minutes higher** (21.67 lower to 43.59 higher)	48 (1 study) [A]
Total Sleep Time (Subjective)	⊕⊕⊕⊖ **moderate**[2]	The mean total sleep time in the Valerian-hops groups was **3.12 minutes higher** (22.08 lower to 28.32 higher)	123 (1 study) [A]
Sleep Efficiency (PSG)	⊕⊖⊖⊖ **very low**[2,4]	The mean sleep efficiency in the Valerian-hops groups was **0.96 percent higher** (5.02 lower to 6.94 higher)	48 (1 study) [A]
Sleep Efficiency (Subjective)	⊕⊕⊕⊖ **moderate**[2]	The mean sleep efficiency in the Valerian-hops groups was **1.85 percent higher** (1.9 lower to 5.6 higher)	123 (1 study) [A]

* 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%)