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*	⊕⊕⊖⊖	The mean sleep latency in the suvorexant group was 2.3 minutes lower (13.68 lower to 9.08 higher)	175		
(PSG)	low ^{1,2}		(1 study) ^A		
Wake After Sleep Onset*	⊕⊕⊖	The mean wake after sleep onset in the suvorexant group was 21.5 minutes lower (36.34 to 6.66 lower)	175		
(PSG)	low ^{2,3}		(1 study) ^A		
Sleep Efficiency	⊕⊕⊖⊖	The mean sleep efficiency in the suvorexant group was 4.7 percent higher (0.97 to 8.43 higher)	175		
(PSG)	low ^{2,4}		(1 study) ^A		

^{*} Critical Outcome, used to determine Quality of Evidence

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*	⊕⊕⊖⊖	The mean sleep latency in the suvorexant group was 8.1 minutes lower (13.85 to 2.35 lower)	423
(PSG)	low ^{1,2}		(1 study) ^A
Sleep Latency	⊕⊕⊕⊖	The mean sleep latency in the suvorexant group was 5.2 minutes lower (10.1 to 0.3 lower)	567
(Subjective)	moderate ²		(1 study) ^A
Total Sleep Time*	⊕⊕⊕⊖	The mean total sleep time in the suvorexant group was 10.6 minutes higher (1.79 to 19.41 higher)	567
(Subjective)	moderate ²		(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 (-13.68 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%)

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*	⊕⊕⊕⊝	The mean sleep latency in the suvorexant group was 22.3 minutes lower (33.77 to 10.83 lower)	173		
(PSG)	moderate²		(1 study) ^A		
Wake After Sleep Onset*	⊕⊕⊖⊖	The mean wake after sleep onset in the suvorexant group was 28.1 minutes lower (43.07 to 13.13 lower)	173		
(PSG)	low ^{1,2}		(1 study) ^A		
Sleep Efficiency	⊕⊕⊕⊝	The mean sleep efficiency in the suvorexant group was 10.4 percent higher (6.65 to 14.15 higher)	173		
(PSG)	moderate²		(1 study) ^A		

Eszopicione - Meta-Analyses and Summary of Findings Tables

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

	2 mg Eszopiclone Placebo							Mean Difference Mean Difference			
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]		
McCall, 2006	19.3	30	133	40.8	33	122	36.2%	-21.50 [-29.26, -13.74]			
Uchimura, 2012	20.9	24.3	69	37.5	37.8	71	30.1%	-16.60 [-27.10, -6.10]			
Zammit, 2004	24	35.8	104	30.2	28.2	99	33.7%	-6.20 [-15.04, 2.64]			
Total (95% CI)			306			292	100.0%	-14.87 [-24.27, -5.47]			
Heterogeneity: Tau² =	47.84; Chi ² =	6.58, df = 2	-20 -10 0 10 20								
Test for overall effect:	Z = 3.10 (P = 0)	0.002)							Favours 2 mg Eszopiclone Favours Placebo		

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

	2 mg E	szopiclone		Pla	icebo		Mean Difference Mean Difference			
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]	
Ancoli-Israel, 2010	73.93	110.08	145	59.17	83.86	146	12.2%	14.76 [-7.74, 37.26]		
Erman, 2008	31.6	25.7	63	54.4	39.3	63	20.0%	-22.80 [-34.40, -11.20]		
McCall, 2006	47.8	59.4	133	77.3	55.7	122	17.9%	-29.50 [-43.63, -15.37]		
Scharf, 2005	47.9	58	79	64.7	65	80	14.2%	-16.80 [-35.94, 2.34]		
Uchimura, 2012	32.6	26.4	69	62	47.8	71	19.0%	-29.40 [-42.14, -16.66]		
Zammit, 2004	48	69.6	104	58.4	42.9	99	16.6%	-10.40 [-26.22, 5.42]		
Total (95% CI)			593			581	100.0%	-17.78 [-28.52, -7.04]	•	
Heterogeneity: Tau² =	: 115.27; Chi ² :	= 14.73, df=	-20 -10 0 10 20							
Test for overall effect:	Z = 3.25 (P = 1)	0.001)	Favours 2 mg Eszoniclone Favours Placeho							

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

•	2 mg E	Eszopiclone Placebo						Mean Difference	Mean Difference			
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]			
Erman, 2008	427.5	246.6	63	362	63.8	63	2.2%	65.50 [2.60, 128.40]				
McCall, 2006	361.9	55	133	332.6	49	122	52.3%	29.30 [16.53, 42.07]				
Scharf, 2005	379.1	68	79	346.5	73	80	17.7%	32.60 [10.67, 54.53]				
Zammit, 2004	381.8	63.8	104	363.8	63.5	99	27.8%	18.00 [0.48, 35.52]	-			
Total (95% CI)			379			364	100.0%	27.53 [18.29, 36.76]	•			
Heterogeneity: Tau² : Test for overall effect		-100 -50 0 50 100 Favours Placebo Favours 2 mg Eszopiclone										

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

	2 mg Eszopiclone Placebo						Mean Difference Mean Difference			
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]	
McCall, 2006	83.6	40.3	133	93.9	35.9	122	60.1%	-10.30 [-19.65, -0.95]		
Zammit, 2004	44.9	34.7	104	54.5	47.5	99	39.9%	-9.60 [-21.09, 1.89]		
Total (95% CI) Heterogeneity: Tau ² =	. በ በበ∙ ∩ы ≥ – በ	01 df = 1/	237	2): IZ — 0.04		221	100.0%	-10.02 [-17.27, -2.77]	_	
Test for overall effect:			r – 0.8.	3),1 = 076					-20 -10 Ö 1Ö Favours 2 mg Eszopiclone Favours Placeb	20 00

^{*} Critical Outcome, used to determine Quality of Evidence 95% CI (-43.07 to -13.13) crosses Clinical Significance Threshold (20 min)

Study funded by industry

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

	2 mg E	szopiclone		Pla	icebo			Mean Difference	Mean Difference				
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]				
Ancoli-Israel, 2010	63.58	63.05	145	68.05	54.63	146	23.6%	-4.47 [-18.03, 9.09]					
Erman, 2008	69	229.8	63	56.6	48.3	63	1.5%	12.40 [-45.58, 70.38]					
McCall, 2006	77.3	45.7	133	88.1	48.3	122	30.7%	-10.80 [-22.37, 0.77]					
Scharf, 2005	54.1	61	79	67.4	56	80	14.0%	-13.30 [-31.51, 4.91]					
Zammit, 2004	53.4	48.1	104	49.1	36.1	99	30.3%	4.30 [-7.36, 15.96]					
Total (95% CI)			524			510	100.0%	-4.74 [-11.87, 2.39]	•				
Heterogeneity: Tau² =	Heterogeneity: Tau² = 8.26; Chi² = 4.55, df = 4 (P = 0.34); l² = 12%												
Test for overall effect: Z = 1.30 (P = 0.19)									-50 -25 0 25 50 Favours 2 mg Eszopiclone Favours Placebo				

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

•	2 mg E	szopic	lone	PI	acebo			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Erman, 2008	57.2	20.9	63	44.4	19.9	63	19.7%	0.62 [0.27, 0.98]	-
Scharf, 2005	7.5	1.7	79	6.6	1.9	80	25.3%	0.50 [0.18, 0.81]	
Uchimura, 2012	6.3	1.8	69	5.2	1.9	71	22.0%	0.59 [0.25, 0.93]	
Zammit, 2004	54.4	18.7	104	49	18.1	99	33.0%	0.29 [0.02, 0.57]	
Total (95% CI)			315			313	100.0%	0.47 [0.32, 0.63]	•
Heterogeneity: Tau² = Test for overall effect:				(P = 0.4	12); I² =	: 0%		-1	-0.5 0 0.5 1 Favours Placebo Favours 2 mg Eszopiclone

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

	2 mg E	szopiclo	ne	Pla	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]	IV, Random, 95% CI [%]
McCall, 2006	79.4	9	133	73.4	9	122	56.8%	6.00 [3.79, 8.21]	
Zammit, 2004	86.2	9.6	104	82.9	11.7	99	43.2%	3.30 [0.35, 6.25]	
Total (95% CI)			237			221	100.0%	4.83 [2.21, 7.46]	
Heterogeneity: Tau² = Test for overall effect:			•	= 0.15); l ^z = :	51%				-10 -5 0 5 10 Favours Placebo Favours 2 mg Eszopiclone

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

	2 mg E	szopicio	ne	Pla	icebo			Mean Difference	Mean Difference
Study or Subgroup	Mean [#]	SD [#]	Total	Mean [#]	SD [#]	Total	Weight	IV, Random, 95% CI [#]	IV, Random, 95% CI [#]
McCall, 2006	9.1	3.3	133	9.5	3.3	122	56.5%	-0.40 [-1.21, 0.41]	
Zammit, 2004	7.3	4	104	6.5	4.5	99	43.5%	0.80 [-0.37, 1.97]	-
Total (95% CI)			237			221	100.0%	0.12 [-1.04, 1.29]	
Heterogeneity: Tau² = Test for overall effect:			f=1 (P	= 0.10); l² =	63%				-2 -1 0 1 2 Favours 2 mg Eszopiclone Favours Placebo

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

	2 mg E	szopick	one	Pla	aceb)		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Erman, 2008	3	1.4	63	3.7	2.1	63	7.9%	-0.70 [-1.32, -0.08]	
McCall, 2006	2	1	133	2.3	1	122	50.9%	-0.30 [-0.55, -0.05]	
Scharf, 2005	1.5	1.1	79	1.8	1	80	28.8%	-0.30 [-0.63, 0.03]	
Zammit, 2004	2.9	1.7	104	3.2	1.9	99	12.4%	-0.30 [-0.80, 0.20]	-
Total (95% CI)			379			364	100.0%	-0.33 [-0.51, -0.16]	•
Heterogeneity: Tau² = Test for overall effect:			•	-1 -0.5 0 0.5 1 Favours 2 mg Eszopiclone Favours Placebo					

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

	Eszopiclone	2 mg	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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; Chi ² = 1	0.93, df	= 3 (P = 0)).01); <mark>[</mark> ²	= 73%		-0.1 -0.05 0 0.05 0.1
Test for overall effect:	Z = 0.18 (P = 0.18)	0.85)					Placebo Eszopiclone 2 mg

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

	6 16 13 71 5 10 CI) 23		Place	bo		Risk Difference	Risk Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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: Test for overall effect		-	1 (P = 0.	04); l² =	: 75%		-0.1 -0.05 0 0.05 0.1 Placebo Eszopiclone 2 mg		

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

	Eszopiclone	Place	bo		Risk Difference	Risk Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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: Tau ² :	= 0.00; Chi ² = 1	.80, df=	3 (P = 0.1	61); l² =	: 0%	-	04 005 0 005 04	
Test for overall effect							-0.1 -0.05 0 0.05 0.1 Placebo Eszopiclone 2 mg	

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

	Eszopiclone	2 mg	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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: Tau ² =	= 0.00; Chi = 3	.98, df=	4 (P = 0.4)	41); l² =	: 0%		
Test for overall effect	Z = 0.72 (P =	0.47)					-0.1 -0.05 0 0.05 0.1 Placebo Eszopiclone 2 mg

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

	Eszopiclone			bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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; Chi ² = 1	9.57, df	= 4 (P = 0)	0.0006)	; I² = 80%		-0.2 -0.1 0 0.1 0.2
Test for overall effect:	Z = 2.20 (P = 1)	0.03)					Placebo Eszopiclone 2 mg

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

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

Outcomes	Quality of the evidence (GRADE)	Absolute Difference 2 mg Eszopiclone vs Placebo	No of Participants (studies)
Sleep Latency*	⊕⊕⊖⊝	The mean sleep latency in the eszopiclone groups was 14.87 minutes lower (24.27 to 5.47 lower)	598
(PSG)	low ^{1,2}		(3 studies) ^{C,E,F}
Sleep Latency	⊕⊕⊖⊝	The mean sleep latency in the eszopiclone groups was 17.78 minutes lower (28.52 to 7.04 lower)	1174
(Subjective)	low ^{2,3}		(6 studies) A,B,C,D,E,F
Total Sleep Time*	⊕⊕⊖⊝	The mean total sleep time in the eszopiclone groups was 27.53 minutes higher (18.29 to 36.76 higher)	743
(Subjective)	low ^{2,4}		(4 studies) ^{B,C,D,F}
Wake After Sleep Onset* (PSG)	⊕⊕⊕⊖ moderate²	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)	⊕⊕⊕⊖ moderate²	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*	⊕⊕⊕⊖	The mean quality of sleep in the eszopiclone groups was 0.47 standard deviations higher (0.32 to 0.63 higher)	628
(Subjective)	moderate ^{2,6}		(4 studies) ^{B,D,E,F}
Sleep Efficiency	⊕⊕⊖⊝	The mean sleep efficiency in the eszopiclone groups was 4.83 percent higher (2.21 to 7.46 higher)	458
(PSG)	low ^{2,5}		(2 studies) ^{C,F}
Sleep Efficiency	⊕⊕⊕⊖	The mean sleep efficiency in the eszopiclone groups was 0.30 percent lower (0.79 lower to 0.19 higher)	203
(Subjective)	moderate²		(1 study) ^F
Number of Awakening	⊕⊕⊕⊝	The mean number awakening in the eszopiclone groups was 0.12 awakenings higher (1.04 lower to 1.29 higher)	458
(PSG)	moderate²		(2 studies) ^{C,F}
Number of Awakenings	⊕⊕⊕⊝	The mean number of awakenings in the eszopiclone groups was 0.33 awakenings lower (0.51 to 0.16 lower)	743
(Subjective)	moderate ²		(4 studies) ^{B,C,D,F}

^{*} Critical Outcome, used to determine Quality of Evidence

^{95%} CI (-24.27, -5.47) crosses Clinical Signficance (10 min) All studies funded by industry

³ 95% CI (18.29, 36.76) crosses Clinical Signficance (20 min) ⁴ 95% CI (18.29, 36.76) crosses Clinical Signficance (20 min)

^{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

	3 mg E	szopiclone		Pla	icebo			Mean Difference	Mean Difference
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]
Boyle, 2008	6.39	1.09	31	12.95	1.4	31	38.9%	-6.56 [-7.18, -5.94]	•
Uchimura, 2012	12.8	11.2	68	37.5	37.8	71	29.2%	-24.70 [-33.89, -15.51]	
Zammit, 2004	18.1	26.1	105	30.2	28.2	99	31.9%	-12.10 [-19.57, -4.63]	
Total (95% CI)			204			201	100.0%	-13.63 [-23.56, -3.70]	
Heterogeneity: Tau² = Test for overall effect:	•	•	2 (P = 0).0002); I² = 88	3%				-20 -10 0 10 20 Favours 3 mg Eszopiclone Favours Placebo

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

	3 mg E		Pla	icebo			Mean Difference	Mean Difference			
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]		
Erman, 2008	32.9	34	64	54.4	39.3	63	25.5%	-21.50 [-34.29, -8.71]			
Krystal, 2003	47	50.6	360	96.1	94.7	111	18.7%	-49.10 [-67.48, -30.72]			
Walsh, 2007	38.1	34.8	548	59.6	49.8	280	34.0%	-21.50 [-28.02, -14.98]			
Zammit, 2004	44.5	68.8	105	58.4	42.9	99	21.8%	-13.90 [-29.54, 1.74]			
Total (95% CI)			1077			553	100.0%	-25.00 [-36.07, -13.94]	•		
Heterogeneity: Tau ² :	= 82.51; Chi ² =	9.30, df = 3	(P = 0.1)	03); I² = 68%							
Test for overall effect	•		•						-50 -25 0 25 50		
1001101 0101411 011001		0.0000.,							Favours 3 mg Eszopiclone Favours Placebo		

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

	3 mg E	szopiclone		Pla	icebo			Mean Difference		Mean Difference		
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	ean [min] SD [min] Total			IV, Random, 95% CI [min]	IV, Random, 95% CI [min]			
Erman, 2008	453.1	462.6	64	362	63.8	63	2.8%	91.10 [-23.32, 205.52]				
Krystal, 2003	378.3	72.3	360	303.6	78.3	111	33.9%	74.70 [58.33, 91.07]				
Walsh, 2007	391.9	68.7	548	346.8	77.4	280	39.1%	45.10 [34.36, 55.84]				
Zammit, 2004	411.8	124	105	363.8	63.5	99	24.3%	48.00 [21.19, 74.81]			-	
Total (95% CI)			1077			553	100.0%	57.10 [37.45, 76.75]			•	
Heterogeneity: Tau ² =	= 226.97; Chi²:	= 9.37, df=	3 (P = 0	0.02); I ^z = 68%)				-100	-50) 50 1	
Test for overall effect	: Z = 5.70 (P < 1	0.00001)									Favours 3 mg Eszopiclone	

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

	3 mg E	szopiclone		Pla	icebo			Mean Difference	Mean Difference
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]
Boyle, 2008	26.61	5.35	31	41.09	7.07	31	91.8%	-14.48 [-17.60, -11.36]	-
Zammit, 2004	39.5	34	105	56.5	41.7	99	8.2%	-17.00 [-27.48, -6.52]	
Total (95% CI)			136			130	100.0%	-14.69 [-17.68, -11.69]	•
Heterogeneity: Tau² = Test for overall effect:			P = 0.6	5); I² = 0%					-20 -10 0 10 20 Favours 3 mg Eszopiclone Favours Placebo

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

	3 mg E	szopiclone		Pla	icebo			Mean Difference	Mean Difference	
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]	
Erman, 2008	50.3	124	64	56.6	48.3	63	4.3%	-6.30 [-38.94, 26.34]		
Krystal, 2003	44.2	74.2	360	70.7	72.8	111	15.9%	-26.50 [-42.06, -10.94]		
Walsh, 2007	22.2	32.8	548	38.6	41.7	280	51.2%	-16.40 [-22.00, -10.80]		
Zammit, 2004	41.2	39	105	49.1	36.1	99	28.6%	-7.90 [-18.21, 2.41]		
Total (95% CI)			1077			553	100.0%	-15.14 [-22.11, -8.16]	•	
Heterogeneity: Tau² =	: 16.58; Chi² =	4.41, df = 3	(P = 0.	22); I² = 32%					-50 -25 0 25	50
Test for overall effect:	Z= 4.25 (P < I	0.0001)							Favours 3 mg Eszopiclone Favours Placebo	30

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

	3 mg E	szopic	lone	Pl	acebo			Std. Mean Difference	Std. Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight IV, Random, 95% CI			IV, Random, 95% CI			
Boyle, 2008	47.6	1.6	31	26.8	2.4	31	7.2%	10.07 [8.17, 11.97]			-		
Erman, 2008	59.9	22.8	64	44.4	19.9	63	18.2%	0.72 [0.36, 1.08]			+		
Krystal, 2003	6.4	1.8	360	3.5	2	111	18.8%	1.57 [1.33, 1.80]			•		
Uchimura, 2012	6.7	1.9	68	5.2	1.9	71	18.2%	0.79 [0.44, 1.13]			+		
Walsh, 2007	7	1.8	548	5.8	1.8	280	19.0%	0.67 [0.52, 0.81]			•		
Zammit, 2004	55.4	16.7	105	49	18.1	99	18.6%	0.37 [0.09, 0.64]			-		
Total (95% CI)			1176			655	100.0%	1.49 [0.84, 2.14]			•		
Heterogeneity: Tau² = Test for overall effect:				= 5 (P <	0.0000	01); l²=	97%		-10	-5 Favours Plac	0 5 ebo Favours 3 mg Eszop	10 piclone	

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

	3 mg E	3 mg Eszopiclone Placebo					Mean Difference Mean I			Mean Dit	fference		
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]		IV, Random	, 95% CI [%]		
Boyle, 2008	91.6	1.19	31	86.67	1.61	31	68.7%	4.93 [4.23, 5.63]			-	-	
Zammit, 2004	88.4	8.5	105	81.3	10.9	99	31.3%	7.10 [4.41, 9.79]			_	-	
Total (95% CI)			136			130	100.0%	5.61 [3.64, 7.58]			•	>	
Heterogeneity: Tau ^z = 1.35; Chi ^z = 2.33, df = 1 (P = 0.13); i ^z = 57% Test for overall effect: Z = 5.57 (P < 0.00001)									-10	-5 (Favours Placebo	Favours 3 mg	Eszopic	10 lone

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

	3 mg E	mg Eszopiclone Placebo						Mean Difference	Mean Difference			
Study or Subgroup	Mean [#]	SD [#]	Total	Mean [#]	SD [#]	Total	Weight	IV, Random, 95% CI [#]	IV, Random, 95% CI [#]			
Krystal, 2003	1.9	1.5	360	3.5	2.8	111	32.0%	-1.60 [-2.14, -1.06]				
Walsh, 2007	1.6	2.3	548	2.1	2	280	36.4%	-0.50 [-0.80, -0.20]				
Zammit, 2004	3	2.2	105	3.2	1.9	99	31.6%	-0.20 [-0.76, 0.36]				
Total (95% CI)			1013			490	100.0%	-0.76 [-1.49, -0.02]	-			
Heterogeneity: Tau² =	0.36; Chi²:	= 15.13,										
Test for overall effect:	Z = 2.02 (P	= 0.04)	Favours 3 mg Eszopiclone Favours Placebo									

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*	⊕⊖⊖	The mean sleep latency in the eszopiclone groups was 13.63 minutes lower (23.56 to 3.7 lower)	405
(PSG)	very low ^{1,2,3}		(3 studies) ^{A,D,F}
Sleep Latency	⊕⊕⊖⊝	The mean sleep latency in the eszopiclone groups was 25.00 minutes lower (36.07 to 13.94 lower)	1630
(Subjective)	low ^{3,4}		(4 studies) ^{B,C,E,F}
Total Sleep Time*	⊕⊕⊕⊝	The mean total sleep time in the eszopiclone groups was 57.10 minutes higher (37.45 to 76.75 higher)	1630
(Subjective)	moderate³		(4 studies) B,C,E,F
Wake After Sleep Onset* (PSG)	⊕⊕⊕⊝ moderate³	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	⊕⊕⊖⊝	The mean wake after sleep onset in the eszopiclone groups was 15.14 minutes lower (22.11 to 8.16 lower)	1630
(Subjective)	low ^{3,5}		(4 studies) ^{B,C,E,F}
Quality of Sleep*	⊕⊕⊝⊝	The mean quality of sleep in the eszopiclone groups was 1.49 standard deviations higher (0.84 to 2.14 higher)	1769
(Subjective)	low ^{3,9}		(6 studies) _{A,B,C,D,E,F}
Sleep Efficiency	⊕⊕⊖⊝	The mean sleep efficiency in the eszopiclone groups was 5.61 percent higher (3.64 to 7.58 higher)	266
(PSG)	low ^{3,6}		(2 studies) ^{A,F}
Number of Awakenings	⊕⊝⊝	The mean number awakenings in the eszopiclone groups was 0.76 awakenings lower (1.49 to 0.02 lower)	1503
(Subjective)	very low ^{3,6,7}		(3 studies) ^{C,E,F}

^{*} Critical Outcome, used to determine Quality of Evidence

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 (I² = 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 (I² = 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

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*	⊕⊕⊖⊝	The mean sleep latency in the zaleplon group was 9.50 minutes lower (18.80 to 0.19 lower)	94		
(PSG)	low ^{1,3}		(1 study) ^B		
Sleep Latency	⊕⊕⊝⊝	The mean sleep latency in the zaleplon group was 11.40 minutes lower (27.36 lower to 4.56 higher)	92		
(Subjective)	low ^{2,3}		(1 study) ^B		
Total Sleep Time*	⊕⊕⊖⊝	The mean total sleep time in the zaleplon group was 21.50 minutes higher (5.60 lower to 48.6 higher)	93		
(Subjective)	low ^{3,4}		(1 study) ^B		
Wake After Sleep Onset	⊕⊕⊕⊝	The mean wake after sleep onset in the zaleplon group was 2.10 minutes lower (10.23 lower to 6.03 higher)	92		
(PSG)	moderate³		(1 study) ^B		
Quality of Sleep*	⊕⊕⊕⊝	The mean quality of sleep in the zaleplon group was 0.10 points ⁵ lower (0.27 lower to 0.07 higher)	283		
(Subjective)	moderate³		(1 study) ^A		

^{*} Critical Outcome, used to determine Quality of Evidence

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*	⊕⊕⊖⊖	The mean sleep latency in the zolpidem group was 5.27 minutes lower (11.47 lower to 0.93 higher)	199
(PSG)	low ^{1,2}		(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	⊕⊕⊕⊝	The mean sleep efficiency in the zolpidem group was 1.60 percent higher (1.4 lower to 4.6 higher)	199
(PSG)	moderate¹		(1 study)

^{*} Critical Outcome, used to determine Quality of Evidence

¹ Study funded by Industry

² 7-point scale (1=excellent, 7=extremely poor)

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)

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

	10 mg	Zolpidem		Co	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]
Herrmann, 1993	28	7	11	41.7	15	10	18.4%	-13.70 [-23.88, -3.52]	
Randal 2012	14.2	12.2	44	29.76	26.9	47	20.5%	-15.56 [-24.05, -7.07]	
Scharf, 1994	25.8	13.7	22	28.1	25.6	22	16.1%	-2.30 [-14.43, 9.83]	
Uchimura 2012	14.3	22.6	70	37.5	37.8	71	18.3%	-23.20 [-33.46, -12.94]	
Ware, 1997	37	6	34	42	5	35	26.8%	-5.00 [-7.61, -2.39]	-
Total (95% CI)			181			185	100.0%	-11.65 [-19.15, -4.15]	-
Heterogeneity: Tau ² =	= 52.80; Chi ² =	17.97, df=							
Test for overall effect	Z = 3.04 (P = 1)	0.002)	•	••					-20 -10 0 10 20
		,							Favours 10 mg Zolpidem Favours Placebo

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

	10 mg	Zolpidem		Co	ntrol			Mean Difference	Mean Difference
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]
Dorsey, 2004	29	2.64	68	37	3.16	73	17.2%	-8.00 [-8.96, -7.04]	•
Elie 1999	30.8	27.8	64	54.4	39.3	63	9.3%	-23.60 [-35.46, -11.74]	
Erman, 2008	30.8	27.8	64	54.4	39.3	63	9.3%	-23.60 [-35.46, -11.74]	
Herrmann, 1993	40.5	10	11	72.8	10	10	12.0%	-32.30 [-40.86, -23.74]	
Jacobs, 2004	45	32.5	14	66.8	37.7	14	3.4%	-21.80 [-47.87, 4.27]	
Perlis, 2004	38.4	33.1	95	55.1	52.3	97	9.0%	-16.70 [-29.05, -4.35]	
Randal 2012	27.33	31.4	44	36.8	35	47	8.1%	-9.47 [-23.12, 4.18]	
Scharf, 1994	38.4	22	22	56.6	39.5	23	5.6%	-18.20 [-36.78, 0.38]	
Uchimura 2012	28	24.6	70	62	47.8	71	8.9%	-34.00 [-46.52, -21.48]	
Walsh, 1998	48.1	3.1	91	64.7	4.6	97	17.2%	-16.60 [-17.72, -15.48]	•
Total (95% CI)			543			558	100.0%	-19.55 [-24.90, -14.20]	•
Heterogeneity: Tau² =			= 9 (P ·	< 0.00001); I² =	= 95%				-50 -25 0 25 50
Test for overall effect:	Z=1.10 (P <	0.00001)							Favours 10 mg Zolpidem Favours Placebo

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

•	10 mg	Zolpidem		Co	ntrol			Mean Difference		Mean D	ifference	
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]		IV, Random,	95% CI [min]	
Herrmann, 1993	381.3	10	11	360.3	23	10	57.6%	21.00 [5.57, 36.43]				_
Randal 2012	411	32.7	44	371.36	65.1	47	42.4%	39.64 [18.67, 60.61]				-
Total (95% CI)			55			57	100.0%	28.91 [10.85, 46.97]				
Heterogeneity: Tau² = Test for overall effect:			(P = 0	.16); I² = 49%					-50	-25 Favours placebo	0 25 Favours 10 m	50 ng Zolpidem

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

	10 mg	Zolpidem		Co	ntrol			Mean Difference	Mean Difference
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]
Elie 1999	324.7	133	94	353	105	104	10.9%	-28.30 [-61.92, 5.32]	
Erman, 2008	438.7	406.4	64	362	63.8	63	2.0%	76.70 [-24.10, 177.50]	
Herrmann, 1993	372.7	12	11	327.4	22	10	19.4%	45.30 [29.93, 60.67]	
Jacobs, 2004	343.4	76.8	14	296.8	99.6	14	4.2%	46.60 [-19.28, 112.48]	
Perlis, 2004	417	64.4	95	359.8	77.1	97	17.0%	57.20 [37.12, 77.28]	
Randal 2012	402	78	44	390	66	47	12.4%	12.00 [-17.79, 41.79]	
Scharf, 1994	369	65	22	356	64	23	9.6%	13.00 [-24.71, 50.71]	
Walsh, 1998	378.8	5.3	91	344.6	5.3	97	24.4%	34.20 [32.68, 35.72]	•
Total (95% CI)			435			455	100.0%	30.04 [15.12, 44.96]	•
Heterogeneity: Tau² = Test for overall effect:			-100 -50 0 50 100						
restion overall ellect.	Z = 3.80 (F %)	0.0001)	Favours Placebo Favours 10 mg Zolpidem						

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

	10 mg	Zoipia	em	Pl	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Herrmann, 1993	34.7	7	11	60	12	10	78.2%	-25.30 [-33.81, -16.79]	
Randal 2012	58.25	32.7	44	84.3	45.2	47	21.8%	-26.05 [-42.19, -9.91]	
Total (95% CI)			55			57	100.0%	-25.46 [-32.99, -17.94]	•
Heterogeneity: Tau² =	= 0.00; Cł	ni = 0.0)1, df=	1 (P = 0	.94); l²	= 0%			-20 -10 0 10 20
Test for overall effect:	Z = 6.63	(P ≤ 0.	00001)				Favours 10 mg Zolpidem Favours PLacebo		

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

	10 mg	Zolpidem		Co	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	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: Tau ² =	= 28.27; Chi ^z =	61.87, df=		-20 -10 0 10 20					
Test for overall effect:	Z= 4.24 (P <	0.0001)		Favours 10 mg Zolpidem Favours Placebo					

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

	10 mg	Zolpid	em	C	ontrol			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		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; Cl	ni = 65	.94, df=	= 5 (P <	0.0000	01); l² =	92%		- -2	-1 0 1 2
Test for overall effect:	Z = 2.05	(P = 0.	04)						_	Favours Placebo Favours 10 mg Zolpidem

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

	10 mg	Zolpid	em	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	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: Tau ² =				,	.20); l²	= 35%		-	-10 -5 0 5 10
Test for overall effect	Z = 6.93	(P < 0.1	00001)						Favours Placebo Favours 10 mg Zolpidem

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

	10 mg	Zolpid	lem	Pla	acebo	0		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	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: Tau ² :			•	1 (P = 0	.34);	² = 0%			-2 -1 0 1 2
Test for overall effect	. ∠= 4.04 ((P < U.	0001)						Favours 10 mg Zolpidem Favours Placebo

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

	10 mg	j Zolpia	em	C	ontroi			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	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; CI	ni = 37	.05, df=	= 5 (P <	0.0000	01); l² =	87%		-1 -0.5 0 0.5 1
Test for overall effect:	Z = 4.37	(P ≤ 0.	0001)						Favours 10 mg Zolpidem Favours Placebo

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

	Zolpidem '	10mg	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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; Chi ^z =	0.27, dt	f=1 (P=	0.60); I	²=0%		04 005 0 005 04
Test for overall effect:	Z = 2.31 (P =	= 0.02)					-0.1 -0.05 0 0.05 0.1 Placebo Zolpidem 10 mg

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

	Zolpidem 1	10mg	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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: Tau ² =	= 0.00; Chi ^z =	1.75, dt	f=3(P=	0.62); I	²= 0%		- 12 14 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Test for overall effect	Z= 3.21 (P=	= 0.001)					-0.2 -0.1 0 0.1 0.2 Placebo Zolpidem 10 mg

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

	Zolpidem '	10mg	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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; Chi ^z =	5.00, dt	f=2(P=	0.08); I	²= 60%		-0.2 -0.1 0 0.1 0.2
Test for overall effect:	Z=1.25 (P=	= 0.21)					Placebo Zolpidem 10mg

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

	Zolpidem 1	0mg	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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 = Test for overall effect:	•		f=1 (P=	0.61); I	²=0%		-0.1 -0.05 0 0.05 0.1 Placebo Zolpidem 10mg

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

	Zolpidem	10mg	Place	bo		Risk Difference		Risk [)ifference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Ran	dom, 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, di	f=5 (P=	0.45);1	²= 0%		-0.2	-0.1	0 0.1	0.2
Test for overall effect:	Z= 3.04 (P:	= 0.002)	l				-0.2	Placeb		

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

	Zolpidem 1	0mg	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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 = Test for overall effect:	•	•	f=1 (P=	0.52); I	²= 0%		-0.05 -0.025 0 0.025 0.05 Placebo Zolpidem 10mg

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*	⊕⊝⊝⊝	The mean sleep latency in the zolpidem groups was 11.65 minutes lower (19.15 to 4.15 lower)	366
(PSG)	very low ^{1,2,3}		(5 studies) ^{D,G,H,J,L}
Sleep Latency	⊕⊝⊝⊝	The mean sleep latency in the zolpidem groups was 19.55 minutes lower (24.90 to 14.20 lower)	1101
(Subjective)	very low ^{3,4,5}		(10 studies) ^{A,B,C,D,E,FG,H,J,K}
Total Sleep Time*	⊕⊕⊝⊝	The mean total sleep time in the zolpidem groups was 28.91 minutes higher (10.85 to 46.97 higher)	112
(PSG)	low ^{3,12}		(2 studies) ^{D,G}
Total Sleep Time*	⊕⊕⊝⊝	The mean total sleep time in the zolpidem groups was 30.04 minutes higher (15.12 to 44.96 higher)	890
(Subjective)	low ^{3,7}		(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*	⊕⊝⊝⊝	The mean quality of sleep in the zolpidem groups was 0.64 standard deviations higher (0.03 to 1.26 higher)	638
(Subjective)	very low ^{3,10,11}		(6 studies) ^{C,G,H,I,J,K}
Sleep Efficiency	⊕⊕⊖⊝	The mean sleep efficiency in the zolpidem groups was 6.12 percent higher (4.39 to 7.85 higher)	226
(PSG)	low ^{3,9}		(4 studies) ^{D,G,H,L}
Number of Awakenings	⊕⊕⊕⊝	The mean number of awakenings in the zolpidem groups was 0.95 awakenings lower (1.41 to 0.49 lower)	113
(PSG)	moderate ³		(2 studies) ^{H,L}
Number of Awakenings	⊕⊕⊖⊝	The mean number of awakenings in the zolpidem groups was 0.31 awakenings lower (0.45 to 0.17 lower)	720
(Subjective)	low ^{3,8}		(6 studies) ^{A,B,D,F,H,K}

^{*} Critical Outcome, used to determine Quality of Evidence

¹ Heterogeneity ($l^2 = 78\%$) greater than allowance (75%)

² 95% CI (-19.15, -4.15) crosses Clinical Significance (10 min)

³ Studies funded by industry

⁴ Heterogeneity (I² = 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 (I² = 87%) greater than allowance (75%)

⁹ 95% CI (4.39, 7.85) crosses Clinical Significance (5%)

Heterogeneity (I² = 92%) greater than allowance (75%)

^{11 95%} CI (0.3, 1.26) crosses Clinical Significance (SMD 0.5)

^{12 95%} CI (10.85, 46.97) crosses Clinical Significance (20 min)

¹³ 95% CI (-32.99, -17.4) crosses Clinical Significance (20 min)

Table S10 - Summary of Findings table for zolpidem 12.5 mg for the treatment of chronic insomnia

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

^{*} Critical Outcome, used to determine Quality of Evidence

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*	⊕⊕⊕	The mean sleep latency in the triazolam group was 9.20 minutes lower (22.3 lower to 3.9 higher)	64
(Subjective)	high		(1 study)
Total Sleep Time	⊕⊕⊕⊝	The mean total sleep time in the triazolam group was 25.20 minutes higher (9.12 lower to 59.52 higher)	64
(Subjective)	moderate¹		(1 study)
Quality of Sleep* (Subjective)	⊕⊕⊕⊕ high	The mean quality of sleep in the triazolam group was 0.37 points³ lower (0.66 to 0.07 lower)	64 (1 study)
Number of Awakenings	⊕⊕⊝⊝	The mean number of awakenings in the triazolam group was 0.37 awakenings lower (1.7 lower to 0.96 higher)	64
(Subjective)	low²		(1 study)

^{*} Critical Outcome, used to determine Quality of Evidence

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

	15 mg T	emazepan	1	Pla	icebo			Mean Difference	Mean Difference			
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [i	nin]		
Glass 2008	25.4	21.5	19	36.8	24.8	19	55.6%	-11.40 [-26.16, 3.36]				
Wu 2006	19.7	10.6	17	50.6	39.7	17	44.4%	-30.90 [-50.43, -11.37]				
Total (95% CI)			36			36	100.0%	-20.06 [-39.05, -1.07]				
Heterogeneity: Tau ² =			-50 -25 0	25	50							
Test for overall effect:	Z = 2.07 (F = 1	3.04)							Favours 15 mg Temazepam Favours	placebo		

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

	15 mg 1	Temazepan	1	Pla	icebo			Mean Difference	Mean Difference			
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]			
Glass 2008	414	60	19	378	78	19	50.6%	36.00 [-8.25, 80.25]	 			
Wu 2006	406.1	59.8	17	312.6	75.8	17	49.4%	93.50 [47.60, 139.40]				
Total (95% CI)			36			36	100.0%	64.41 [8.07, 120.76]				
Heterogeneity: Tau ² Test for overall effect		•	1 (P =	0.08); I² = 689	6				-100 -50 0 50 100 Favours Placebo Favours 15 mg Temazepam			

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)

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)

³4-point scale (1=good, 4=poor)

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

	15 mg 1	Temaze _l	pam	PI	acebo			Std. Mean Difference	Std. Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	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 = Test for overall effect: .	•		,	° = 0.34);	1%			-1 -0.5 0 0.5 1 Favours Placebo Favours 15 mg Temazepam			

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	⊕⊕⊕⊖	The mean sleep latency in the temazepam group was 20.06 minutes lower (39.05 to 1.07 lower)	72
(Subjective)	moderate ²		(2 studies) ^{A,C}
Total Sleep Time*	⊕⊕⊕⊕	The mean total sleep time in the temazepam group was 99.1 minutes higher (63.4 to 134.7 lower)	34
(PSG)	high		(1 study) ^C
Total Sleep Time	⊕⊕⊕⊖	The mean total sleep time in the temazepam groups was 64.41 minutes higher (8.07 to 120.76 higher)	72
(Subjective)	moderate³		(2 studies) ^{A,C}
Quality of Sleep*	⊕⊕⊕⊖	The mean quality of sleep in the temazepam group was 0.25 standard deviations higher (0.2 lower to 0.7 higher)	39
(Subjective)	moderate ¹		(2 studies) ^{A,B}
Sleep Efficiency	⊕⊕⊕⊝	The mean sleep efficiency in the temazepam group was 13.3 percent higher (3.9 to 22.6 higher)	34
(PSG)	moderate ⁵		(1 study) ^c
Sleep Efficiency	⊕⊕⊕⊝	The mean sleep efficiency in the temazepam group was 14.1 percent higher (5.8 to 22.3 higher)	34
(Subjective)	moderate ⁶		(1 study) ^C
Number of Awakenings	⊕⊕⊕⊖	The mean number of awakenings in the temazepam group was 0.5 awakenings lower (1.29 lower to 0.29 higher)	38
(Subjective)	moderate ⁴		(1 study) ^A

^{*} Critical Outcome, used to determine Quality of Evidence

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)	⊕⊕⊕⊝ moderate¹	The mean quality of sleep in the temazepam group was 0.69 cm ² higher	40 (1 study)
(Subjective)	moderate	(0.28 lower to 1.66 higher)	(1 Study)

^{*} Critical Outcome, used to determine Quality of Evidence

^{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)

^{95%} CI (-1.29, 0.29) crosses Clinical Significance (0.5 awakenings)

^{95%} CI (3.9, 22.6) crosses Clinical Significance (5%)

⁶ 95% CI (5.8, 22.3) crosses Clinical Significance (10%)

^{95%} CI (-0.28, 1.66) crosses Clinical Significance (1.0 cm)

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

_	8 mg F	amelteon		Pla	icebo			Mean Difference	Mean Difference			
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random,	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 : Test for overall effect				-20 -10 (Favours 8 mg Ramelteon) 10 Favours Placebo	20						

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

	8 mg R	amelteon		Placebo				Mean Difference	Mean Difference
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	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 = Test for overall effect			= 2 (P =	< 0.00001); l² =	= 99%		-20 -10 0 10 20 Favours 8 mg Ramelteon Favours Placebo		

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

-		,							3
	8 mg R		Pla	icebo			Mean Difference	Mean Difference	
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	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: Tau ² =	= 22.59; Chi ^z =	183.95, df	= 3 (P •	< 0.00001); l ^z :	= 98%				-20 -10 0 10 20
Test for overall effect:	Z = 2.47 (P = 1)	0.01)							Favours Placebo Favours 8 mg Ramelteon

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

	8 mg R	amelteon		Pla	cebo			Mean Difference	Mean Difference				
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]		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: Tau ² = Test for overall effect:			-20	-10	1	0 20							
restiui uverali ellect.	Z = 0.04 (F = 1	0.40)								Favours Placebo	Favours 8	mg Ramelteo	n

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

	8 mg R	amelteon		Pla	cebo			Mean Difference	Mean Di	fference			
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]		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 =			(P = 0.9)	8); I² = 0%					-10	-5	 		10
Test for overall effect:	Z = 9.36 (P < 0)	0.00001)						3 mg Ramelteon	Favours Place	bo			

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

8 mg R	amelteon		Pla	icebo			Mean Difference	Mean Difference			
Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]			
90.89	3.796	159	79.54	3.822	176	50.1%	11.35 [10.53, 12.17]	-			
70.3	4.7	139	71.2	4.8	131	49.9%	-0.90 [-2.03, 0.23]				
		202			307	100.0%	5 23 [6 77 17 24]				
74.70: Obiz =	20515 46.		0.000043-12-	- 1000	301	100.070	3.23 [-0.11, 11.24]				
	•		'-20 -1'0 Ó 1'0	20'							
Z = 0.85 (P = l	J.39)	Favours 8 mg Ramelteon Favours Placebo									
	Mean [min] 90.89 70.3 74.78; Chi ² =	90.89 3.796 70.3 4.7	Mean [min] SD [min] Total 90.89 3.796 159 70.3 4.7 139 298 74.78; Chi² = 295.15, df = 1 (P	Mean [min] SD [min] Total Mean [min] 90.89 3.796 159 79.54 70.3 4.7 139 71.2 298 74.78; Chi² = 295.15, df = 1 (P < 0.00001); F =	Mean [min] SD [min] Total Mean [min] SD [min] 90.89 3.796 159 79.54 3.822 70.3 4.7 139 71.2 4.8 298 74.78; Chi² = 295.15, df = 1 (P < 0.00001); I² = 100%	Mean [min] SD [min] Total Mean [min] SD [min] Total 90.89 3.796 159 79.54 3.822 176 70.3 4.7 139 71.2 4.8 131 298 307 74.78; Chi² = 295.15, df = 1 (P < 0.00001); P = 100%	Mean [min] SD [min] Total Mean [min] SD [min] Total Weight 90.89 3.796 159 79.54 3.822 176 50.1% 70.3 4.7 139 71.2 4.8 131 49.9% 298 307 100.0% 74.78; Chi² = 295.15, df = 1 (P < 0.00001); l² = 100%	Mean [min] SD [min] Total Mean [min] SD [min] Total Weight IV, Random, 95% CI [min] 90.89 3.796 159 79.54 3.822 176 50.1% 11.35 [10.53, 12.17] 70.3 4.7 139 71.2 4.8 131 49.9% -0.90 [-2.03, 0.23]	Mean [min] SD [min] Total Mean [min] SD [min] Total Weight IV, Random, 95% CI [min] IV, Random, 95% CI [min] 90.89 3.796 159 79.54 3.822 176 50.1% 11.35 [10.53, 12.17] ————————————————————————————————————		

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

	8 mg	Ramelt	eon	P	lacebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	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 = Test for overall effect:				: 2 (P <	0.00001); I² = 9	18%		-0.2 -0.1 0 0.1 0.2 Favours 8 mg Ramelteon Favours Placebo

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

	8 mg Ramelteon Placebo				acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	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: Tau 2 = 0.47; Chi 2 = 30.72, df = 2 (P < 0.00001); I 2 = ! Test for overall effect: Z = 4.05 (P < 0.0001)						93%		-4 -2 0 2 4 Favours Placebo Favours 8 mg Ramelteon

Figure \$50 – Meta-analysis of data for the occurrence of headache in response to ramelteon 8 mg

•	,						3
	Ramelteon	8 mg	placebo			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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: Tau ² =	= 0.00; Chi ^z =	0.57, df	= 2 (P = 0)	0.75); l ^z	= 0%		14 005 04
Test for overall effect	Z = 0.79 (P =	0.43)					-0.1 -0.05 0 0.05 0.1 Placebo Ramelteon 8 mg

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

	Ramelteon	8 mg	place	bo		Risk Difference	Risk Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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: Tau ² :	= 0.00; Chi ² = I	0.20, df:	= 1 (P = 0)	l.65); l²	= 0%	_	-0.05 -0.025 0 0.025 0.05		
Test for overall effect	Z = 0.37 (P =	0.72)					Placebo Ramelteon 8 mg		

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	⊕⊕⊝⊝	The mean sleep latency in the ramelteon groups was 11.44 minutes lower (19.56 to 3.31 lower)	592
(Subjective)	low ^{3,7,8}		(3 studies) ^{A,C,D}
Total Sleep Time	⊕⊕⊖⊖	The mean total sleep time in the ramelteon groups was 6.58 minutes higher (1.36 to 11.80 higher)	927
(PSG)	low ^{1,3}		(4 studies) ^{A,B,C,D}
Total Sleep Time	⊕⊕⊖⊖	The mean total sleep time in the ramelteon groups was 5.70 minutes higher (7.65 lower to 19.04 higher)	927
(Subjective)	low ^{3,6}		(4 studies) ^{A,B,C,D}
Wake After Sleep Onset (PSG)	⊕⊕⊕⊖ moderate³	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	⊕⊕⊖⊖	The mean wake after sleep onset in the ramelteon groups was 5.23 minutes higher (6.77 lower to 17.24 higher)	605
(Subjective)	low ^{3,6}		(2 studies) ^{B,D}
Quality of Sleep*	⊕⊕⊖	The mean quality of sleep in the ramelteon groups was 0.04 points lower ⁵ (0.13 lower to 0.05 higher)	805
(Subjective)	low ^{1,3}		(3 studies) ^{B,C,D}
Sleep Efficiency	⊕⊕⊝⊝	The mean sleep efficiency in the ramelteon groups was 1.93 percent higher (1.00 to 2.87 higher)	592
(PSG)	low ^{3,4}		(3 studies) ^{A,C,D}
Number of Awakenings	⊕⊕⊕⊝	The mean number of awakenings in the ramelteon group was 0.12 awakenings higher (0.08 to 0.15 higher)	335
(Subjective)	moderate³		(1 study) ^B

^{*} Critical Outcome, used to determine Quality of Evidence

Doxepin - Meta-Analyses and Summary of Findings Tables

Figure \$4952 - Meta-analysis of data for PSG-determined sleep latency in response to doxepin 3 mg

	3 mg	Doxepin		Pla	icebo		•	Mean Difference	Mean Difference			
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]			
Krystal 2010	37.5	32.7	74	34.9	33	70	13.3%	2.60 [-8.14, 13.34]				
Krystal 2011	28.5	26	68	32	35.3	67	14.0%	-3.50 [-13.97, 6.97]	• + -			
Roth 2007	31	20.72	66	33	22.02	66	28.8%	-2.00 [-9.29, 5.29]				
Scharf 2008	23.2	17.21	74	26.8	19.29	73	43.9%	-3.60 [-9.51, 2.31]				
Total (95% CI)			282			276	100.0%	-2.30 [-6.22, 1.62]				
Heterogeneity: Tau² = Test for overall effect:			(P = 0.7	?9); I² = 0%				-	-10 -5 0 5 10 Favours 3 mg Doxepin Favours Placebo			

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

		3 mg	Doxepin		Pla	cebo			Mean Difference	Mean Difference
Stu	dy or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]
Krys	stal 2010	39.9	30.3	74	55.5	39.5	70	51.2%	-15.60 [-27.14, -4.06]	
Sch	arf 2008	42.7	39.76	74	45.5	35.48	73	48.8%	-2.80 [-14.98, 9.38]	
Tota	al (95% CI)			148			143	100.0%	-9.35 [-21.89, 3.19]	
Hete	erogeneity: Tau² =	45.27; Chi²=	2.24, df = 1	(P = 0	.13); P= 55%					-20 -10 0 10 20
Tes	t for overall effect:	Z=1.46 (P=1	0.14)							Favours 3 mg Doxepin Favours Placebo

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

Heterogeneity ($I^2 = 93\%$) greater than allowance (75%)

⁵ 7-point Likert scale (1=excellent, 7=very poor)

⁶ Heterogeneity (I² =100%) greater than allowance (75%)

Heterogeneity (I² =99%) greater than allowance (75%)

^{95%} CI (-21.45, 2.90) crossses Clinical Significance (20 min)

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

	3 mg	Doxepin		Pla	icebo			Mean Difference	Mean Difference				
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]		IV, Random,	95% CI [m	nin]	
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 = Test for overall effect		•	(P = 0.6	64); I² = 0%					-50	-25 Favours Placebo	0 Favours	25 3 mg Doxep	50 oin

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

_	3 mg		Pla	cebo			Mean Difference	Mean Difference			
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	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 = Test for overall effect	•		1 (P =	0.02); I² = 829	6			-	-50 -25 0 25 50 Favours Placebo Favours 3 mg Doxepin		

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

•	3 mg	Doxepin		Pla	cebo			Mean Difference	Mean Difference			
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	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 = Test for overall effect:			3 (P = 0	.27); I²= 23%					-50 -25 0 25 50 Favours 3 mg Doxepin Favours Placebo			

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

	3 mg Doxepin Placebo							Std. Mean Difference	Std. Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	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: Test for overall effect	•			,	0.18);	l² = 439	%		-1 -0.5 0 0.5 1 Favours Placebo Favours 3 mg Doxepin				

Figure \$58 – Meta-analysis of data for PSG-determined sleep efficiency in response to doxepin 3 mg

	3 mg	Doxepin		Pla	cebo			Mean Difference	Mean D	Mean Difference			
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]		IV, Randon	n, 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 = Test for overall effect:			,	= 0.30); ==	17%				-20	-10 Favours Placebo	0 Favours 3	10 mg Doxep	20 oin

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

	3 mg	Doxe	pin	PI	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	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: Tau ² :	= 0.00; C	$hi^2 = 0$.50, df=	= 2 (P =	0.78);	² = 0%		-	
Test for overall effect	: Z = 1.18	(P = 0	0.25)						Favours 3 mg Doxepin Favours Placebo

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

	Doxepin	3 mg	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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; Chi ²	= 0.61,	df = 2 (P	= 0.74)	; I² = 0%		-0.1 -0.05 0 0.05 0.1
Test for overall effect:	Z = 2.58 (F	P = 0.01	0)				Placebo Doxepine 3 mg

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

	Doxepin	3 mg	Place	Placebo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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%)	-0.1 -0.05 0 0.05 0.1
Test for overall effect:	Z = 0.29 (F	P = 0.77)				Placebo Doxepine 3 mg

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

	Doxepin	3 mg	Place	bo		Risk Difference		Risk	Difference	ce	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Ra	andom, 95	5% 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 = Test for overall effect:				= 0.31)	; I² = 4%		-0.1	-0.05 Place	0 bo Doxe	0.05 pine 3 mg	0.1

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

	Doxepin	3 mg	Place	bo		Risk Difference		Risk Di	fference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rand	dom, 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 = Test for overall effect:				= 0.65)	; I² = 0%		-0.1	-0.05 Placebo	0 Doxepin	0.05 e 3 mg	0.1

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*	⊕⊕⊕⊝	The mean sleep latency in the doxepin groups was 2.3 minutes lower (6.22 lower to 1.62 higher)	558
(PSG)	moderate ¹		(4 studies) ^{A,B,C,D}
Sleep Latency	⊕⊕⊝⊝	The mean sleep latency in the doxepin groups was 9.35 minutes lower (21.89 lower to 3.19 higher)	291
(Subjective)	low ^{1,6}		(2 studies) ^{A,D}
Total Sleep Time*	⊕⊕⊝⊝	The mean total sleep time in the doxepin groups was 26.14 minutes higher (18.49 to 33.79 higher)	558
(PSG)	low ^{1,3}		(4 studies) ^{A,B,C,D}
Total Sleep Time	⊕⊖⊝⊖	The mean total sleep time in the doxepin groups was 43.57 minutes higher (5.16 to 81.98 higher)	291
(Subjective)	very low ^{1,7,8}		(2 studies) ^{A,D}
Wake After Sleep Onset*	⊕⊕⊝⊝	The mean wake after sleep onset in the doxepin groups was 22.17 minutes lower (29.62 to 14.72 lower)	558
(PSG)	low ^{1,2}		(4 studies) A,B,C,D
Wake After Sleep Onset	⊕⊕⊝⊝	The mean wake after sleep onset in the doxepin group was 20.0 minutes lower (39.07 to 0.92 lower)	147
(Subjective)	low ^{1,9}		(1 study) ^D
Quality of Sleep*	⊕⊕⊝⊝	The mean quality of sleep in the doxepin groups was 0.57 standard deviations higher (0.26 to 0.88 higher)	291
(Subjective)	low ^{1,5}		(2 studies) ^{A,D}
Sleep Efficiency	⊕⊕⊝⊝	The mean sleep efficiency in the doxepin groups was 6.78 percent higher (4.5 to 9.07 higher)	423
(PSG)	low ^{1,4}		(3 studies) ^{A,C,D}
Number of Awakenings	⊕⊕⊕⊝	The mean number of awakenings in the doxepin groups was 0.53 awakenings higher (0.37 lower to 1.42 higher)	423
(PSG)	moderate ¹		(3 studies) ^{A,C,D}

^{*} Critical Outcome, used to determine Quality of Evidence

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

	6 mg	6 mg Doxepin			ntrol			Mean Difference	Mean Difference				
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]		IV, Rando	m, 95%	CI [min]	
Krystal 2011	24.6	21.1	68	32	35.3	67	16.2%	-7.40 [-17.23, 2.43]		-	_		
Roth 2007	27.3	19.44	67	33	22.02	66	31.3%	-5.70 [-12.76, 1.36]		-	+		
Scharf 2008	22.4	14.04	74	26.8	19.29	73	52.5%	-4.40 [-9.86, 1.06]			+		
Total (95% CI)			209			206	100.0%	-5.29 [-9.25, -1.34]		•	-		
Heterogeneity: Tau² =	0.00; Chi ² = 0	.29, df = 2	(P = 0.8)	36); I² = 0%					-20	-10	_	10	20
Test for overall effect:	Z = 2.62 (P = 1	0.009)								ours 6 mg Doxep	in Favo		20

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

	6 mg	6 mg Doxepin						Mean Difference	Mean Difference			
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]		IV, Random,	95% CI [min]	
Krystal 2011	419.5	44.2	68	391.5	48.9	67	26.1%	28.00 [12.27, 43.73]				
Roth 2007	418.4	32.03	67	389.6	48.86	66	32.6%	28.80 [14.74, 42.86]				
Scharf 2008	398.4	32.29	74	360.7	43.98	73	41.4%	37.70 [25.21, 50.19]			_	_
Total (95% CI)			209			206	100.0%	32.27 [24.24, 40.30]			-	▶
Heterogeneity: Tau² = Test for overall effect:			-50	-25 Favours Placebo	D 25 Favours 6 mg l	50 Doxepin						

¹ All studies funded by Industry

² 95% CI (-29.62, -14.72) crosses Clinical Significance (20 min)

³ 95% CI (18.49, 33.79) crosses Clinical Significance (20 min)

⁴ 95% CI (4.50, 9.07) crosses Clinical Significance (5%)

⁵ 95% CI (0.26, 0.88) crosses Clinical Significance (SMD 0.5)

⁶ 95% CI (-21.89, 3.19) crosses Clinical Significance (20 min)

⁷ Heterogeneity (I² = 82%) greater than allowance (75%)

^{8 95%} CI (5.16, 81.98) crosses Clinical Significance (30 min)

⁹ 95% CI (-39.07, -0.92) crosses Clinical Significance (30 min)

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

_	6 mg	6 mg Doxepin			ntrol			Mean Difference	Mean Difference			
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]		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 = Test for overall effect:			1 (P=	0.13); I² = 569	6				-50	-25 Favours Placebo) 25 Favours 6 mg	50 Doxepin

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

	6 mg	6 mg Doxepin			ntrol			Mean Difference	Mean Difference		
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	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 = Test for overall effect:			(P = 0.7	75); I² = 0%					-20 -10 0 10 20 Favours 6 mg Doxepin Favours Placebo		

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

	6 mg	6 mg Doxepin						Mean Difference	Mean Difference
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	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; Chi ² = 0	0.33, df = 1	(P = 0.9)	57); I² = 0%				-	-20 -10 0 10 20
Test for overall effect	: Z = 2.70 (P =	0.007)							Favours 6 mg Doxenin Favours Placeho

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

_	6 mg	Doxe	pin	C	ontrol	-		Std. Mean Difference	Std. Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	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 : Test for overall effect				= 1 (P =	0.28);	l² = 159	%		-1 -0.5 0 0.5 1 Favours Placebo Favours 6 mg Doxepin			

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

•	,							, ,			
	6 mg	Doxepin		Co	ontrol			Mean Difference	Mean Difference		
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]	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; Chi ² =	= 0.90, df	10 5 10								
Test for overall effect	: Z = 7.12 (P	< 0.0000	01)						-10 -5 0 5 10 Favours Placeho, Favours 6 mg Doxenin		

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

	6 mg	Doxe	pin	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	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: Test for overall effect	•			= 1 (P =	0.77);	l² = 0%			-2 -1 0 1 2 Favours 6 mg Doxepin Favours Placebo

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

	Doxepin	6 mg	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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 = Test for overall effect:				= 0.40)	; I² = 0%		-0.2 -0.1 0 0.1 0.2 Placebo Doxepin 6 mg

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

	Doxepin	6 mg	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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%		-0.1 -0.05 0 0.05 0.1
Test for overall effect:	Z = 2.30 (F	P = 0.02)				Placebo Doxepin 6 mg

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*	⊕⊕⊕⊖	The mean sleep latency in the doxepin groups was 5.29 minutes lower (9.25 to 1.34 lower)	415
(PSG)	moderate ¹		(3 studies) ^{A,B,D}
Total Sleep Time* (PSG)	⊕⊕⊕⊝ moderate¹	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	⊕⊕⊝⊝	The mean total sleep time in the doxepin groups was 18.84 minutes higher (1.65 lower to 39.34 higher)	401
(Subjective)	low ^{1,3}		(2 studies) ^{C,D}
Wake After Sleep Onset*	⊕⊕⊝⊝	The mean wake after sleep onset in the doxepin groups was 23.4 minutes lower (30.34 to 16.46 lower)	415
(PSG)	low ^{1,2}		(3 studies) ^{A,B,D}
Wake After Sleep Onset	⊕⊕⊕⊝	The mean wake after sleep onset in the doxepin groups was 14.39 minutes lower (24.86 to 3.93 lower)	401
(Subjective)	moderate¹		(2 studies) ^{C,D}
Quality of Sleep* (Subjective)	⊕⊕⊕⊝ moderate¹	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	⊕⊕⊕⊝	The mean sleep efficiency in the doxepin groups was 7.06 percent higher (5.12 to 9.01 higher)	280
(PSG)	moderate¹		(2 studies) ^{B,D}
Number of Awakenings	⊕⊕⊕⊝	The mean number of awakenings in the doxepin groups was 0.44 awakenings higher (0.57 lower to 1.44 higher)	280
(PSG)	moderate¹		(2 studies) ^{B,D}

^{*} Critical Outcome, used to determine Quality of Evidence

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*	⊕⊕⊕⊖	The mean sleep latency in the trazadone group was 10.20 minutes lower (11.44 to 8.95 lower)	187		
(Subjective)	moderate ¹		(1 study) ^A		
Total Sleep Time*	⊕⊕⊕⊖	The mean total sleep time in the trazadone group was 21.80 minutes higher (20.10 to 23.49 higher)	187		
(Subjective)	moderate ¹		(1 study) ^A		
Wake After Sleep Onset*	⊕⊕⊕⊖	The mean wake after sleep onset in the trazadone group was 7.70 minutes lower (8.89 to 6.5 lower)	187		
(Subjective)	moderate ¹		(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	⊕⊕⊕⊖	The mean number of awakenings in the trazadone group was 0.40 awakenings lower (0.42 to 0.37 lower)	187		
(Subjective)	moderate¹		(1 study) ^A		

^{*} Critical Outcome, used to determine Quality of Evidence

Tiagabine - Meta-Analyses and Summary of Findings Tables

Figure \$74 – Meta-analysis of data for PSG-determined sleep latency in response to tiagabine 4 mg

J														
	4 mg 1	Fiagabine		Pla	icebo			Mean Difference	Mean Diff	ference				
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 9	95% CI [min]				
Roth, 2006	40.2	3.9	38	30.9	3.3	38	36.2%	9.30 [7.68, 10.92]		-				
Walsh, 2006	32.8	2.8	50	37.6	2.8	50	36.4%	-4.80 [-5.90, -3.70]	-					
Walsh, 2006 JCSM	41.9	25.2	46	34.5	29.2	47	27.4%	7.40 [-3.68, 18.48]		•				
Total (95% CI)			134			135	100.0%	3.65 [-8.00, 15.31]						
Heterogeneity: Tau ² : Test for overall effect				-20 -10 0 Favours 4 mg Tiagabine	10 Eavours Placebo	20								

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

	4 mg T	iagabine		Pla	icebo			Mean Difference	Mean Difference
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]
Roth, 2006	64.3	8.6	8	49.6	7	38	81.6%	14.70 [8.34, 21.06]	
Walsh, 2006 JCSM	52.7	29	46	45.6	36.8	47	18.4%	7.10 [-6.35, 20.55]	•
Total (95% CI)			54			85	100.0%	13.31 [7.54, 19.07]	
Heterogeneity: Tau² = Test for overall effect:	•		(P = 0.3	32); I² = 0%					-20 -10 0 10 20 Favours 4 mg Tiagabine Favours Placebo

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

	4 mg T	iagabine		Pla	icebo			Mean Difference	Mean Difference
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]
Roth, 2006	336.1	7.3	38	338.7	7.6	38	42.8%	-2.60 [-5.95, 0.75]	
Walsh, 2006	383.1	4.4	50	379.8	4.4	50	47.0%	3.30 [1.58, 5.02]	
Walsh, 2006 JCSM	367.8	43.6	46	384	41.78	47	10.2%	-16.20 [-33.56, 1.16]	
Total (95% CI)			134			135	100.0%	-1.21 [-7.44, 5.02]	-
Heterogeneity: Tau ² =	20.70; Chi² =	13.63, df=	2 (P =	0.001); I² = 85	5%			-	-20 -10 0 10 20
Test for overall effect:	Z = 0.38 (P = 1	0.70)		Favours Placebo Favours 4 mg Tiagabine					

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

	4 mg I	iagabine		Pla	cebo			Mean Difference	Mean Difference
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]
Roth, 2006	312.3	13.9	38	332.1	10.3	38	96.6%	-19.80 [-25.30, -14.30]	
Walsh, 2006 JCSM	331.4	77.9	46	355.5	65.6	47	3.4%	-24.10 [-53.40, 5.20]	
Total (95% CI) Heterogeneity: Tau² = Test for overall effect:	•		84 (P = 0.7	'8); I² = 0%		85	100.0%	-19.95 [-25.35, -14.54]	-20 -10 0 10 20 Favours Placebo Favours 4 mg Tiagabine

¹ Study funded by industry

² 4-point scale (1=Excellent, 4=Poor)

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

	4 mg T	Tiagabine		Pla	icebo			Mean Difference	Mean Difference
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]
Roth, 2006	112.5	6.6	38	118.2	6.6	38	40.7%	-5.70 [-8.67, -2.73]	
Walsh, 2006	68.2	3.9	50	66.9	3.9	50	43.6%	1.30 [-0.23, 2.83]	
Walsh, 2006 JCSM	76.1	34	46	68.5	27.8	47	15.7%	7.60 [-5.04, 20.24]	
Total (95% CI)			134			135	100.0%	-0.56 [-6.77, 5.65]	-
Heterogeneity: Tau² = Test for overall effect:			-20 -10 0 10 20 Favours 4 mg Tiagabine Favours Placebo						

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

	4 mg T	Tiagabine		Pla	icebo			Mean Difference	Mean Difference
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]
Roth, 2006	97.6	9.5	38	93.2	10.8	38	97.1%	4.40 [-0.17, 8.97]	-
Walsh, 2006 JCSM	75.4	62.8	46	74.9	66.3	47	2.9%	0.50 [-25.74, 26.74]	
Total (95% CI)			84			85	100.0%	4.29 [-0.22, 8.79]	•
Heterogeneity: Tau² = Test for overall effect:	•		-20 -10 0 10 20 Favours 4 mg Tiagabine Favours Placebo						

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

J	4 mg	Tiagab	ine	Pl	acebo	,		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Roth, 2006	2.7	0.1	38	2.6	0.1	38	49.2%	0.99 [0.51, 1.47]	
Walsh, 2006 JCSM	56.9	21.8	46	57.1	20.7	47	50.8%	-0.01 [-0.42, 0.40]	
Total (95% CI)			84			85	100.0%	0.48 [-0.50, 1.46]	
Heterogeneity: Tau² : Test for overall effect				1 (P = 0	0.002)	; I² = 90	%	-	-1 -0.5 0 0.5 1 Favours Placebo Favours 4 mg Tiagabine

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

_	4 mg 1	Гiagab	ine	Pla	aceb	0		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Roth, 2006	70	1.5	38	70.6	1.6	38	36.3%	-0.60 [-1.30, 0.10]	
Walsh, 2006	85.6	1.1	50	86	1.1	50	61.8%	-0.40 [-0.83, 0.03]	-
Walsh, 2006 JCSM	76.6	9.1	46	80	8.7	47	2.0%	-3.40 [-7.02, 0.22]	
Total (95% CI)			134			135	100.0%	-0.53 [-1.05, -0.02]	•
Heterogeneity: Tau² : Test for overall effect			•	2 (P = 1		-4 -2 0 2 4 Favours Placebo Favours 4 mg Tiagabine			

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

	4 mg T	ïagab	ine	Pla	acebo)		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Walsh, 2006	10.6	5	50	9.8	5	50	83.5%	0.80 [-1.16, 2.76]	- •	
Walsh, 2006 JCSM	31.1	12	46	32.1	9.5	47	16.5%	-1.00 [-5.40, 3.40]	•	
Total (95% CI)			96			97	100.0%	0.50 [-1.29, 2.29]		
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0% Test for overall effect: Z = 0.55 (P = 0.58) Test for overall effect: Z = 0.55 (P = 0.58) Test for overall effect: Z = 0.55 (P = 0.58)										

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

	4 mg T	iagab	ine	Pla	icebo)		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Roth, 2006	3.4	0.3	38	3.4	0.4	38	73.7%	0.00 [-0.16, 0.16]	-	
Walsh, 2006 JCSM	3.4	1.9	46	4.2	3.3	47	26.3%	-0.80 [-1.89, 0.29]		
Total (95% CI)			84			85	100.0%	-0.21 [-0.90, 0.48]		
Heterogeneity: Tau ² = Test for overall effect:	•	-2 -1 0 1 :	-1 2							
		,	•						Favours 4 mg Tiagabine Favours Placebo	

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

	Tiagabine	4 mg	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
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 = 1)	0.63); P	²= 0%		-0.1 -0.05 0 0.05 0.1
Test for overall effect:	Z= 0.17 (P=	0.86)					Placebo Tiagabine 4 mg

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

	Tiagabine	4 mg	Place	bo		Risk Difference		Risk Dif	ference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rand	om, 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 = 1)	0.68); P	²=0%		-0.1	-0.05	0.05	0.1
Test for overall effect:	Z= 0.66 (P=	0.51)					-0.1	Placebo	Tiagabine 4 mg	

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	⊕⊕⊕⊝	The mean sleep latency in the tiagabine groups was 13.31 minutes higher (7.54 to 19.07 higher)	139
(Subjective)	moderate³		(2 studies) ^{A,C}
Total Sleep Time*	⊕⊕⊝⊝	The mean total sleep time in the tiagabine groups was 1.21 minutes lower (7.44 lower to 5.02 higher)	269
(PSG)	low ^{3,5}		(3 studies) ^{A,B,C}
Total Sleep Time	⊕⊕⊕⊝	The mean total sleep time in the tiagabine groups was 19.95 minutes lower (25.35 to 14.54 lower)	169
(Subjective)	moderate³		(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	⊕⊕⊕⊝	The mean wake after sleep onset in the tiagabine groups was 4.29 minutes higher (0.22 lower to 8.79 higher)	169
(Subjective)	moderate³		(2 studies) ^{A,C}
Quality of Sleep*	⊕⊖⊝	The mean quality of sleep in the tiagabine groups was 0.48 standard deviations higher (0.5 lower to 1.46 higher)	169
(Subjective)	very low ^{3,7,8}		(2 studies) ^{A,C}
Sleep Efficiency	⊕⊕⊕⊝	The mean sleep efficiency in the tiagabine groups was 0.53 percent lower (1.05 to 0.02 lower)	269
(PSG)	moderate³		(3 studies) ^{A,B,C}
Number of Awakenings	⊕⊕⊝⊝	The mean number of awakenings in the tiagabine groups was 0.5 awakenings higher (1.29 lower to 2.29 higher)	193
(PSG)	low ^{3,6}		(2 studies) ^{B,C}
Number of Awakenings	⊕⊕⊝⊝	The mean number of awakenings in the tiagabine groups was 0.21 awakenings lower (0.9 lower to 0.48 higher)	169
(Subjective)	low ^{3,9}		(2 studies) ^{A,C}

^{*} Critical Outcome, used to determine Quality of Evidence
1 Heterogeneity (I² = 99%) greater than allowance (75%)

^{95%} CI (-8.0, 15.31) crosses Clinical Significance (10 min)
All studies funded by industry

All studies runded by findustry

4 Heterogeneity (I² = 89%) greater than allowance (75%)

5 Heterogeneity (I² = 85%) greater than allowance (75%)

6 95% CI (-1.29, 2.29) crosses Clinical Significance (2 awakenings)

7 Heterogeneity (I² = 90%) greater than allowance (75%)

 ^{8 95%} CI (-0.50, 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	⊕⊕⊖⊝	The mean sleep latency in the tiagabine groups was 6.9 minutes higher (2.22 to 11.58 higher)	175	
(PSG)	low³,7		(2 studies) ^{A,B}	
Sleep Latency	⊕⊕⊕⊝	The mean sleep latency in the tiagabine groups was 5.68 minutes higher (3.05 to 8.3 higher)	175	
(Subjective)	moderate³		(2 studies) ^{A,B}	
Total Sleep Time*	⊕⊕⊕⊝	The mean total sleep time in the tiagabine groups was 7.17 minutes higher (0.26 lower to 14.59 higher)	175	
(PSG)	moderate ³		(2 studies) ^{A,B}	
Total Sleep Time (Subjective)	⊕⊕⊕⊝ moderate³	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*	⊕⊖⊝⊝	The mean wake after sleep onset in the tiagabine groups was 9.24 minutes lower (24.78 lower to 6.3 higher)	175	
(PSG)	very low ^{1,2,3}		(2 studies) ^{A,B}	
Wake After Sleep Onset	⊕⊕⊕⊝	The mean wake after sleep onset in the tiagabine groups was 5.68 minutes higher (3.05 to 8.3 higher)	175	
(Subjective)	moderate³		(2 studies) ^{A,B}	
Quality of Sleep*	⊕⊕⊖⊝	The mean quality of sleep in the tiagabine groups was 0.01 standard deviations higher (0.28 lower to 0.31 higher)	175	
(Subjective)	low ^{3,4}		(2 studies) ^{A,B}	
Sleep Efficiency	⊕⊕⊕⊝	The mean sleep efficiency in the tiagabine groups was 1.46 percent higher (0.15 lower to 3.06 higher)	175	
(PSG)	moderate³		(2 studies) ^{A,B}	
Number of Awakenings	⊕⊖⊝⊝	The mean number of awakenings in the tiagabine groups was 0.49 awakenings lower (1.84 lower to 0.87 higher)	175	
(Subjective)	very low ^{3,5,6}		(2 studies) ^{A,B}	

^{*} Critical Outcome, used to determine Quality of Evidence
1 Heterogeneity (I² = 81%) crosses threshold (75%)

^{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

Heterogeneity (I² = 83%) crosses threshold (75%)
 95% CI (-1.84, 0.87) crosses Clinical Significance (0.5 awakenings)
 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	⊕⊕⊕⊝	The mean sleep latency in the tiagabine groups was 1.22 minutes lower (2.66 lower to 0.22 higher)	271
(PSG)	moderate ¹		(3 studies) ^{A,B,C}
Sleep Latency	⊕⊕⊕⊝	The mean sleep latency in the tiagabine groups was 2.12 minutes lower (3.48 to 0.76 lower)	171
(Subjective)	moderate ¹		(2 studies) ^{A,C}
Total Sleep Time*	⊕⊕⊖	The mean total sleep time in the tiagabine groups was 3.49 minutes higher (6.43 lower to 13.42 higher)	271
(PSG)	low ^{1,3}		(3 studies) ^{A,B,C}
Total Sleep Time	⊕⊝⊝	The mean total sleep time in the tiagabine groups was 16.09 minutes lower (44.97 lower to 12.79 higher)	171
(Subjective)	very low ^{1,7,8}		(2 studies) ^{A,C}
Wake After Sleep Onset*	⊕⊕⊝⊝	The mean wake after sleep onset in the tiagabine groups was 2.42 minutes lower (10.35 lower to 5.51 higher)	271
(PSG)	low ^{1,2}		(3 studies) ^{A,B,C}
Wake After Sleep Onset	⊕⊕⊕⊖	The mean wake after sleep onset in the tiagabine groups was 9.71 minutes higher (5.7 to 13.72 higher)	171
(Subjective)	moderate ¹		(2 studies) ^{A,C}
Quality of Sleep*	⊕⊖⊖⊖	The mean quality of sleep in the tiagabine groups was 0.37 standard deviations higher (0.65 lower to 1.39 higher)	171
(Subjective)	very low ^{1,5,6}		(2 studies) ^{A,C}
Sleep Efficiency	⊕⊕⊖	The mean sleep efficiency in the tiagabine groups was 0.68 percent higher (1.41 lower to 2.76 higher)	271
(PSG)	low ^{1,3}		(3 studies) ^{A,B,C}
Number of Awakenings	⊕⊕⊖⊝	The mean number of awakenings in the tiagabine groups was 0.88 awakenings lower (3.7 lower to 1.95 higher)	192
(PSG)	low ^{1,4}		(2 studies) ^{B,C}
Number of Awakenings	⊕⊕⊖⊝	The mean number of awakenings in the tiagabine groups was 0.3 awakenings higher (0.38 lower to 0.98 higher)	171
(Subjective)	low ^{1,9}		(2 studies) ^{A,C}

^{*} Critical Outcome, used to determine Quality of Evidence

All studies funded by industry

All studies runded by industry

Heterogeneity (I² = 93%) greater than allowance (75%)

Heterogeneity (I² = 94%) greater than allowance (75%)

Heterogeneity (I² = 94%) greater than allowance (75%)

String (I² = 94%) greater than allowance (2 awakenings)

⁵ Heterogeneity (I² = 91%) greater than allowance (75%) ⁶ 95% CI (-0.65, 1.39) crosses zero standard mean difference

⁷ Heterogeneity (I² = 89%) greater than allowance (75%)

^{8 95%} CI (-44.97, 12.79) crosses Clinical Significance 9 95% CI (-0.38, 0.98) crosses Clinical Significance (0.5 awakenings)

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

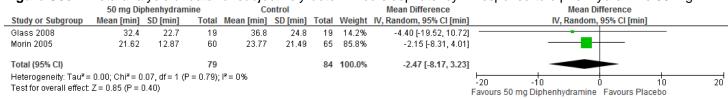


Figure S87 - Meta-analysis of data for subjectively-determined total sleep time in response to diphenhydramine 50 mg

	50 mg Dij	phenhydram	ine	Co	ntrol			Mean Difference	Mean Difference
Study or Subgroup	Mean [min]	SD [min]	Total	Mean [min]	SD [min]	Total	Weight	IV, Random, 95% CI [min]	IV, Random, 95% CI [min]
Glass 2008	396	78	19	378	78	19	19.0%	18.00 [-31.60, 67.60]	- •
Morin 2005	419.59	60.62	58	401.76	75.35	65	81.0%	17.83 [-6.23, 41.89]	
Total (95% CI)			77			84	100.0%	17.86 [-3.79, 39.51]	
Heterogeneity: Tau² = Test for overall effect:	-50 -25 0 25 50 Favours Placebo Favours 50 mg Diphenhydramine								

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*	⊕⊕⊝	The mean sleep latency in the diphenhydramine group was 7.89 minutes lower (17.40 lower to 1.62 higher)	52	
(PSG)	low ^{5,7}		(1 study) ^A	
Sleep Latency	⊕⊕⊖	The mean sleep latency in the diphenhydramine groups was 2.47 minutes lower (8.17 lower to 3.23 higher)	163	
(Subjective)	low ^{1,2}		(2 studies) ^{A,B}	
Total Sleep Time*	⊕⊕⊖	The mean total sleep time in the diphenhydramine group was 12.37 minutes higher (13.38 lower to 38.12 higher)	52	
(PSG)	low ^{5,8}		(1 study) ^A	
Total Sleep Time	⊕⊕⊖	The mean total sleep time in the diphenhydramine groups was 17.86 minutes higher (3.79 lower to 39.51 higher)	161	
(Subjective)	low ^{1,2}		(2 studies) ^{A,B}	
Quality of Sleep*	⊕⊕⊕⊝	The mean quality of sleep in the diphenhydramine group was 0.1 points ⁹ higher (0.45 lower to 0.65 higher)	38	
(Subjective)	moderate⁵		(1 study) ^A	
Sleep Efficiency	⊕⊕⊖⊝	The mean sleep efficiency in the diphenhydramine group was 2.59 percent higher (3.25 lower to 8.43 higher)	52	
(PSG)	low ^{4,5}		(1 study) ^B	
Sleep Efficiency	⊕⊕⊕⊝	The mean sleep efficiency in the diphenhydramine group was 4.61 percent higher (1.33 to 7.88 higher)	123	
(Subjective)	moderate ⁵		(1 study) ^A	
Number of Awakenings	⊕⊕⊕⊖	The mean number of awakenings in the diphenhydramine group was 0.3 awakenings lower (1.03 lower to 0.43 higher)	38	
(Subjective)	moderate³		(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

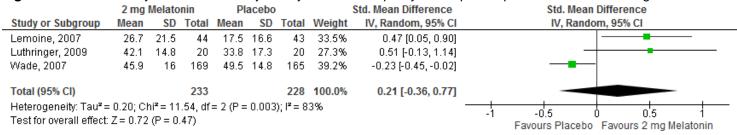


Table S22 - Summary of Findings table for melatonin 2 mg for the treatment of chronic insomnia

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*	⊕⊕⊝⊝	The mean sleep latency in the melatonin group was 8.9 minutes lower (15.45 to 2.35 lower)	40
(PSG)	low ^{3,4}		(1 study) ^B
Total Sleep Time	⊕⊝⊝	The mean total sleep time in the melatonin group was 2.2 minutes higher (19.13 lower to 23.53 higher)	40
(PSG)	very low ^{3,6}		(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*	⊕⊝⊝	The mean quality of sleep in the melatonin group was 0.21 standard deviations higher (0.36 lower to 0.77 higher)	461
(Subjective)	very low ^{1,2,3}		(3 studies) ^{A,B,C}
Number of Awakenings	⊕⊝⊝	The mean number of awakenings in the melatonin group was 1.4 awakenings higher (4.59 lower to 7.39 higher)	40
(PSG)	very low ^{3,7}		(1 study) ^B

^{*} Critical Outcome, used to determine Quality of Evidence

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 Heterogeneity (I² = 83%) greater than allowance (75%)

² 95% CI (-0.36, 0.77) crosses zero standard mean difference

³ All studies funded by industry

^{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

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

Outcomes	Quality of the evidence (GRADE)	Absolute Difference Valerian-hops vs Placebo	No of Participants (studies)
Sleep Latency*	⊕⊕⊖⊝	The mean sleep latency in the Valerian-hops groups was 9.29 minutes lower (18.3 to 0.27 lower)	48
(PSG)	low ^{1,2}		(1 study) ^A
Sleep Latency	⊕⊕⊕⊝	The mean sleep latency in the Valerian-hops groups was 3.77 minutes higher (4.47 lower to 12.01 higher)	124
(Subjective)	moderate²		(1 study) ^A
Total Sleep Time	⊕⊖⊖	The mean total sleep time in the Valerian-hops groups was 10.96 minutes higher (21.67 lower to 43.59 higher)	48
(PSG)	very low ^{2,3}		(1 study) ^A
Total Sleep Time	⊕⊕⊕⊖	The mean total sleep time in the Valerian-hops groups was 3.12 minutes higher (22.08 lower to 28.32 higher)	123
(Subjective)	moderate ²		(1 study) ^A
Sleep Efficiency	⊕⊖⊖	The mean sleep efficiency in the Valerian-hops groups was 0.96 percent higher (5.02 lower to 6.94 higher)	48
(PSG)	very low ^{2,4}		(1 study) ^A
Sleep Efficiency	⊕⊕⊕⊝	The mean sleep efficiency in the Valerian-hops groups was	123
(Subjective)	moderate²	1.85 percent higher (1.9 lower to 5.6 higher)	(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%)