#### PEER Systematic Review of Randomized Controlled Trials: Management of Chronic Neuropathic Pain in Primary Care Appendix 2

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### Table 1: Neuropathic Pain Outcomes Hierarchy

- This hierarchy outlines the priority of outcomes used for overall meta-analyses presented in the systematic review.
- When there are studies that report a scale change on: Pain only or pain and function, we would prefer to use assessments on pain only. We are not including assessments or responder analyses that only focus on function.
  - **Rationale:** As clinicians we understand function is crucial however, we also know that pain is the presenting issue for patients. Therefore, we wanted to develop information around pain to allow for shared decision-making with our patients.
- 1. Percent improvement on a pain scale that is closest to 30% improvement
  - a. If there is a tie, e.g., 25% and 35% improvement, we would use the higher number.
- 2. Clinically meaningful change on any low back pain scale
  - a. This includes achieving a particular back pain scale score that reaches a certain threshold on the low back pain scale at the study endpoint.
- 3. Change of **at least** 1 on a VAS / NRS scale (out of 11 or 10); Or change of ≥10 on a VAS/NRS (out of scale 100).
  - a. If multiple outcomes included are reported, order of preference is:
    - ≥2 change on VAS/NRS out of 10-11 or change of ≥20 on VAS/NRS out of 100.
    - ii.  $\geq$ 3 change on VAS/NRS out of 10-11 or change of  $\geq$ 30 on VAS/NRS out of 100.
    - iii.  $\geq$ 1 change on VAS / NRS out of 10-11 or change of  $\geq$ 10 on VAS / NRS out of 100.

**Note:** Change of at least 2 is preferred because if an average baseline pain of 5-6 is seen, a change of 2 would be closest to a 30% improvement in change.

- Reaching a score of ≤4 on VAS / NRS scale (out of 11 or 10); Or score of ≤40 on a VAS/NRS (out of scale 100).
  - a. If multiple is present, order of preference is:
    - Reaching a score of ≤4 on VAS / NRS scale (out of 11 or 10); Or score of ≤40 on a VAS/NRS (out of scale 100).
    - Reaching a score of ≤3 on VAS / NRS scale (out of 11 or 10); Or score of ≤30 on a VAS/NRS (out of scale 100).
    - iii. Reaching a score of ≤2 on VAS / NRS scale (out of 11 or 10); Or score of ≤20 on a VAS/NRS (out of scale 100).
    - iv. Reaching a score of  $\leq 1$  on VAS / NRS scale (out of 11 or 10); Or score of  $\leq 10$  on a VAS/NRS (out of scale 100).

**Note:** Reaching a score of <4/10 is preferred because if an average baseline pain of 5-6/10 is seen, obtaining a score of 4 or less would be closest to a 30% improvement in change.

5. Change in a scale that are out of a score not mentioned above (example out of 20). (We will have to adjust so it comes close to that 30% improvement.)

- 6. Patient Global Assessment of Change / Improvement (e.g., None/Slight/Moderate/Very Good/Excellent (or similar language).
  - a. If multiple outcomes involving the assessment is available or calculatable, preference is:
    - i. Patients achieving at least a **moderate/good** (or similar wording) or greater change.
    - ii. Patients achieving at least a **very good** (or similar wording) or greater change.
    - iii. Patients achieving at least an **excellent** (or similar wording) or greater change.
  - b. Notes:
    - i. We are not including caregiver or clinician assessment of change.
    - ii. If there is an undefined % improved as determined by **patient**, we would include.
    - iii. There may be times when authors need to combine raw event numbers to obtain the above pre-specified outcomes, this would occur following data extraction step.

### **Table 2: Included Randomized Controlled Trials**

Intervention	Author, Year	Sample	Duration of	Mean	Outcome	Intervention(s)	Outcome used in
Туре		Size	Neuropathic Pain (weeks)/Type of Neuropathic Pain	Age	Measured At		Meta-Analysis
Acupuncture	Garrow 2014	59	Not Reported/ Diabetic Neuropathy	65	10 weeks	Standardized Acupuncture; 10 weekly sessions Sham Acupuncture; 10 weekly sessions	>25% Improvement in Pain
Acupuncture	Lewith 1983	62	65 weeks/ Postherpetic Neuralgia	72	8 weeks	Auricular Acupuncture; maximum 8 weekly sessions Sham TENS machine; maximum 8 weekly sessions	2-point Improvement on a 7-point Pain Scale
Acupuncture	Shin 2018	126	183 weeks/ Diabetic Neuropathy	NR	9 weeks	Electroacupuncture; twice weekly sessions over 8 weeks + Diet/Lifestyle Brochure Diet/Lifestyle Brochure	<u>&gt;</u> 50% Reduction in Pain
Anticonvulsants	Achar 2010	30	Not reported/ Postherpetic Neuralgia	NR	8 weeks	Pregabalin 75 mg twice daily + Amitriptyline 25 mg daily Amitriptyline 25 mg daily	<u>&gt;</u> 75% Improvement in Pain
Anticonvulsants	Arezzo 2008	167	242 weeks/ Diabetic Neuropathy	58	13 weeks	Pregabalin 300 mg twice daily Placebo	<u>&gt;</u> 50% Reduction in Pain
Anticonvulsants	Baba 2020	450	144 weeks/ Diabetic Neuropathy	60	7 weeks	Pregabalin 150 mg twice daily Placebo	≥30% Reduction in Pain
Anticonvulsants	Backonja 1998	165	Not Reported/ Diabetic Neuropathy	53	8 weeks	Gabapentin 3600 mg daily (max) Placebo	PGIC "Much" or "Moderate" Improvement
Anticonvulsants	Backonja 2011	101	170 weeks/ Postherpetic Neuralgia	64	2 weeks	Gabapentin 624 mg daily Placebo	30% Improvement in Pain
Anticonvulsants	Beydoun 2006	347	144 weeks/ Diabetic Neuropathy	61	16 weeks	Oxcarbazepine 300 mg twice daily Oxcarbazepine 600 mg twice daily Oxcarbazepine 900 mg twice daily Placebo	PGIC "Much" or "Very Much" Improved

Anticonvulsants	CTRI476G230 1	141	151 weeks/ Diabetic Neuropathy	61	16 weeks	Oxcarbazepine 1200 mg daily Placebo	PGIC "Much" or "Very Much" Improved
Anticonvulsants	Dogra 2005	146	138 weeks/ Diabetic Neuropathy	60	16 weeks	Oxcarbazepine 900 mg twice daily Placebo	≥30% Reduction in Pain
Anticonvulsants	Dworkin 2003	173	135 weeks/ Postherpetic Neuralgia	72	8 weeks	Pregabalin 100-200 mg thrice daily Placebo	≥30% Reduction in Pain
Anticonvulsants	Guan 2011	308	149 weeks/ Diabetic Neuropathy	60	8 weeks	Pregabalin 150-600 mg daily Placebo	≥30% Reduction in Pain
Anticonvulsants	Freynhagen 2005	338	149 weeks (PHN), 244 weeks (DN)/ Postherpetic Neuralgia + Diabetic Neuropathy	62	12 weeks	Pregabalin Flexible Dose 75-300 mg twice daily (mean 372 mg daily) Pregabalin Fixed Dose 300 mg twice daily Placebo	≥30% Reduction in Pain
Anticonvulsants	Huffman 2015	203	247 weeks/ Diabetic Neuropathy	59	6 weeks	Pregabalin 150-300 mg thrice daily Placebo	≥30% Reduction in Pain
Anticonvulsants	Lesser 2004	337	Not Reported/ Diabetic Neuropathy	60	5 weeks	Pregabalin 25 mg thrice daily Pregabalin 100 mg thrice daily Pregabalin 300 mg thrice daily Placebo	≥30% Reduction in Pain
Anticonvulsants	Liu 2017	220	18 weeks/ Postherpetic Neuralgia	65	8 weeks	Pregabalin 300 mg daily Placebo	≥30% Reduction in Pain
Anticonvulsants	McDonnell 2018	91	387 weeks/ Diabetic Neuropathy	59	4 weeks	Pregabalin 150 mg twice daily Placebo	≥30% Reduction in Pain
Anticonvulsants	Moon 2010	240	111 weeks/ Postherpetic Neuralgia (primarily)	60	8 weeks	Pregabalin 600 mg daily Placebo	<u>&gt;</u> 30% Reduction in Pain

Anticonvulsants	Mu 2018	620	120 weeks/ Diabetic Neuropathy	61	11 weeks	Pregabalin 300 mg daily Placebo	≥30% Reduction in Pain
Anticonvulsants	NCT0221525 2 2014	91	Not Reported/ Diabetic Neuropathy	59	4 weeks	Pregabalin 300 mg daily Placebo	≥30% Reduction in Pain
Anticonvulsants	NCT0039490 1 2006	372	Not Reported/ Diabetic Neuropathy	70	13 weeks	Pregabalin 150 mg daily Pregabalin 300 mg daily Pregabalin 600 mg daily Placebo	<u>&gt;</u> 50% Reduction in Pain
Anticonvulsants	Perez 2000	32	Not Reported/ Diabetic Neuropathy	54	12 weeks	Gabapentin 1200 mg daily (max) Placebo	Pain Relief
Anticonvulsants	Raskin 2004	323	166 weeks/Diabetic Neuropathy	59	12 weeks	Topiramate 400 mg daily Placebo	≥30% Reduction in Pain
Anticonvulsants	Rauck 2012	420	Not Reported/ Diabetic Neuropathy	59	13 weeks	Gabapentin 1200 mg daily Gabapentin 2400 mg daily Gabapentin 3600 mg daily Pregabalin 300 mg daily Placebo	<u>&gt;</u> 30% Reduction in Pain
Anticonvulsants	Rice 2001	334	114 weeks/ Postherpetic Neuralgia	75	7 weeks	Gabapentin 1800 mg daily Gabapentin 2400 mg daily Placebo	≥50% Reduction in Pain
Anticonvulsants	Richter 2005	246	Not Reported/ Diabetic Neuropathy	57	6 weeks	Pregabalin 150 mg daily Pregabalin 600 mg daily Placebo	≥50% Reduction in Pain
Anticonvulsants	Rosenstock 2004	146	Not Reported/ Diabetic Neuropathy	60	8 weeks	Pregabalin 300 mg daily Placebo	≥50% Reduction in Pain
Anticonvulsants	Rowbotham 1998	229	Not Reported/ Postherpetic Neuralgia	74	8 weeks	Gabapentin 3600 mg daily (max) Placebo	PGIC "Much" or "Moderately" Improved
Anticonvulsants	Sabatowski 2004	238	169 weeks/ Postherpetic Neuralgia	72	8 weeks	Pregabalin 150 mg daily Pregabalin 300 mg daily Placebo	≥50% Reduction in Pain

Anticonvulsants	Sandercock 2012	147	Not Reported/ Diabetic Neuropathy	59	4 weeks	Gabapentin 3000 mg daily (single) Gabapentin 3000 mg daily (divided 1200 mg AM; 1800 mg PM) Placebo	≥50% Reduction in Pain
Anticonvulsants	Sang 2013	452	81 weeks/ Postherpetic Neuralgia	66	10 weeks	Gabapentin 1800 mg daily Placebo	≥50% Reduction in Pain
Anticonvulsants	Satoh 2011	314	223 weeks/ Diabetic Neuropathy	61	13 weeks	Pregabalin 150 mg twice daily Pregabalin 300 mg twice daily Placebo	≥30% Reduction in Pain
Anticonvulsants	Shabbir 2011	210	Not Reported/ Diabetic Neuropathy	NR	6 weeks	Pregabalin 600 mg daily Placebo	≥50% Reduction in Pain
Anticonvulsants	Sharma 2006	167	260 weeks/ Diabetic Neuropathy	58	13 weeks	Pregabalin 300 mg twice daily Placebo	≥50% Reduction in Pain
Anticonvulsants	Smith 2014	383	Not Reported/ Diabetic Neuropathy	58	15 weeks	Pregabalin 300 mg daily Placebo	≥30% Reduction in Pain
Anticonvulsants	Stacey 2008	269	130 weeks/ Postherpetic Neuralgia	67	4 weeks	Pregabalin Flexible Dose (mean 396 mg daily) Pregabalin Fixed Dose (mean 295.4 mg daily) Placebo	≥30% Reduction in Pain
Anticonvulsants	Tolle 2008	395	Not Reported/ Diabetic Neuropathy	59	12 weeks	Pregabalin 150 mg daily Pregabalin 300 mg daily Pregabalin 600 mg daily Placebo	≥50% Reduction in Pain
Anticonvulsants	Van-Seventer 2006	368	163 weeks/ Postherpetic Neuralgia	71	13 weeks	Pregabalin 150 mg daily Pregabalin 300 mg daily Pregabalin 600 mg daily Placebo	≥30% Reduction in Pain
Anticonvulsants	Vinik 2014	452	302 weeks/ Diabetic Neuropathy	60	5 weeks	Pregabalin 300 mg daily Placebo	≥30% Reduction in Pain
Anticonvulsants	Wallace 2010	405	Not Reported/	67	10 weeks	Gabapentin 1800 mg daily (single) Gabapentin 1800 mg daily (divided)	≥50% Reduction in Pain

			Postherpetic Neuralgia			Placebo	
Anticonvulsants	Zhang 2013	371	Not Reported/ Postherpetic Neuralgia	62	13 weeks	Gabapentin 1200 mg daily Gabapentin 2400 mg daily Gabapentin 3600 mg daily Placebo	≥30% Reduction in Pain
Anticonvulsants	Ziegler 2015	132	295 weeks/ Diabetic Neuropathy	59	6 weeks	Pregabalin 150 mg twice daily Placebo	≥30% Reduction in Pain
Opioids	Freeman 2007	313	192 weeks/ Diabetic Neuropathy	56	9 weeks	Tramadol 37.5 mg/Acetaminophen 325 mg; 1-2 tablets, four times daily Placebo	30% Improvement in Pain
Opioids	Hanna 2008	338	Not Reported/ Diabetic Neuropathy	60	12 weeks	Oxycodone 10-80 mg daily Placebo	PGIC "good" or "very good" improvement
Opioids	Jensen 2006	159	Not Reported/ Diabetic Neuropathy	59	6 weeks	Oxycodone 60 mg twice daily Placebo	33% Reduction in Pain
Opioids	NCT0112461 7 2010	91	Not Reported/ Diabetic Neuropathy + Postherpetic Neuralgia	66	12 weeks	Tapentadol 25-250 mg twice daily Placebo	30% Reduction in Pain
Opioids	Simpson 2016	186	Not Reported/ Diabetic Neuropathy	63	12 weeks	Buprenorphine Patch 5-40 mg/hour Placebo Patch	30% Reduction in Pain
Opioids	Zin 2010	62	189 weeks/ Diabetic Neuropathy + Postherpetic Neuralgia	68	5 weeks	Oxycodone 2 mg/ml (5 mg) twice daily + Pregabalin (max 300 mg twice daily) Placebo + Pregabalin (max 300 mg twice daily)	50% Reduction in Pain
Rubefacients	Backonja 2008	402	203 weeks/ Postherpetic Neuralgia	71	12 weeks	8% Capsaicin Patch applied once for 60 minutes 0.04% Capsaicin Patch	30% Reduction in Pain
Rubefacients	Bernstein 1989	32	144 weeks/ Postherpetic Neuralgia	72	6 weeks	0.075% Capsaicin Cream applied 3-4 times daily Vehicle Cream	≥40% Pain Improvement

Rubefacients	Capsaicin Study Group 1992	277	216 weeks/ Diabetic Neuropathy	60	8 weeks	0.075% Capsaicin Cream applied 4 times daily Vehicle Cream	PGIC "Improved"
Rubefacients	Irving 2011	416	166 weeks/ Postherpetic Neuralgia	70	12 weeks	8% Capsaicin Patch; Applied for one, 60- minute session 0.04% Capsaicin Placebo Patch	≥30% Reduction in Pain
Rubefacients	Moon 2017	60	146 weeks/ Postherpetic Neuralgia	70	6 weeks	0.075% Capsaicin Cream applied 3-4 times daily 0.625% Capsaicin Patch applied in 4-day cycles (3 days on, 1 day off) 1.25% Capsaicin Patch applied in 4-day cycles (3 days on, 1 day off) Placebo Patch	≥30% Reduction in Pain
Rubefacients	Simpson 2017	369	299 weeks/ Diabetic Neuropathy	63	12 weeks	8% Capsaicin Patch (Applied for a single, 30-minute session) Placebo Patch	≥30% Reduction in Pain
Rubefacients	Tandan 1992	22	257 weeks/ Diabetic Neuropathy	54	8 weeks	0.075% Capsaicin Cream applied 4 times daily Vehicle Cream	Categorical Pain Scale ("improved")
Rubefacients	Vinik 2015	468	229 weeks/ Diabetic Neuropathy	60	52 weeks	8% Capsaicin Patch (Applied for 60 minutes for 1-7 treatments with 8-week intervals between each treatment) + Standard of Care	≥30% Pain Improvement
						8% Capsaicin Patch (Applied for 30 minutes for 1-7 treatments with 8-week intervals between each treatment) + Standard of Care	
						Standard of Care	
Rubefacients	Watson 1993	143	128 weeks/ Postherpetic Neuralgia	71	6 weeks	0.075% Capsaicin Cream applied 4 times daily Vehicle Cream	Decreased pain (at least a one-point change on a categoric pain scale)
Rubefacients	Webster 2010	155	153 weeks/ Postherpetic Neuralgia	70	12 weeks	8% Capsaicin Patch; Applied for one, 60- minute session 0.04% Capsaicin Placebo Patch	≥30% Reduction in Pain

SNRIs	Allen 2014	408	168 weeks/ Diabetic Neuropathy	60	13 weeks	Desvenlafaxine 50 mg daily Desvenlafaxine 100 mg daily Desvenlafaxine 200 mg daily Desvenlafaxine 400 mg daily Placebo	≥30% Improvement on Numerical Pain Rating Scale
SNRIs	Gao 2010	215	166 weeks/ Diabetic Neuropathy	59	12 weeks	Duloxetine 60-120 mg daily Placebo	30% Reduction in Pain
SNRIs	Gao 2014	405	172 weeks/ Diabetic Neuropathy	61	12 weeks	Duloxetine 60 mg daily Placebo	≥30% Improvement in Pain
SNRIs	Goldstein 2005	457	192 weeks/ Diabetic Neuropathy	60	12 weeks	Duloxetine 20 mg daily Duloxetine 60 mg daily Duloxetine 120 mg daily (60mg twice daily) Placebo	50% Reduction in Pain
SNRIs	Raskin 2005	348	224 weeks/ Diabetic Neuropathy	59	12 weeks	Duloxetine 60 mg daily Duloxetine 60 mg twice daily Placebo	30% Reduction in Pain
SNRIs	Rowbotham 2005	245	253 weeks/ Diabetic Neuropathy	59	6 weeks	Venlafaxine 75 mg daily Venlafaxine 150-225 mg daily Placebo	50% Reduction in Pain
SNRIs	Wernicke 2006	334	198 weeks/ Diabetic Neuropathy	61	12 weeks	Duloxetine 60 mg daily Duloxetine 60 mg twice daily Placebo	30% Reduction in Pain
SNRIs	Yasuda 2011	339	224 weeks/ Diabetic Neuropathy	61	13 weeks	Duloxetine 40 mg daily Duloxetine 60 mg daily Combined Arm (40 mg and 60 mg) Placebo	30% Reduction in Pain
TCAs	Achar 2010	45	Not Reported/ Postherpetic Neuralgia	NR	8 weeks	Pregabalin 75 mg twice daily Amitriptyline 25 mg daily Combination Amitriptyline 25 mg once daily + Pregabalin 75 mg twice daily	≥75% Improvement in Pain
TCAs	Shabbir 2011	210	Not Reported/ Diabetic Neuropathy	NR	6 weeks	Amitriptyline 10 mg daily (max dose 75 mg daily) Placebo	<u>&gt;</u> 50% Improvement in Pain

NR: Not Reported; PGIC: Patient Global Impression of Change; SNRIs: Serotonin–Norepinephrine Reuptake Inhibitors; TCAs: Tricyclic Antidepressants

# Table 3: Overall proportion of patients with meaningful response at less than or equal to four weeks, four to twelve weeks and at greater than twelve weeks

Intervention Type	Number of RCTs	Subgroup	Intervention Event Rate	Control Event Rate	Risk Ratio (95% Cl)	NNT
Acupuncture	3	Overall Efficacy	22% (27/121)	13% (16/126)	RR 1.81 (95% Cl 0.55, 5.98)	NSS
	-	Assessed at: <u>&lt;</u> 4 weeks	-	-	-	-
	3	Assessed at: >4 weeks to <12 weeks	22% (27/121)	13% (16/126)	RR 1.81 (95% Cl 0.55, 5.98)	NSS
	-	Assessed at: ≥12 weeks	-	-	-	-
Anticonvulsants	40	Overall Efficacy	46% (2698/5837)	30% (1120/3738)	RR 1.54 (95% Cl 1.45, 1.63)	7
	6	Assessed at: <u>&lt;</u> 4 weeks	49% (211/431)	21% (63/300)	RR 2.26 (95% Cl 1.78, 2.87)	4
	20	Assessed at: >4 weeks to <12 weeks	45% (1202/2659)	29% (627/2128)	RR 1.56 (95% Cl 1.44, 1.68)	7
	14	Assessed at: <u>&gt;</u> 12 weeks	47% (1285/2747)	33% (430/1310)	RR 1.42 (95% Cl 1.30, 1.55)	8
Opioids	6	Overall Efficacy	49% (289/593)	36% (198/556)	RR 1.37 (95% Cl 1.19, 1.57)	8
	1	Assessed at: <u>&lt;</u> 4 weeks	41% (12/29)	36% (12/33)	RR 1.14 (95% Cl 0.61, 2.13)	NSS
	3	Assessed at: >4 weeks to <12 weeks	52% (142/271)	37% (96/263)	RR 1.45 (95% Cl 1.19, 1.76)	7
	3	Assessed at: <u>&gt;</u> 12 weeks	46% (147/322)	35% (102/293)	RR 1.30 (95% Cl 1.07, 1.58)	10
Rubefacients (Capsaicin)	10	Overall Efficacy	49% (635/1303)	34% (350/1041)	RR 1.40 (95% Cl 1.26, 1.55)	7
	2	Assessed at: <u>&lt;</u> 4 weeks	30% (27/90)	19% (16/85)	RR 1.60 (95% Cl 0.93, 2.75)	NSS
	8	Assessed at: >4 weeks to <12 weeks	41% (365/888)	30% (254/833)	RR 1.37 (95% Cl 1.20, 1.56)	10

	5	Assessed at: ≥12 weeks	52% (529/1018)	36% (288/792)	RR 1.36 (95% Cl 1.22, 1.52)	7
SNRIs	8	Overall Efficacy	57% (995/1759)	41% (405/987)	RR 1.45 (95% Cl 1.33, 1.59)	7
	-	Assessed at: <4 weeks	-	-	-	-
	1	Assessed at: >4 weeks to <12 weeks	47% (77/164)	35% (28/81)	RR 1.36 (95% Cl 0.97, 1.91)	NSS
	7	Assessed at: ≥12 weeks	58% (918/1595)	42% (377/906)	RR 1.46 (95% Cl 1.34, 1.60)	7
TCAs	2	Overall Efficacy	78% (66/85)	26% (22/85)	RR 3.00 (95% Cl 2.05, 4.38)	8
	-	Assessed at: <4 weeks	-	-	-	-
	2	Assessed at: >4 weeks to <12 weeks	78% (66/85)	26% (22/85)	RR 3.00 (95% Cl 2.05, 4.38)	8
	-	Assessed at: <a>&gt;12</a> weeks	-	-	-	-

Cl: Confidence Interval; NNT: Number Needed to Treat; NSS: Not Statistically Significant; RCTs: Randomized Controlled Trials; RR: Risk Ratio; SNRIs: Serotonin– Norepinephrine Reuptake Inhibitors; TCAs: Tricyclic Antidepressants

# Table 4: Overall proportion of patients with meaningful response at longest follow-up point after intervention (ordered by certainty of evidence)

Intervention Type	Certainty of Evidence (GRADE)	Number of RCTs	Intervention Event Rate	Control Event Rate	Outcome Measured At	Risk Ratio (95% Cl)	NNT
Anticonvulsants	Moderate	40	46% (2698/5837)	30% (1120/3738)	2 to 16 weeks	RR 1.54 (95% Cl 1.45, 1.63)	7
SNRIs	Moderate	8	57% (995/1759)	41% (405/987)	6 to 13 weeks	RR 1.45 (95% Cl 1.33 1.59)	7
Opioids	Low	6	49% (289/593)	36% (198/556)	5 to 12 weeks	RR 1.37 (95% Cl 1.19, 1.57)	8
Rubefacients	Low	10	49% (635/1303)	34% (350/1041)	6 to 52 weeks	RR 1.40 (95% Cl 1.26, 1.55)	7
Acupuncture	Very Low	3	22% (27/121)	13% (16/126)	8 to 10 weeks	RR 1.81 (95% Cl 0.55, 5.98)	NSS
TCAs	Very Low	2	78% (66/85)	26% (22/85)	6-8 weeks	RR 3.00 (95% Cl 2.05, 4.38) (Fixed Effects)	2
						RR 2.35 (95% Cl 0.79, 6.95) (Random Effects)	NSS

Cl: Confidence Interval; GRADE: Grading of Recommendations, Assessment, Development and Evaluations; NNT: Number Needed to Treat; NSS: Not Statistically Significant; RCTs: Randomized Controlled Trials; RR: Risk Ratio; SNRIs: Serotonin Norepinephrine Reuptake Inhibitors; TCAs: Tricyclic Antidepressants

Intervention Type	Number of RCTs	Subgroup	Intervention Event Rate	Control Event Rate	Risk Ratio (95% Cl)	NNT	p-value*
Acupuncture	3	Public Funding	22% (27/121)	13% (16/126)	RR 1.81 (95% Cl 0.55, 5.98)	NSS	NA
	-	Industry Funding	-	-	-	-	
Anticonvulsants	-	Public Funding	-	-	-	-	NA
	37	Industry Funding	45% (2609/5735)	30% (1102/3642)	RR 1.49 (95% Cl 1.41, 1.58)	7	
Opioids	1	Public Funding	52% (15/29)	58% (19/33)	RR 0.90 (95% Cl 0.57, 1.42)	NSS	P=0.06
	5	Industry Funding	49% (274/564)	34% (179/523)	RR 1.41 (95% Cl 1.22, 1.64)	7	
Rubefacients	-	Public Funding	-	-	-	-	NA
	10	Industry Funding	49% (635/1303)	34% (350/1041)	RR 1.40 (95% Cl 1.26, 1.55)	7	
SNRIs	-	Public Funding	-	-	-	-	NA
	8	Industry Funding	57% (995/1759)	41% (405/987)	RR 1.45 (95% Cl 1.33, 1.59)	7	

Table 5: Proportion of pati	tients with clinically i	meaningful resp	oonse based on funding	source (clearly	publicly	/ or industry	funding)

Cl: Confidence Interval; NA: Not Applicable; NNT: Number Needed to Treat; NSS: Not Statistically Significant; RCTs: Randomized Controlled Trials; RR: Risk Ratio; SNRIs: Serotonin–Norepinephrine Reuptake Inhibitors

\*A p-value of <0.05 would indicate that different sources of funding have statistically different effects on the outcome of interest.

Intervention Type	Number of RCTs	Subgroup	Intervention Event Rate	Control Event Rate	Risk Ratio (95% Cl)	NNT	p-value†
Anticonvulsants	16	Less than the median risk of bias score	48% (995/2083)	33% (527/1574)	RR 1.41 (95% Cl 1.30, 1.54)	7	P=0.01
	24	Greater than or equal to the median risk of bias score	45% (1703/3754)	27% (593/2164)	RR 1.64 (95% Cl 1.51, 1.77)	6	
Opioids	3	Less than the median risk of bias score	44% (124/280)	32% (90/279)	RR 1.38 (95% Cl 1.12, 1.72)	9	P=0.88
	3	Greater than or equal to the median risk of bias score	53% (165/313)	39% (108/277)	RR 1.36 (95% Cl 1.13, 1.62)	8	
Rubefacients	5	Less than the median risk of bias score	45% (326/721)	34% (225/653)	RR 1.29 (95% Cl 1.13, 1.48)	10	P=0.08
	5	Greater than or equal to the median risk of bias score	53% (309/582)	32% (125/388)	RR 1.56 (95% Cl 1.32, 1.83)	5	
SNRIs	4	Less than the median risk of bias score	55% (619/1116)	37% (157/428)	RR 1.56 (95% Cl 1.37, 1.79)	6	P=0.12
	4	Greater than or equal to the median risk of bias score	58% (376/643)	44% (248/559)	RR 1.36 (95% Cl 1.21, 1.52)	8	

#### Table 6: Proportion of patients with clinically meaningful response based on median risk of bias scores

Cl: Confidence Interval; NNT: Number Needed to Treat; RCTs: Randomized Controlled Trials; RR: Risk Ratio; SNRIs: Serotonin–Norepinephrine Reuptake Inhibitors

\*For each intervention, a median risk of bias score was calculated and trials were then grouped based on whether they fell at or above the median (higher risk of bias) or below the median (lower risk of bias). Only interventions with at least four trials were included in this subgroup analysis.

<sup>†</sup>A p-value of <0.05 would indicate that quality scores lying above and below the median risk of bias score have statistically different effects on the outcome of interest.

Intervention Type	Number of RCTs	Subgroup	Intervention Event Rate	Control Event Rate	Risk Ratio (95% Cl)	NNT	p-value*
Acupuncture	2	DN	24% (22/91)	7% (7/94)	RR 3.35 (95% Cl 1.53, 7.33)	6	P=0.006
	1	PHN	17% (5/30)	28% (9/32)	RR 0.59 (95% Cl 0.22, 1.57)	NSS	
	-	Trigeminal Neuralgia	-	-	-	-	
Anticonvulsants	24	DN	47% (1377/2947)	33% (720/2185)	RR 1.42 (95% Cl 1.32, 1.53)	8	P=0.0008
	14	PHN	42% (1020/2411)	23% (323/1386)	RR 1.81 (95% Cl 1.62, 2.01)	6	
	-	Trigeminal Neuralgia	-	-	-	-	
	2	Mixed Population	63% (301/479)	46% (77/167)	RR 1.39 (95% Cl 1.15, 1.66)	6	
Opioids	4	DN	49% (245/504)	34% (166/492)	RR 1.44 (95% Cl 1.24, 1.68)	7	P=0.07
	-	PHN	-	-	-	-	
	-	Trigeminal Neuralgia	-	-	-	-	
	2	Mixed Population	49% (44/89)	50% (32/64)	RR 1.02 (95% Cl 0.73, 1.43)	NSS	
Rubefacients	4	DN	54% (347/648)	34% (168/488)	RR 1.45 (95% Cl 1.25, 1.67)	6	P=0.48
	6	PHN	44% (288/655)	33% (182/553)	RR 1.34 (95% Cl 1.16, 1.55)	10	
	-	Trigeminal Neuralgia	-	-	-	-	
SNRIs	8	DN	57% (995/1759)	41% (405/987)	RR 1.45 (95% Cl 1.33, 1.59)	7	NA
	-	PHN	-	-	-	-	
	-	Trigeminal Neuralgia	-	-	-	-	

## Table 7: Proportion of patients with clinically meaningful response based on neuropathic pain type

TCAs	1	DN	79% (55/70)	20% (14/70)	RR 3.93 (95% Cl 2.42, 6.38)	2	P=0.006
	1	PHN	73% (11/15)	53% (8/15)	RR 1.38 (95% Cl 0.78, 2.41)	NSS	
	-	Trigeminal Neuralgia	-	-	-	-	

Cl: Confidence Interval; DN: Diabetic Neuropathy; NA: Not Applicable; NNT: Number Needed to Treat; NSS: Not Statistically Significant; PHN: Postherpetic Neuralgia; RCTs: Randomized Controlled Trials; RR: Risk Ratio; SNRIs: Serotonin–Norepinephrine Reuptake Inhibitors; TCAs: Tricyclic Antidepressants

\* A p-value of <0.05 would indicate that different types of neuropathic pain have statistically different effects on the outcome of interest.

Intervention Type	Number of RCTs	Subgroup	Intervention Event Rate	Control Event Rate	Risk Ratio (95% Cl)	NNT	p-value*
Anticonvulsants	10	Gabapentin	43% (678/1578)	25% (246/974)	RR 1.60 (95% Cl 1.42, 1.81)	6	P=0.17
	27	Pregabalin	48% (1747/3650)	31% (758/2419)	RR 1.56 (95% Cl 1.45, 1.67)	7	
	3	Oxcarbazepine	43% (170/395)	33% (79/236)	RR 1.22 (95% Cl 0.98, 1.52)	NSS	
	1	Topiramate	48% (103/214)	34% (37/109)	RR 1.42 (95% Cl 1.05, 1.91)	8	
Rubefacients	5	Frequent Application (Creams or Low Dose Patches)	37% (106/285)	25% (62/249)	RR 1.56 (95% Cl 1.20, 2.03)	9	P=0.35
	5	Less Frequent Application (High Potency Patches)	52% (529/1018)	36% (288/792)	RR 1.36 (95% Cl 1.22, 1.52)	7	
SNRIs	6	Duloxetine	59% (759/1279)	42% (344/817)	RR 1.48 (95% Cl 1.34, 1.62)	6	P=0.48
	2	Venlafaxine/Desvenlafaxine	49% (236/480)	36% (61/170)	RR 1.35 (95% Cl 1.08, 1.69)	8	

#### Table 8: Proportion of patients with clinically meaningful response based on drug type

Cl: Confidence Interval; NNT: Number Needed to Treat; RCTs: Randomized Controlled Trials; RR: Risk Ratio; SNRIs: Serotonin-Norepinephrine Reuptake Inhibitors

\*A p-value of <0.05 would indicate that different drugs within a drug class have statistically different effects on the outcome of interest.

Intervention Type	Number of RCTs	Subgroup	Intervention Event Rate	Control Event Rate	Risk Ratio (95% Cl)	NNT	p-value*
Acupuncture	3	<150 patients	22% (27/121)	13% (16/126)	RR 1.81 (95% Cl 0.55, 5.98)	NSS	NA
	-	>150 patients	-	-	-	-	
Anticonvulsants	21	<150 patients	46% (1302/2846)	28% (417/1501)	RR 1.66 (95% Cl 1.51, 1.81)	6	P=0.03
	20	>150 patients	47% (1396/2991)	31% (703/2237)	RR 1.46 (95% Cl 1.35, 1.57)	7	
Opioids	2	<150 patients	49% (44/89)	50% (32/64)	RR 1.02 (95% Cl 0.73, 1.43)	NSS	P=0.07
	4	>150 patients	49% (245/504)	34% (166/492)	RR 1.44 (95% Cl 1.24, 1.68)	7	
Rubefacients	4	<150 patients	37% (54/147)	16% (18/110)	RR 2.35 (95% Cl 1.49, 3.73)	5	P=0.02
	6	>150 patients	50% (581/1156)	36% (332/931)	RR 1.34 (95% Cl 1.21, 1.49)	7	
SNRIs	2	<150 patients	49% (236/480)	36% (61/170)	RR 1.35 (95% Cl 1.08, 1.69)	8	P=0.48
	6	>150 patients	59% (759/1279)	42% (344/817)	RR 1.48 (95% Cl 1.34, 1.62)	6	
TCAs	2	<150 patients	78% (66/85)	26% (22/85)	RR 3.00 (95% Cl 2.05, 4.38)	2	NA
	-	>150 patients	-	-	-	-	

#### Table 9: Proportion of patients with clinically meaningful response based on sample size

Cl: Confidence Interval; NA: Not Applicable; NNT: Number Needed to Treat; NSS: Not Statistically Significant; RCTs: Randomized Controlled Trials; RR: Risk Ratio; SNRIs: Serotonin–Norepinephrine Reuptake Inhibitors; TCAs: Tricyclic Antidepressants

\*A p-value of <0.05 would indicate that smaller and larger trials have statistically different effects on the outcome of interest.

### Table 10: Proportion of patients with clinically meaningful response based on sham or not-sham control group

Intervention Type	Number of RCTs	Subgroup	Intervention Event Rate	Control Event Rate	Risk Ratio (95% Cl)	NNT	p-value*
Acupuncture	2	Non-Sham Comparator	15% (14/93)	13% (12/95)	RR 1.27 (95% Cl 0.26, 6.29)	NSS	P=0.28
	1	Sham Comparator	46% (13/28)	13% (4/31)	RR 3.60 (95% Cl 1.33, 9.76)	3	

CI: Confidence Interval; NNT: Number Needed to Treat; NSS: Not Statistically Significant; RCTs: Randomized Controlled Trials; RR: Risk Ratio \*A p-value of <0.05 would indicate that sham and non-sham comparators have statistically different effects on the outcome of interest.

### Data Analysis

#### Acupuncture

# Figure 1.1: Acupuncture versus control; Outcome: Proportion of patients with a meaningful response to treatment

	Acupun	cture	Cont	rol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% Cl	
Garrow 2014	13	28	4	31	34.6%	3.60 [1.33, 9.76]			
Lewith 1983	5	30	9	32	35.1%	0.59 [0.22, 1.57]			
Shin 2018	9	63	3	63	30.3%	3.00 [0.85, 10.57]			
Total (95% CI)		121		126	100.0%	1.81 [0.55, 5.98]			
Total events	27		16					_	
Heterogeneity: Tau <sup>2</sup> =	= 0.81; Ch	$i^2 = 7.4$	9, df = 2	P = 0	.02); I <sup>2</sup> =	73%	0.01	0.1 1 10	100
Test for overall effect	z = 0.97	P = 0.	33)				0.01	Favours control Favours acupuncture	

# Figure 1.2: Acupuncture versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater

	Acupun	cture	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% Cl
1.3.1 Outcome data	reported	at less	than or (	equal t	o 4 weeks	5		
Subtotal (95% CI)		0		0		Not estimable		
Total events	0		0					
Heterogeneity: Not ap	oplicable							
Test for overall effect	:: Not appl	icable						
1.3.2 Outcome data	reported	at grea	ter than	4 week	s to less	than 12 weeks		
Garrow 2014	13	28	4	31	34.6%	3.60 [1.33, 9.76]		—— <b>—</b> —
Lewith 1983	5	30	9	32	35.1%	0.59 [0.22, 1.57]		
Shin 2018	9	63	3	63	30.3%	3.00 [0.85, 10.57]		
Subtotal (95% CI)		121		126	100.0%	1.81 [0.55, 5.98]		
Total events	27		16					
Heterogeneity: Tau2 =	= 0.81; Ch	$i^2 = 7.4$	9, df = 2	P = 0	.02); $I^2 = 1$	73%		
Test for overall effect	:: Z = 0.97	(P = 0.	33)					
1.3.3 Outcome data	reported	at grea	ter than	or equ	al to 12 w	veeks		
Subtotal (95% CI)		0		0		Not estimable		
Total events	0		0					
Heterogeneity: Not ap	oplicable							
Test for overall effect	Not appl	icable						
							<u> </u>	
							0.01	0.1 İ 10 100 Favours control Favours acupuncture

Figure 1.3: Acupuncture versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source

	Acupun	cture	Conti	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% Cl
1.7.1 Public Funding								
Garrow 2014	13	28	4	31	34.6%	3.60 [1.33, 9.76]		<b>_</b>
Lewith 1983	5	30	9	32	35.1%	0.59 [0.22, 1.57]		
Shin 2018	9	63	3	63	30.3%	3.00 [0.85, 10.57]		
Subtotal (95% CI)		121		126	100.0%	1.81 [0.55, 5.98]		
Total events	27		16					
Heterogeneity: Tau <sup>2</sup> =	0.81; Ch	$i^2 = 7.4$	9, df = 2	(P = 0)	$.02$ ; $I^2 =$	73%		
Test for overall effect:		(P = 0.	33)					
1.7.2 Industry Fundin	g							
Subtotal (95% CI)		0		0		Not estimable		
Total events	0		0					
Heterogeneity: Not app	olicable							
Test for overall effect:	Not appl	icable						
Total (95% CI)		121		126	100.0%	1.81 [0.55, 5.98]		
Total events	27		16					
Heterogeneity: $Tau^2 =$	0.81; Ch	$i^2 = 7.4$	9, $df = 2$	(P = 0)	.02); $I^2 =$	73%		
Test for overall effect:	Z = 0.97	(P = 0.	33)				0.01	0.1 İ 10 100 Favours control Favours acupuncture

Figure 1.4: Acupuncture versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by neuropathic pain type

	Acupun	cture	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% CI
1.4.1 Diabetic Neuro	pathy						
Garrow 2014	13	28	4	31	34.6%	3.60 [1.33, 9.76]	— <b>•</b> — •
Shin 2018	9	63	3	63	30.3%	3.00 [0.85, 10.57]	+ <b>-</b>
Subtotal (95% CI)		91		94	64.9%	3.35 [1.53, 7.33]	
Total events	22		7				
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Ch	$i^2 = 0.0$	5, df = 1	(P = 0)	.82); I <sup>2</sup> =	0%	
Test for overall effect	: Z = 3.03	(P = 0.	002)				
1.4.2 Postherpetic N	euralgia						
Lewith 1983	5	30	9	32	35.1%	0.59 [0.22, 1.57]	
Subtotal (95% CI)		30		32	35.1%	0.59 [0.22, 1.57]	
Total events	5		9				
Heterogeneity: Not ap	plicable						
Test for overall effect	: Z = 1.05	(P = 0.	29)				
1.4.3 Trigeminal Neu	ıralgia						
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect	Not appl	icable					
Total (95% CI)		121		126	100.0%	1.81 [0.55, 5.98]	
Total events	27		16				
Heterogeneity: Tau <sup>2</sup> =	= 0.81; Ch	$i^2 = 7.4$	9, df = 2	(P = 0)	.02); I <sup>2</sup> =	73%	0.01 0.1 1 10 100
Test for overall effect	: Z = 0.97	(P = 0.	33)				0.01 0.1 1 10 10 Favours control Favours acupuncture
Test for subgroup dif	ferences:	$Chi^2 = 7$	7.41. df =	= 1 (P =	0.006).	$^{2} = 86.5\%$	ravours control Favours acupuncture

Figure 1.5: Acupuncture versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size

	Acupun	cture	Conti	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M–H, Random, 95% Cl
1.2.1 Less than or eq	qual to 15	0 patie	nts					
Garrow 2014	13	28	4	31	34.6%	3.60 [1.33, 9.76]		
Lewith 1983	5	30	9	32	35.1%	0.59 [0.22, 1.57]		
Shin 2018	9	63	3	63	30.3%	3.00 [0.85, 10.57]		
Subtotal (95% CI)		121		126	100.0%	1.81 [0.55, 5.98]		
Total events	27		16					
Heterogeneity: Tau <sup>2</sup> =	= 0.81; Ch	$i^2 = 7.4$	9, df = 2	(P = 0)	.02); I <sup>2</sup> =	73%		
Test for overall effect:	: Z = 0.97	(P = 0.	33)					
1.2.2 Greater than 15	50 patien	ts						
Subtotal (95% CI)		0		0		Not estimable		
Total events	0		0					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Not appl	icable						
Total (95% CI)		121		126	100.0%	1.81 [0.55, 5.98]		
Total events	27		16					
Heterogeneity: Tau <sup>2</sup> =	= 0.81; Ch	$i^2 = 7.4$	9, df = 2	(P = 0)	.02); I <sup>2</sup> =	73%		
Test for overall effect:							0.01	0.1 1 10 100 Favours control Favours acupuncture
Test for subgroup diff	ferences:	Not app	licable					ravours control ravours acupuncture

Figure 1.6: Acupuncture versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by control group characteristics

	Acupun	cture	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% CI
1.5.1 Non-Sham Cor	nparator						
Lewith 1983	5	30	9	32	35.1%	0.59 [0.22, 1.57]	]
Shin 2018 Subtotal (95% CI)	9	63 <b>93</b>	3	63 <b>95</b>	30.3% <b>65.4%</b>		
Total events	14		12				
Heterogeneity: Tau <sup>2</sup> = Test for overall effect				(P = 0	.04); I <sup>2</sup> =	75%	
1.5.2 Sham Compara	tor						
Garrow 2014 Subtotal (95% CI)	13	28 <b>28</b>	4	31 <b>31</b>	34.6% <b>34.6%</b>		
Total events	13		4				
Heterogeneity: Not ap	plicable						
Test for overall effect	: Z = 2.52	(P = 0.	01)				
Total (95% CI)		121		126	100.0%	1.81 [0.55, 5.98]	
Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect Test for subgroup dif	: Z = 0.97	(P = 0.	33)				0.01 0.1 i 10 100 Favours control Favours acupuncture

### Anticonvulsants

Figure 2.1: Anticonvulsants versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by drug type

itudy or Subgroup	Anticonvu Events		Placel Events		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% Cl
.1.1 Pregabalin							
char 2010	11	15	2	15	0.2%	5.50 [1.46, 20.71]	
rezzo 2008	40	82	20	85	1.5%	2.07 [1.33, 3.23]	
aba 2020	38	85	37	88	2.8%	1.06 [0.76, 1.49]	T
workin 2003 reynhagen 2005 (Fixed)	56 88	89 132	21 12	84 32	1.7% 1.5%	2.52 [1.68, 3.77] 1.78 [1.12, 2.83]	
reynhagen 2005 (Flexed)	83	141	12	33	1.5%	1.62 [1.01, 2.60]	
Guan 2011	130	206	53	102	5.5%	1.21 [0.98, 1.50]	-
luffman 2015	39	101	25	102	1.9%	1.58 [1.04, 2.40]	
.esser 2004 (300 mg)	50	81	16	48	1.6%	1.85 [1.20, 2.86]	<del></del>
esser 2004 (600 mg)	53	82	16	49	1.6%	1.98 [1.28, 3.05]	
iu 2017	58	111	33	109	2.6%	1.73 [1.23, 2.41]	
AcDonnell 2018	15	46	7	45	0.5%	2.10 [0.94, 4.65]	
Noon 2010	68	162	27	78	2.8%	1.21 [0.85, 1.73]	
/u 2018 VCT00394901 2006 (150 mg)	157 21	314 87	136 5	308 32	10.7% 0.6%	1.13 [0.96, 1.34] 1.54 [0.64, 3.75]	
CT00394901 2006 (130 mg)	32	90	5	33	0.6%	2.35 [1.00, 5.51]	
CT00394901 2006 (600 mg)	30	97	5	33	0.6%	2.04 [0.86, 4.83]	
CT02215252 2014	12	46	7	45	0.5%	1.68 [0.73, 3.87]	
Rauck 2012 (300 mg)	28	66	15	30	1.6%	0.85 [0.54, 1.34]	
Richter 2005 (600 mg)	32	82	13	85	1.0%	2.55 [1.44, 4.51]	
Rosenstock 2004	30	76	10	70	0.8%	2.76 [1.46, 5.23]	
abatowski 2004 (150 mg)	21	81	4	40	0.4%	2.59 [0.95, 7.05]	
abatowski 2004 (300 mg)	21	76	4	41	0.4%	2.83 [1.04, 7.70]	
atoh 2011 (300 mg)	66	134	24	67	2.5%	1.38 [0.96, 1.98]	<u></u>
atoh 2011 (600 mg)	25	45	25	68	1.5%	1.51 [1.01, 2.27]	
habbir 2011	64	70	14	70	1.1%	4.57 [2.85, 7.34]	
harma 2006 mith 2014	40	82	20	85	1.5%	2.07 [1.33, 3.23]	
mith 2014 itacey 2008 (Fixed)	49 51	98 88	45 14	93 45	3.6% 1.4%	1.03 [0.77, 1.38] 1.86 [1.16, 2.98]	T_
itacey 2008 (Flexed)	64	88 91	14	45	1.4%	2.26 [1.43, 3.56]	
facey 2008 (Flexed) Folle 2008 (150 mg)	33	99	9	32	1.5%	1.19 [0.64, 2.20]	
olle 2008 (300 mg)	32	99	9	32	1.1%	1.15 [0.62, 2.14]	<del></del>
olle 2008 (600 mg)	45	101	10	32	1.2%	1.43 [0.82, 2.49]	
/an-Seventer 2006 (150 mg)	34	87	5	31	0.6%	2.42 [1.04, 5.64]	
/an-Seventer 2006 (300 mg)	40	98	5	31	0.6%	2.53 [1.10, 5.85]	
/an-Seventer 2006 (600 mg)	47	90	6	31	0.7%	2.70 [1.28, 5.68]	
/inik 2014	19	50	45	108	2.2%	0.91 [0.60, 1.39]	
liegler 2015 Subtotal (95% CI)	25	70	28	62 2419	2.3%	0.79 [0.52, 1.20]	
	1747	3650	75.0	2419	65.6%	1.56 [1.45, 1.67]	•
ōtal events Ieterogeneity: Chi² = 111.21, d	1747 If = 27 (P <	0.00001	758	70/			
Test for overall effect: $Z = 12.43$			, 1 = 07	70			
.1.2 Gabapentin			25		2.0%	1 02 [1 26 2 67]	
Backonja 1998	47	82	25	80	2.0%	1.83 [1.26, 2.67]	
Backonja 2011 Perez 2000	26 14	47 17	15 2	54 15	1.1% 0.2%	1.99 [1.21, 3.29]	
auck 2012 (1200 mg)	31	62	14	30	1.5%	6.18 [1.67, 22.86] 1.07 [0.68, 1.69]	
Rauck 2012 (2400 mg)	25	56	14	30	1.4%	0.96 [0.59, 1.55]	
auck 2012 (3600 mg)	66	116	14	30	1.7%	1.22 [0.81, 1.84]	
Rice 2001 (1800 mg)	37	115	8	55	0.8%	2.21 [1.11, 4.42]	
Rice 2001 (2400 mg)	37	108	8	56	0.8%	2.40 [1.20, 4.79]	
lowbotham 1998	49	113	14	116	1.1%	3.59 [2.11, 6.13]	
andercock 2012 (Daily)	16	46	2	25	0.2%	4.35 [1.09, 17.40]	
andercock 2012 (Divided)	13	50	2	26	0.2%	3.38 [0.82, 13.86]	
ang 2013	65	221	52	231	3.9%	1.31 [0.95, 1.79]	-
Vallace 2010 (Daily)	49 46	134 135	18 18	66 65	1.9% 1.9%	1.34 [0.85, 2.11]	
Vallace 2010 (Divided) (hang 2013 (1200 mg)	40	107	13	32	1.9%	1.23 [0.78, 1.94] 1.31 [0.83, 2.07]	
hang 2013 (2400 mg)	48	82	13	32	1.5%	1.44 [0.91, 2.28]	
(hang 2013 (3600 mg)	52	87	14	31	1.6%	1.32 [0.87, 2.02]	
iubtotal (95% CI)	52	1578	1.	974	23.3%	1.60 [1.42, 1.81]	♦
otal events	678		246				
leterogeneity: Chi <sup>2</sup> = 33.57, df			= 52%				
est for overall effect: Z = 7.69	(P < 0.0000	)1)					
.1.3 Oxcarbazepine							
eydoun 2006 (1200 mg)	44	85	11	30	1.3%	1.41 [0.85, 2.36]	+
Beydoun 2006 (1800 mg)	43	87	11	29	1.3%	1.30 [0.78, 2.17]	+
leydoun 2006 (600 mg)	30	83	11	30	1.3%	0.99 [0.57, 1.71]	- <b>+</b> -
TRI476G2301	22	71	24	70	1.9%	0.90 [0.56, 1.45]	-+-
Dogra 2005	31	69	22	77	1.6%	1.57 [1.01, 2.44]	
		395		236	7.3%	1.22 [0.98, 1.52]	•
	170	n 12	79				
otal events		4); $I^{2} = 0$	6				
otal events leterogeneity: Chi <sup>2</sup> = 3.76, df =							
otal events leterogeneity: Chi <sup>2</sup> = 3.76, df = lest for overall effect: Z = 1.81							
iubtotal (95% CI) Total events leterogeneity: Chi <sup>2</sup> = 3.76, df = Test for overall effect: Z = 1.81 L1.5 Topiramate taskin 2004	(P = 0.07)	214	37	100	3 <b>8</b> %	1.42 [1.05 1.91]	
otal events Heterogeneity: Chi <sup>2</sup> = 3.76, df = Test for overall effect: Z = 1.81		214 <b>214</b>	37	109 <b>109</b>	3.8% <b>3.8%</b>	1.42 [1.05, 1.91] <b>1.42 [1.05, 1.91]</b>	
Total events leterogeneity: Chi <sup>2</sup> = 3.76, df = Test for overall effect: Z = 1.81 1.1.5 Topiramate Raskin 2004	(P = 0.07)		37 37				<b></b>
Total events leterogeneity. Chi <sup>2</sup> = 3.76, df = Test for overall effect: Z = 1.81 <b>1.1.5 Topiramate</b> kaskin 2004 <b>ubtotal (95% CI)</b> Total events	(P = 0.07) 103						•
otal events leterogeneity: Chi <sup>2</sup> = 3.76, df = est for overall effect: Z = 1.81 .1.5 Topiramate askin 2004 ubtotal (95% Cl) otal events leterogeneity: Not applicable	(P = 0.07) 103 103						•
otal events leterogeneity: Chi <sup>2</sup> = 3.76, df = est for overall effect: Z = 1.81 <b>.1.5 Topiramate</b> askin 2004 <b>ubtotal (95% CI)</b> otal events leterogeneity: Not applicable est for overall effect: Z = 2.31	(P = 0.07) 103 103	214		109	3.8%	1.42 [1.05, 1.91]	•
Total events teterogeneity: Chi <sup>2</sup> = 3.76, df = test for overall effect: Z = 1.81 <b>1.1.5 Topiramate</b> taskin 2004 <b>Jubtotal (95% CI)</b> Total events teterogeneity: Not applicable test for overall effect: Z = 2.31 <b>Total (95% CI)</b>	(P = 0.07) 103 103 (P = 0.02)		37	109			•
otal events leterogeneity: Chi <sup>2</sup> = 3.76, df = est for overall effect: Z = 1.81 L.1.5 Topiramate taskin 2004 lubtotal (95% CI) otal events leterogeneity: Not applicable est for overall effect: Z = 2.31	(P = 0.07) 103 103 (P = 0.02) 2698	214 5837	37 1120	109 3738	3.8%	1.42 [1.05, 1.91]	• • •

Figure 2.2: Anticonvulsants versus control; Outcome: Proportion of patients with a meaningful
response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater

Study or Subgroup 2.5.1 Outcome data reported at	Events	Total	Events	oo Total	Weiaht	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% Cl
					Acigin	ii, iixcu, 55% Cl	
Backonja 2011	26	47	15	54	19.2%	1.99 [1.21, 3.29]	
		46		45			
McDonnell 2018	15		7		9.7%	2.10 [0.94, 4.65]	-
NCT02215252 2014	12	46	7	45	9.7%	1.68 [0.73, 3.87]	
Perez 2000	14	17	2	15	2.9%	6.18 [1.67, 22.86]	
Sandercock 2012 (Daily)	16	46	2	25	3.6%	4.35 [1.09, 17.40]	
Sandercock 2012 (Divided)	13	50	2	26	3.6%	3.38 [0.82, 13.86]	
Stacey 2008 (Fixed)	51	88	14	45	25.5%	1.86 [1.16, 2.98]	
Stacey 2008 (Flexed)	64	91	14	45	25.8%	2.26 [1.43, 3.56]	
Subtotal (95% CI)		431		300	100.0%	2.26 [1.78, 2.87]	•
Total events	211		63				
Heterogeneity: Chi <sup>2</sup> = 4.86, df = Test for overall effect: Z = 6.73 (I			6				
2.5.2 Outcome data reported at	greater th	nan 4 wee	eks to l	ess tha	an 12 wee	ks	
Achar 2010	11	15	2	15	0.3%	5.50 [1.46, 20.71]	
Baba 2020	38	85	37	88	5.4%	1.06 [0.76, 1.49]	
						• • •	
Backonja 1998	47	82	25	80	3.8%	1.83 [1.26, 2.67]	
Dworkin 2003	56	89	21	84	3.2%	2.52 [1.68, 3.77]	
Guan 2011	130	206	53	102	10.6%	1.21 [0.98, 1.50]	-
Huffman 2015	39	101	25	102	3.7%	1.58 [1.04, 2.40]	<b>└</b> ──
Lesser 2004 (300 mg)	50	81	16	48	3.0%	1.85 [1.20, 2.86]	
Lesser 2004 (600 mg)	53	82	16	49	3.0%	1.98 [1.28, 3.05]	
Liu 2017	58	111	33	109	5.0%	1.73 [1.23, 2.41]	
Moon 2010	68	162	27	78	5.5%	1.21 [0.85, 1.73]	+
Mu 2018	157	314	136	308	20.5%	1.13 [0.96, 1.34]	<b>⊢</b>
Rice 2001 (1800 mg)	37	115	8	55	1.6%	2.21 [1.11, 4.42]	
Rice 2001 (2400 mg)							
	37	108	8	56	1.6%	2.40 [1.20, 4.79]	
Richter 2005 (600 mg)	32	82	13	85	1.9%	2.55 [1.44, 4.51]	
Rosenstock 2004	30	76	10	70	1.6%	2.76 [1.46, 5.23]	
Rowbotham 1998	49	113	14	116	2.1%	3.59 [2.11, 6.13]	
Sabatowski 2004 (150 mg)	21	81	4	40	0.8%	2.59 [0.95, 7.05]	
			4			2.83 [1.04, 7.70]	
Sabatowski 2004 (300 mg)	21	76		41	0.8%	• • •	
Sang 2013	65	221	52	231	7.6%	1.31 [0.95, 1.79]	
Shabbir 2011	64	70	14	70	2.1%	4.57 [2.85, 7.34]	
Vinik 2014	19	50	45	108	4.3%	0.91 [0.60, 1.39]	
Wallace 2010 (Daily)	49	134	18	66	3.6%	1.34 [0.85, 2.11]	
Wallace 2010 (Divided)	46	135	18	65	3.6%	1.23 [0.78, 1.94]	
Ziegler 2015	25	70	28	62	4.4%	0.79 [0.52, 1.20]	- <b>T</b> .
Subtotal (95% CI)		2659		2128	100.0%	1.56 [1.44, 1.68]	•
Total events	1202		627				
Heterogeneity: Chi <sup>2</sup> = 96.75, df = Test for overall effect: Z = 11.07			12 = 76%	6			
2.5.3 Outcome data reported at	greater tl	1an or eq	ual to 1	2 wee	ks		
-		-		85	3.6%	2 07 [1 22 2 22]	
Arezzo 2008	40	82	20			2.07 11.33, 3.23	
		82 85	20 11	30		2.07 [1.33, 3.23] 1.41 [0.85, 2.36]	
Beydoun 2006 (1200 mg)	44	85	11	30 29	3.0%	1.41 [0.85, 2.36]	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg)	44 43	85 87	11 11	29	3.0% 3.0%	1.41 [0.85, 2.36] 1.30 [0.78, 2.17]	+
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg)	44 43 30	85 87 83	11 11 11	29 30	3.0% 3.0% 3.0%	1.41 [0.85, 2.36] 1.30 [0.78, 2.17] 0.99 [0.57, 1.71]	
Arezzo 2008 Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301	44 43 30 22	85 87 83 71	11 11 11 24	29 30 70	3.0% 3.0% 3.0% 4.4%	1.41 [0.85, 2.36] 1.30 [0.78, 2.17] 0.99 [0.57, 1.71] 0.90 [0.56, 1.45]	 
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301	44 43 30	85 87 83	11 11 11	29 30	3.0% 3.0% 3.0%	1.41 [0.85, 2.36] 1.30 [0.78, 2.17] 0.99 [0.57, 1.71]	 
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTR(476G2301 Dogra 2005	44 43 30 22	85 87 83 71	11 11 11 24	29 30 70	3.0% 3.0% 3.0% 4.4%	1.41 [0.85, 2.36] 1.30 [0.78, 2.17] 0.99 [0.57, 1.71] 0.90 [0.56, 1.45] 1.57 [1.01, 2.44]	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed)	44 43 30 22 31 88	85 87 83 71 69 132	11 11 24 22 12	29 30 70 77 32	3.0% 3.0% 3.0% 4.4% 3.8% 3.5%	1.41 [0.85, 2.36] 1.30 [0.78, 2.17] 0.99 [0.57, 1.71] 0.90 [0.56, 1.45] 1.57 [1.01, 2.44] 1.78 [1.12, 2.83]	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476C2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fiexed)	44 43 30 22 31 88 83	85 87 83 71 69 132 141	11 11 24 22 12 12	29 30 70 77 32 33	3.0% 3.0% 4.4% 3.8% 3.5% 3.6%	1.41 [0.85, 2.36] 1.30 [0.78, 2.17] 0.99 [0.57, 1.71] 0.90 [0.56, 1.45] 1.57 [1.01, 2.44] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60]	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476C2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg)	44 43 30 22 31 88 83 21	85 87 83 71 69 132 141 87	11 11 24 22 12 12 5	29 30 70 77 32 33 32	3.0% 3.0% 4.4% 3.8% 3.5% 3.6% 1.3%	1.41 [0.85, 2.36] 1.30 [0.78, 2.17] 0.99 [0.57, 1.71] 0.90 [0.56, 1.45] 1.57 [1.01, 2.44] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75]	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476C2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg)	44 43 30 22 31 88 83 21 32	85 87 83 71 69 132 141 87 90	11 11 24 22 12 12 5 5	29 30 70 77 32 33 32 33	3.0% 3.0% 4.4% 3.8% 3.5% 3.6% 1.3% 1.3%	1.41 [0.85, 2.36] 1.30 [0.78, 2.17] 0.99 [0.57, 1.71] 0.90 [0.56, 1.45] 1.57 [1.01, 2.44] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75] 2.35 [1.00, 5.51]	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476C2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg)	44 43 30 22 31 88 83 21 32 30	85 87 83 71 69 132 141 87	11 11 24 22 12 12 5	29 30 70 77 32 33 32	3.0% 3.0% 4.4% 3.8% 3.5% 3.6% 1.3%	1.41 [0.85, 2.36] 1.30 [0.78, 2.17] 0.99 [0.57, 1.71] 0.90 [0.56, 1.45] 1.57 [1.01, 2.44] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75]	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (600 mg)	44 43 30 22 31 88 83 21 32 30	85 87 83 71 69 132 141 87 90	11 11 24 22 12 12 5 5 5	29 30 70 77 32 33 32 33	3.0% 3.0% 4.4% 3.8% 3.5% 3.6% 1.3% 1.3% 1.4%	$\begin{array}{c} 1.41 & [0.85, 2.36] \\ 1.30 & [0.78, 2.17] \\ 0.99 & [0.57, 1.71] \\ 0.90 & [0.56, 1.45] \\ 1.57 & [1.01, 2.44] \\ 1.78 & [1.12, 2.83] \\ 1.62 & [1.01, 2.60] \\ 1.54 & [0.64, 3.75] \\ 2.35 & [1.00, 5.51] \\ 2.04 & [0.86, 4.83] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476C2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004	44 43 30 22 31 88 83 21 32 30 103	85 87 83 71 69 132 141 87 90 97 214	11 11 24 22 12 12 5 5 5 37	29 30 70 77 32 33 32 33 33 33 109	3.0% 3.0% 4.4% 3.8% 3.5% 3.6% 1.3% 1.3% 1.4% 9.0%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.55, 1.45 \right] \\ 1.57 \left[ 1.01, 2.44 \right] \\ 1.78 \left[ 1.12, 2.83 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476C2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Raskin 2004	44 43 30 22 31 88 83 21 32 30 103 31	85 87 83 71 69 132 141 87 90 97 214 62	11 11 24 22 12 5 5 5 37 14	29 30 70 77 32 33 32 33 33 109 30	3.0% 3.0% 4.4% 3.8% 3.5% 3.6% 1.3% 1.3% 1.4% 9.0% 3.5%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.44 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.69 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fiexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (1200 mg) Rauck 2012 (2400 mg)	44 43 30 22 31 88 83 21 32 30 103 31 25	85 87 83 71 69 132 141 87 90 97 214 62 56	11 11 24 22 12 5 5 5 37 14 14	29 30 70 77 32 33 32 33 33 109 30 30	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.3%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.43 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg)	44 43 30 22 31 88 83 21 32 30 103 31	85 87 83 71 69 132 141 87 90 97 214 62	11 11 24 22 12 5 5 5 37 14 14 15	29 30 70 77 32 33 32 33 33 109 30 30 30	3.0% 3.0% 4.4% 3.8% 3.5% 3.6% 1.3% 1.3% 1.4% 9.0% 3.5% 3.3% 3.8%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.44 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.69 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476C2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (2400 mg) Rauck 2012 (2400 mg) Rauck 2012 (300 mg)	44 43 30 22 31 88 83 21 32 30 103 31 25	85 87 83 71 69 132 141 87 90 97 214 62 56	11 11 24 22 12 5 5 5 37 14 14	29 30 70 77 32 33 32 33 33 109 30 30	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.3%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.43 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476C2301 Dogra 2005 Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (1200 mg) Rauck 2012 (300 mg) Rauck 2012 (300 mg) Rauck 2012 (3600 mg)	44 43 30 22 31 88 83 21 32 30 103 31 25 28	85 87 83 71 69 132 141 87 90 97 214 62 56 66	11 11 24 22 12 5 5 5 37 14 14 15	29 30 70 77 32 33 32 33 33 109 30 30 30	3.0% 3.0% 4.4% 3.5% 3.5% 1.3% 1.3% 1.4% 9.0% 3.3% 3.8% 4.1%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.48 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.05 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.85 \left[ 0.54, 1.34 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (1200 mg) Rauck 2012 (2400 mg) Rauck 2012 (3600 mg) Satch 2011 (300 mg)	44 43 30 22 31 88 83 21 30 103 31 25 28 66 66	85 87 83 71 69 132 141 87 90 97 214 62 56 66 116 134	11 11 24 22 12 5 5 5 37 14 14 15 14 24	29 30 70 77 32 33 32 33 30 30 30 30 30 67	3.0% 3.0% 4.4% 3.8% 3.5% 3.6% 1.3% 1.3% 1.4% 9.0% 3.5% 3.8% 3.8% 4.1% 5.9%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.43 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.95 \left[ 0.54, 1.34 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.38 \left[ 0.96, 1.98 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476C2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (2400 mg) Rauck 2012 (2400 mg) Rauck 2012 (300 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (600 mg)	44 43 30 22 31 88 83 21 32 30 103 31 25 28 66 66 66 25	85 87 83 71 69 132 141 87 90 97 214 62 56 66 116 134 45	11 11 24 22 12 5 5 5 37 14 14 15 14 24 25	29 30 70 77 32 33 32 33 33 30 30 30 30 67 68	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.3% 3.8% 4.1% 5.9% 3.6%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.57, 1.71 \right] \\ 1.78 \left[ 1.12, 2.43 \right] \\ 1.78 \left[ 1.12, 2.83 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.63 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.85 \left[ 0.54, 1.34 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.38 \left[ 0.96, 1.98 \right] \\ 1.51 \left[ 1.01, 2.27 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (1200 mg) Rauck 2012 (2400 mg) Rauck 2012 (300 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (600 mg) Sharma 2006	44 43 30 23 31 88 83 31 32 30 103 31 25 28 66 66 66 25 40	85 87 83 71 69 132 141 87 90 97 214 62 56 66 116 134 45 82	11 11 24 22 12 5 5 5 37 14 14 15 14 24 25 20	29 30 70 77 32 33 32 33 33 30 30 30 30 67 68 85	3.0% 3.0% 4.4% 3.5% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.3% 3.8% 4.1% 5.9% 3.6%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.57, 1.45 \right] \\ 1.57 \left[ 1.01, 2.44 \right] \\ 1.78 \left[ 1.12, 2.83 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.85 \left[ 0.54, 1.34 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.38 \left[ 0.96, 1.22 \right] \\ 2.07 \left[ 1.33, 3.23 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (1200 mg) Rauck 2012 (2400 mg) Rauck 2012 (3600 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (600 mg) Sharma 2006 Smith 2014	44 43 30 22 31 88 83 21 32 30 103 31 25 28 66 66 66 25 40 49	85 87 83 71 69 132 141 87 90 97 214 62 56 66 66 116 134 45 82 98	11 11 24 22 12 5 5 5 37 14 14 14 24 25 20 45	29 30 70 77 32 33 32 33 109 30 30 30 30 67 68 85 93	3.0% 3.0% 4.4% 3.8% 3.6% 1.3% 1.3% 1.3% 1.3% 3.5% 3.3% 3.5% 3.3% 4.1% 5.9% 3.6% 8.4%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.48 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.85 \left[ 0.54, 1.34 \right] \\ 1.28 \left[ 0.81, 1.84 \right] \\ 1.28 \left[ 0.91, 1.84 \right] \\ 1.38 \left[ 0.96, 1.98 \right] \\ 1.51 \left[ 1.01, 2.27 \right] \\ 2.07 \left[ 1.33, 3.23 \right] \\ 1.03 \left[ 0.77, 1.38 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (1200 mg) Rauck 2012 (2400 mg) Rauck 2012 (3600 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (600 mg) Sharma 2006 Smith 2014	44 43 30 23 31 88 83 31 32 30 103 31 25 28 66 66 66 25 40	85 87 83 71 69 132 141 87 90 97 214 62 56 66 116 134 45 82	11 11 24 22 12 5 5 5 37 14 14 15 14 24 25 20	29 30 70 77 32 33 32 33 33 30 30 30 30 67 68 85	3.0% 3.0% 4.4% 3.5% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.3% 3.8% 4.1% 5.9% 3.6%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.78 \left[ 1.12, 2.43 \right] \\ 1.78 \left[ 1.12, 2.83 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.68 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.68 \right] \\ 1.42 \left[ 1.08, 0.68 \right] \\ 1.51 \left[ 1.01, 2.27 \right] \\ 2.07 \left[ 1.33, 3.23 \right] \\ 1.38 \left[ 0.96, 1.98 \right] \\ 1.51 \left[ 1.01, 2.27 \right] \\ 2.07 \left[ 1.33, 3.23 \right] \\ 1.39 \left[ 0.64, 2.20 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (1200 mg) Rauck 2012 (2400 mg) Rauck 2012 (300 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Sharma 2006 Smith 2014 Tolle 2008 (150 mg)	44 43 30 22 31 88 83 21 32 30 103 31 25 28 66 66 66 25 40 9 33	85 87 83 71 69 132 141 87 90 97 214 62 56 66 66 116 134 45 82 98	11 11 24 22 12 5 5 5 37 14 14 14 24 25 20 45	29 30 70 77 32 33 32 33 30 30 30 30 67 68 85 93 32	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.8% 4.1% 5.9% 3.6% 3.6% 3.6% 3.6%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.78 \left[ 1.12, 2.43 \right] \\ 1.78 \left[ 1.12, 2.83 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.68 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.68 \right] \\ 1.42 \left[ 1.08, 0.68 \right] \\ 1.51 \left[ 1.01, 2.27 \right] \\ 2.07 \left[ 1.33, 3.23 \right] \\ 1.38 \left[ 0.96, 1.98 \right] \\ 1.51 \left[ 1.01, 2.27 \right] \\ 2.07 \left[ 1.33, 3.23 \right] \\ 1.39 \left[ 0.64, 2.20 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (1200 mg) Rauck 2012 (2400 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (600 mg) Sharma 2006 Smith 2014 Smith 2014 Tolle 2008 (150 mg)	44 43 300 22 31 88 83 21 32 300 103 31 25 28 66 66 65 25 40 49 33 32	85 87 83 71 69 132 141 87 90 97 214 62 56 66 116 134 45 82 98 99 99	11 11 24 22 12 12 5 5 5 37 14 14 14 14 24 25 20 45 20 9 9	29 30 70 77 32 33 32 33 33 109 30 30 30 30 67 68 5 93 32 32	3.0% 3.0% 4.4% 3.8% 3.5% 3.6% 1.3% 1.4% 9.0% 3.5% 3.8% 4.1% 5.9% 3.6% 3.6% 3.6% 8.4% 2.5%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.57, 1.71 \right] \\ 1.57 \left[ 1.01, 2.44 \right] \\ 1.78 \left[ 1.12, 2.83 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.54 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.28 \left[ 0.96, 1.98 \right] \\ 1.51 \left[ 1.01, 2.27 \right] \\ 2.07 \left[ 1.33, 3.23 \right] \\ 1.09 \left[ 0.64, 2.20 \right] \\ 1.15 \left[ 0.64, 2.14 \right] \\ \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (300 mg) Raskin 2004 Rauck 2012 (1200 mg) Rauck 2012 (2400 mg) Rauck 2012 (300 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Sharma 2006 Smith 2014 Tolle 2008 (150 mg) Tolle 2008 (600 mg)	44 43 300 22 31 88 32 30 103 31 25 28 66 66 25 40 66 25 40 933 32 245	85 87 83 71 69 132 141 87 90 97 214 62 56 66 116 134 45 82 98 99 99 101	11 11 12 12 12 12 12 12 12 12	29 30 70 77 32 33 32 33 30 30 30 30 67 68 85 93 32 32 32 32	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.3% 3.8% 4.1% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 2.5% 2.5% 2.8%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.43 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.85 \left[ 0.54, 1.34 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.38 \left[ 0.96, 1.98 \right] \\ 1.51 \left[ 1.01, 2.27 \right] \\ 2.07 \left[ 1.33, 3.23 \right] \\ 1.03 \left[ 0.77, 1.38 \right] \\ 1.19 \left[ 0.64, 2.20 \right] \\ 1.5 \left[ 0.62, 2.14 \right] \\ 1.43 \left[ 0.82, 2.49 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Rauck 2012 (2400 mg) Rauck 2012 (2400 mg) Rauck 2012 (300 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Sharma 2006 Simith 2014 Tolle 2008 (150 mg) Tolle 2008 (300 mg) Van–Seventer 2006 (150 mg)	44 43 30 22 31 88 83 21 32 30 103 31 25 28 66 66 66 66 25 40 9 33 32 25 40 9 33 32 5 34	85 87 87 87 169 132 141 87 90 97 214 62 56 66 116 134 45 82 99 99 99 101 87	11 11 11 22 12 5 5 37 14 14 24 25 5 37 14 15 14 24 20 45 9 9 10 5 5 5 5 5 5 5 5 5 5 5 5 5	29 30 70 77 32 33 32 33 30 30 30 30 30 67 68 85 93 32 232 32 32 31	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.8% 4.1% 3.3% 3.8% 4.1% 3.6% 3.6% 3.6% 3.6% 2.5% 2.5% 2.5% 2.8%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.44 \right] \\ 1.78 \left[ 1.12, 2.83 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 0.70 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.85 \left[ 0.54, 1.34 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.38 \left[ 0.96, 1.98 \right] \\ 1.51 \left[ 1.01, 2.27 \right] \\ 2.07 \left[ 1.33, 3.27 \right] \\ 1.03 \left[ 0.77, 1.38 \right] \\ 1.19 \left[ 0.64, 2.20 \right] \\ 1.15 \left[ 0.62, 2.14 \right] \\ 1.43 \left[ 0.82, 2.49 \right] \\ 2.42 \left[ 1.04, 5.64 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476C2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (2400 mg) Rauck 2012 (2400 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (600 mg) Sharma 2006 Smith 2014 Tolle 2008 (150 mg) Tolle 2008 (600 mg) Van-Seventer 2006 (150 mg) Van-Seventer 2006 (300 mg)	44 43 300 22 31 88 83 21 32 30 103 31 25 28 66 65 25 40 49 33 32 45 34 40	85 87 83 71 69 132 141 87 90 97 214 62 56 66 116 134 45 82 98 99 99 101 87 87 98	11 11 11 24 22 12 5 5 5 7 14 14 15 20 45 20 45 20 9 9 10 5 5 5 5 5 5 5 5 5 5 5 5 5	29 300 770 322 333 32 33 30 300 300 300 300 300 3	3.0% 3.0% 3.0% 4.4% 3.8% 3.5% 3.6% 1.3% 1.4% 9.0% 3.5% 3.8% 4.1% 5.9% 3.6% 3.6% 3.6% 3.6% 2.5% 2.8% 1.3%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.78 \left[ 1.05, 1.91 \right] \\ 1.79 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.91 \left[ 0.54, 1.24 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.38 \left[ 0.96, 1.98 \right] \\ 1.51 \left[ 1.01, 2.27 \right] \\ 2.07 \left[ 1.33, 3.23 \right] \\ 1.9 \left[ 0.64, 2.20 \right] \\ 1.15 \left[ 0.62, 2.14 \right] \\ 1.43 \left[ 0.82, 2.49 \right] \\ 2.42 \left[ 1.04, 5.64 \right] \\ 2.53 \left[ 1.10, 5.85 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476C2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (2400 mg) Rauck 2012 (2400 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (600 mg) Sharma 2006 Smith 2014 Tolle 2008 (150 mg) Tolle 2008 (600 mg) Van-Seventer 2006 (150 mg) Van-Seventer 2006 (300 mg)	44 43 30 22 31 88 83 21 32 30 103 31 25 28 66 66 66 66 25 40 9 33 32 25 40 9 33 32 5 34	85 87 87 169 132 141 87 90 97 214 62 56 66 116 134 45 82 99 99 99 101 87	11 11 11 22 12 5 5 37 14 14 24 25 5 37 14 15 14 24 20 45 9 9 10 5 5 5 5 5 5 5 5 5 5 5 5 5	29 30 70 77 32 33 32 33 30 30 30 30 30 67 68 85 93 32 232 32 32 31	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.8% 4.1% 3.3% 3.8% 4.1% 3.6% 3.6% 3.6% 3.6% 2.5% 2.5% 2.5% 2.8%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.44 \right] \\ 1.78 \left[ 1.12, 2.83 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 0.70 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.85 \left[ 0.54, 1.34 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.38 \left[ 0.96, 1.98 \right] \\ 1.51 \left[ 1.01, 2.27 \right] \\ 2.07 \left[ 1.33, 3.27 \right] \\ 1.03 \left[ 0.77, 1.38 \right] \\ 1.19 \left[ 0.64, 2.20 \right] \\ 1.15 \left[ 0.62, 2.14 \right] \\ 1.43 \left[ 0.82, 2.49 \right] \\ 2.42 \left[ 1.04, 5.64 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (1200 mg) Rauck 2012 (2400 mg) Rauck 2012 (3600 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (600 mg) Sharma 2006 Smith 2014 Tolle 2008 (150 mg) Tolle 2008 (300 mg) Van-Seventer 2006 (300 mg) Van-Seventer 2006 (600 mg)	44 43 300 22 31 88 83 21 30 103 31 25 28 66 66 25 40 66 25 40 49 33 32 45 34 40 47	85 87 83 71 69 132 141 87 90 97 214 62 56 66 116 134 45 82 98 99 99 101 87 99	$\begin{array}{c} 11\\ 11\\ 11\\ 12\\ 42\\ 22\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\$	29 30 70 77 32 33 33 32 33 30 30 30 30 30 30 30 30 30 30 30 30	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.3% 3.3% 3.8% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 1.3% 1.3% 1.3%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.43 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 0.76 \left[ 0.68, 1.69 \right] \\ 0.76 \left[ 0.58, 1.69 \right] \\ 1.67 \left[ 0.68, 1.69 \right] \\ 0.76 \left[ 0.59, 1.55 \right] \\ 0.85 \left[ 0.54, 1.34 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.38 \left[ 0.96, 1.98 \right] \\ 1.51 \left[ 1.01, 2.27 \right] \\ 2.07 \left[ 1.33, 3.23 \right] \\ 1.03 \left[ 0.77, 1.38 \right] \\ 1.19 \left[ 0.64, 2.20 \right] \\ 1.55 \left[ 0.62, 2.14 \right] \\ 1.43 \left[ 0.82, 2.49 \right] \\ 2.42 \left[ 1.04, 5.68 \right] \\ 2.70 \left[ 1.28, 5.68 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (2400 mg) Rauck 2012 (2400 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Tolle 2008 (150 mg) Tolle 2008 (150 mg) Tolle 2008 (600 mg) Van-Seventer 2006 (150 mg) Van-Seventer 2006 (300 mg) Zanag 2013 (1200 mg)	44 43 30 22 31 88 83 21 32 30 103 31 25 28 66 66 66 66 66 66 25 40 49 33 32 5 34 40 47 57	85 87 87 87 169 132 141 87 90 97 214 62 56 66 116 134 45 82 98 99 99 90 101 87 98 107	11 11 11 12 12 22 22 5 5 5 5 5 5 5 5 5 5 5	29 30 70 77 32 33 32 33 30 30 30 30 30 30 30 67 68 85 93 32 32 32 32 31 31 31 32 32 32 32 32 32 32 32 32 32 32 32 32	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.8% 4.1% 3.6% 3.6% 3.6% 3.6% 2.5% 2.8% 1.3% 1.4% 1.6% 3.7%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.78 \left[ 1.12, 2.83 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.41 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 0.70 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.85 \left[ 0.54, 1.34 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.38 \left[ 0.96, 1.98 \right] \\ 1.51 \left[ 1.01, 2.27 \right] \\ 2.07 \left[ 1.33, 3.22 \right] \\ 1.9 \left[ 0.64, 2.20 \right] \\ 1.15 \left[ 0.62, 2.14 \right] \\ 1.43 \left[ 0.82, 2.49 \right] \\ 2.42 \left[ 1.04, 5.64 \right] \\ 2.53 \left[ 1.10, 5.85 \right] \\ 2.70 \left[ 1.28, 5.68 \right] \\ 1.31 \left[ 0.83, 2.07 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476C2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (2400 mg) Rauck 2012 (2400 mg) Rauck 2012 (360 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Sharma 2006 Smith 2014 Tolle 2008 (150 mg) Tolle 2008 (150 mg) Tolle 2008 (150 mg) Van-Seventer 2006 (150 mg)	44 43 300 22 31 88 83 21 32 30 103 31 25 28 66 625 40 49 33 32 45 40 45 34 40 47 7 7 48	85 87 83 71 69 132 141 87 90 97 214 62 56 66 116 134 45 82 99 99 99 101 87 98 90 107 82	11 11 11 12 12 22 5 5 37 12 12 12 12 5 5 37 14 14 15 14 14 25 20 20 9 9 9 9 10 0 5 5 5 5 37 7 12 2 12 2 12 2 12 2 12 2 12 2 12 2 12 2 12 2 12 2 12 2 12 2 12 2 5 5 37 7 14 14 15 5 5 5 37 7 14 14 15 5 5 5 5 5 5 5 5 5 5 5 5 5	29 30 700 777 32 33 33 32 30 30 30 30 30 30 30 30 30 30 30 30 30	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.3% 3.6% 3.3% 3.8% 4.1% 5.9% 3.6% 3.6% 3.6% 2.5% 2.5% 2.5% 2.8% 1.4% 1.6% 3.7%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.85, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.78 \left[ 1.05, 1.91 \right] \\ 1.79 \left[ 0.68, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.79 \left[ 0.68, 1.94 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.38 \left[ 0.96, 1.98 \right] \\ 1.51 \left[ 1.01, 2.27 \right] \\ 2.07 \left[ 1.33, 3.23 \right] \\ 1.39 \left[ 0.64, 2.20 \right] \\ 1.15 \left[ 0.62, 2.14 \right] \\ 1.43 \left[ 0.82, 2.49 \right] \\ 1.42 \left[ 1.04, 5.64 \right] \\ 2.53 \left[ 1.10, 5.85 \right] \\ 2.70 \left[ 1.28, 5.68 \right] \\ 1.31 \left[ 0.83, 2.07 \right] \\ 1.44 \left[ 0.91, 2.28 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (300 mg) Raskin 2004 Rauck 2012 (1200 mg) Rauck 2012 (2400 mg) Rauck 2012 (3000 mg) Satoh 2011 (300 mg) Tolle 2008 (150 mg) Tolle 2008 (150 mg) Tolle 2008 (600 mg) Van-Seventer 2006 (300 mg) Van-Seventer 2006 (300 mg) Van-Seventer 2006 (300 mg) Zhang 2013 (1200 mg) Zhang 2013 (2400 mg)	44 43 30 22 31 88 83 21 32 30 103 31 25 28 66 66 66 66 66 66 25 40 49 33 32 5 34 40 47 57	85 87 71 69 132 141 87 90 97 214 62 56 66 116 134 45 82 98 99 99 99 101 87 90 107 87 87	11 11 11 11 12 12 22 22 5 5 5 5 5 5 5 5 5 5	29 30 700 32 33 33 32 30 30 30 30 30 30 30 67 68 85 32 32 32 32 32 31 31 31 31 32 33 31 31 31 31 31 32 32 32 32 32 33 33 30 30 30 30 30 30 30 30 30 30 30	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.3% 3.8% 4.1% 3.3% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.43 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 1.21 \left[ 0.81, 1.84 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.23 \left[ 1.03, 2.27 \right] \\ 1.03 \left[ 0.07, 1.38 \right] \\ 1.19 \left[ 0.64, 2.20 \right] \\ 1.15 \left[ 0.62, 2.14 \right] \\ 1.43 \left[ 0.82, 2.49 \right] \\ 2.42 \left[ 1.04, 5.68 \right] \\ 1.31 \left[ 0.83, 2.07 \right] \\ 1.44 \left[ 0.95, 1.28 \right] \\ 1.32 \left[ 0.87, 2.02 \right] \\ 1.5 \left[ 0.87,$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (2400 mg) Rauck 2012 (2400 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Tolle 2008 (150 mg) Tolle 2008 (150 mg) Tolle 2008 (600 mg) Van-Seventer 2006 (150 mg) Van-Seventer 2006 (300 mg) Zanag 2013 (1200 mg)	44 43 300 22 31 88 83 21 32 30 103 31 25 28 66 625 40 49 33 32 45 40 45 34 40 47 7 7 48	85 87 83 71 69 132 141 87 90 97 214 62 56 66 116 134 45 82 99 99 99 101 87 98 90 107 82	11 11 11 12 12 22 5 5 37 12 12 12 12 12 5 5 37 14 14 15 14 14 25 20 20 20 9 9 9 9 10 0 5 5 5 37 7 12 20 20 20 12 20 20 20 10 10 10 10 10 10 10 10 10 1	29 30 700 32 33 33 32 30 30 30 30 30 30 30 67 68 85 32 32 32 32 32 31 31 31 31 32 33 31 31 31 31 31 32 32 32 32 32 33 33 30 30 30 30 30 30 30 30 30 30 30	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.3% 3.6% 3.3% 3.8% 4.1% 5.9% 3.6% 3.6% 3.6% 2.5% 2.5% 2.5% 2.8% 1.4% 1.6% 3.7%	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.57, 1.71 \right] \\ 0.91 \left[ 0.85, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.78 \left[ 1.05, 1.91 \right] \\ 1.79 \left[ 0.68, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.79 \left[ 0.68, 1.94 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.38 \left[ 0.96, 1.98 \right] \\ 1.51 \left[ 1.01, 2.27 \right] \\ 2.07 \left[ 1.33, 3.23 \right] \\ 1.39 \left[ 0.64, 2.20 \right] \\ 1.15 \left[ 0.62, 2.14 \right] \\ 1.43 \left[ 0.82, 2.49 \right] \\ 1.42 \left[ 1.04, 5.64 \right] \\ 2.53 \left[ 1.10, 5.85 \right] \\ 2.70 \left[ 1.28, 5.68 \right] \\ 1.31 \left[ 0.83, 2.07 \right] \\ 1.44 \left[ 0.91, 2.28 \right] \end{array}$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (1200 mg) Rauck 2012 (2400 mg) Rauck 2012 (3600 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Sharma 2006 Simith 2014 Tolle 2008 (150 mg) Tolle 2008 (150 mg) Van-Seventer 2006 (150 mg) Van-Seventer 2006 (300 mg) Van-Seventer 2006 (300 mg) Zhang 2013 (1200 mg) Zhang 2013 (2400 mg) Zhang 2013 (3600 mg)	44 43 30 22 31 88 83 21 32 30 103 31 25 28 66 66 66 66 66 25 40 49 33 32 53 4 40 47 57 48 52	85 87 71 69 132 141 87 90 97 214 62 56 66 116 134 45 82 98 99 99 99 101 87 90 107 87 87	11 11 14 12 12 24 22 5 5 5 37 14 15 14 15 20 0 9 9 9 10 10 25 5 5 5 5 5 5 5 5 5 5 5 5 5	29 30 700 32 33 33 32 30 30 30 30 30 30 30 67 68 85 32 32 32 32 32 31 31 31 31 32 33 31 31 31 31 31 32 32 32 32 32 33 33 30 30 30 30 30 30 30 30 30 30 30	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.3% 3.8% 4.1% 3.3% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.43 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 1.21 \left[ 0.81, 1.84 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.23 \left[ 1.03, 2.27 \right] \\ 1.03 \left[ 0.07, 1.38 \right] \\ 1.19 \left[ 0.64, 2.20 \right] \\ 1.15 \left[ 0.62, 2.14 \right] \\ 1.43 \left[ 0.82, 2.49 \right] \\ 2.42 \left[ 1.04, 5.68 \right] \\ 1.31 \left[ 0.83, 2.07 \right] \\ 1.44 \left[ 0.95, 1.28 \right] \\ 1.32 \left[ 0.87, 2.02 \right] \\ 1.5 \left[ 0.87,$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Rauck 2012 (2400 mg) Rauck 2012 (2400 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Tolle 2008 (150 mg) Tolle 2008 (300 mg) Tolle 2008 (300 mg) Van-Seventer 2006 (150 mg) Van-Seventer 2006 (150 mg) Van-Seventer 2006 (150 mg) Van-Seventer 2006 (150 mg) Zhang 2013 (1200 mg) Zhang 2013 (1200 mg) Zhang 2013 (1200 mg) Zhang 2013 (3600 mg) Subtotal (95% CI)	44 43 300 22 31 88 83 21 32 30 103 31 25 28 66 66 65 25 40 49 33 32 45 34 40 47 7 57 48 52	85 87 83 71 69 132 141 87 90 97 214 62 56 66 116 134 45 82 99 99 99 101 87 98 90 107 82 87 2747	11 11 12 12 12 22 5 5 37 14 14 15 14 14 25 20 9 9 9 10 0 5 5 5 5 5 37 7 14 12 20 20 20 20 20 20 20 20 20 2	29 30 700 32 33 33 32 30 30 30 30 30 30 30 67 68 85 32 32 32 32 32 31 31 31 31 32 33 31 31 31 31 31 31 32 32 32 32 33 33 30 30 30 30 30 30 30 30 30 30 30	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.3% 3.8% 4.1% 3.3% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.43 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 1.21 \left[ 0.81, 1.84 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.23 \left[ 1.03, 2.27 \right] \\ 1.03 \left[ 0.07, 1.38 \right] \\ 1.19 \left[ 0.64, 2.20 \right] \\ 1.15 \left[ 0.62, 2.14 \right] \\ 1.43 \left[ 0.82, 2.49 \right] \\ 2.42 \left[ 1.04, 5.68 \right] \\ 1.31 \left[ 0.83, 2.07 \right] \\ 1.44 \left[ 0.95, 1.28 \right] \\ 1.32 \left[ 0.87, 2.02 \right] \\ 1.5 \left[ 0.87,$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Rauck 2012 (1200 mg) Rauck 2012 (2400 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (600 mg) Sharma 2006 Smith 2014 Tolle 2008 (150 mg) Tolle 2008 (300 mg) Tolle 2008 (600 mg) Van-Seventer 2006 (150 mg) Van-Seventer 2006 (150 mg) Van-Seventer 2006 (150 mg) Van-Seventer 2006 (150 mg) Zhang 2013 (1200 mg) Zhang 2013 (2400 mg) Zha	44 43 30 22 31 88 83 21 32 30 103 31 25 28 66 66 25 28 66 66 25 40 49 33 32 24 5 34 40 47 57 8 8 52 2 8 28 52 28 52 28 52 28 52 28 52 28 52 52 52 52 52 52 52 52 52 52 52 52 52	85 87 83 71 69 132 141 87 90 97 214 62 56 66 116 134 45 89 99 99 101 87 99 101 87 99 90 101 87 87 2747	11 11 12 12 12 22 5 5 37 14 14 15 14 14 25 20 9 9 9 10 0 5 5 5 5 5 37 7 14 12 20 20 20 20 20 20 20 20 20 2	29 30 700 32 33 33 32 30 30 30 30 30 30 30 67 68 85 32 32 32 32 32 31 31 31 31 32 33 31 31 31 31 31 31 32 32 32 32 33 33 30 30 30 30 30 30 30 30 30 30 30	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.3% 3.8% 4.1% 3.3% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.43 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 1.21 \left[ 0.81, 1.84 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.23 \left[ 1.03, 2.27 \right] \\ 1.03 \left[ 0.07, 1.38 \right] \\ 1.19 \left[ 0.64, 2.20 \right] \\ 1.15 \left[ 0.62, 2.14 \right] \\ 1.43 \left[ 0.82, 2.49 \right] \\ 2.42 \left[ 1.04, 5.68 \right] \\ 1.31 \left[ 0.83, 2.07 \right] \\ 1.44 \left[ 0.95, 1.28 \right] \\ 1.32 \left[ 0.87, 2.02 \right] \\ 1.5 \left[ 0.87,$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Raskin 2004 Rauck 2012 (2400 mg) Rauck 2012 (2400 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Tolle 2008 (150 mg) Tolle 2008 (300 mg) Tolle 2008 (300 mg) Van-Seventer 2006 (150 mg) Van-Seventer 2006 (150 mg) Van-Seventer 2006 (150 mg) Van-Seventer 2006 (150 mg) Zhang 2013 (1200 mg) Zhang 2013 (1200 mg) Zhang 2013 (1200 mg) Zhang 2013 (300 mg) Subtotal (95% CI)	44 43 30 22 31 88 83 21 32 30 103 31 25 28 66 66 25 28 66 66 25 40 49 33 32 24 5 34 40 47 57 8 8 52 2 8 28 52 28 52 28 52 28 52 28 52 28 52 52 52 52 52 52 52 52 52 52 52 52 52	85 87 83 71 69 132 141 87 90 97 214 62 56 66 116 134 45 89 99 99 101 87 99 101 87 99 90 101 87 87 2747	11 11 12 12 12 22 5 5 37 14 14 15 14 14 25 20 9 9 9 10 0 5 5 5 5 5 37 7 14 12 20 20 20 20 20 20 20 20 20 2	29 30 700 32 33 33 32 30 30 30 30 30 30 30 67 68 85 32 32 32 32 32 31 31 31 31 32 33 31 31 31 31 31 31 32 32 32 32 33 33 30 30 30 30 30 30 30 30 30 30 30	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.3% 3.8% 4.1% 3.3% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.43 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 1.21 \left[ 0.81, 1.84 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.23 \left[ 1.03, 2.27 \right] \\ 1.03 \left[ 0.07, 1.38 \right] \\ 1.19 \left[ 0.64, 2.20 \right] \\ 1.15 \left[ 0.62, 2.14 \right] \\ 1.43 \left[ 0.82, 2.49 \right] \\ 2.42 \left[ 1.04, 5.68 \right] \\ 1.31 \left[ 0.83, 2.07 \right] \\ 1.44 \left[ 0.95, 1.28 \right] \\ 1.32 \left[ 0.87, 2.02 \right] \\ 1.5 \left[ 0.87,$	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg) Beydoun 2006 (600 mg) CTRI476G2301 Dogra 2005 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (300 mg) Rauck 2012 (1200 mg) Rauck 2012 (2400 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (600 mg) Sharma 2006 Smith 2014 Tolle 2008 (300 mg) Tolle 2008 (300 mg) Tolle 2008 (300 mg) Tolle 2008 (300 mg) Yan-Seventer 2006 (150 mg) Van-Seventer 2006 (150 mg) Van-Seventer 2006 (150 mg) Zhang 2013 (1200 mg) Zhang 2013 (2400 mg) Zhang 2014	44 43 30 22 31 88 83 21 32 30 103 31 25 28 66 66 25 28 66 66 25 40 49 33 32 24 5 34 40 47 57 8 8 52 2 8 28 52 28 52 28 52 28 52 28 52 28 52 52 52 52 52 52 52 52 52 52 52 52 52	85 87 83 71 69 132 141 87 90 97 214 62 56 66 116 134 45 89 99 99 101 87 99 101 87 99 90 101 87 87 2747	11 11 12 12 12 22 5 5 37 14 14 15 14 14 25 20 9 9 9 10 0 5 5 5 5 5 37 7 14 12 20 20 20 20 20 20 20 20 20 2	29 30 700 32 33 33 32 30 30 30 30 30 30 30 67 68 85 32 32 32 32 32 31 31 31 31 32 33 31 31 31 31 31 31 32 32 32 32 33 33 30 30 30 30 30 30 30 30 30 30 30	3.0% 3.0% 4.4% 3.8% 3.5% 1.3% 1.3% 1.4% 9.0% 3.5% 3.3% 3.8% 4.1% 3.3% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6	$\begin{array}{c} 1.41 \left[ 0.85, 2.36 \right] \\ 1.30 \left[ 0.78, 2.17 \right] \\ 0.99 \left[ 0.57, 1.71 \right] \\ 0.90 \left[ 0.56, 1.45 \right] \\ 1.57 \left[ 1.01, 2.43 \right] \\ 1.62 \left[ 1.01, 2.60 \right] \\ 1.54 \left[ 0.64, 3.75 \right] \\ 2.35 \left[ 1.00, 5.51 \right] \\ 2.04 \left[ 0.86, 4.83 \right] \\ 1.42 \left[ 1.05, 1.91 \right] \\ 1.07 \left[ 0.68, 1.69 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 0.96 \left[ 0.59, 1.55 \right] \\ 1.21 \left[ 0.81, 1.84 \right] \\ 1.22 \left[ 0.81, 1.84 \right] \\ 1.23 \left[ 1.03, 2.27 \right] \\ 1.03 \left[ 0.07, 1.38 \right] \\ 1.19 \left[ 0.64, 2.20 \right] \\ 1.15 \left[ 0.62, 2.14 \right] \\ 1.43 \left[ 0.82, 2.49 \right] \\ 2.42 \left[ 1.04, 5.68 \right] \\ 1.31 \left[ 0.83, 2.07 \right] \\ 1.44 \left[ 0.95, 1.28 \right] \\ 1.32 \left[ 0.87, 2.02 \right] \\ 1.5 \left[ 0.87,$	

Study or Subgroup	Anticonv Events		Placeb Events		Weight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl
2.2.1 Public Funding					~		
Subtotal (95% CI)		0		0		Not estimable	
Fotal events	0		0				
Heterogeneity: Not applicable							
Fest for overall effect: Not appli	icable						
2.2.2 Inductor Funding							
2.2.2 Industry Funding	10		20	0.5	1 50/	2 07 [1 22 2 22]	
Arezzo 2008	40	82	20	85	1.5%	2.07 [1.33, 3.23]	
Saba 2020	38	85	37	88	2.9%	1.06 [0.76, 1.49]	
Backonja 1998	47	82	25	80	2.0%	1.83 [1.26, 2.67]	
Backonja 2011	26	47	15	54	1.1%	1.99 [1.21, 3.29]	
Beydoun 2006 (1200 mg)	44	85	11	30	1.3%	1.41 [0.85, 2.36]	Τ
Beydoun 2006 (1800 mg)	43	87	11	29	1.3%	1.30 [0.78, 2.17]	
Beydoun 2006 (600 mg)	30	83	11	30	1.3%	0.99 [0.57, 1.71]	
CTRI476G2301	22	71	24	70	1.9%	0.90 [0.56, 1.45]	
Dogra 2005	31	69	22	77	1.6%	1.57 [1.01, 2.44]	
Dworkin 2003	56	89	21	84	1.7%	2.52 [1.68, 3.77]	
Freynhagen 2005 (Fixed)	88	132	12	32	1.5%	1.78 [1.12, 2.83]	
Freynhagen 2005 (Flexed)	83	141	12	33	1.5%	1.62 [1.01, 2.60]	
Guan 2011	130	206	53	102	5.6%	1.21 [0.98, 1.50]	-
Huffman 2015	39	101	25	102	2.0%	1.58 [1.04, 2.40]	<b>⊢</b>
Lesser 2004 (300 mg)	50	81	16	48	1.6%	1.85 [1.20, 2.86]	<del></del>
_esser 2004 (600 mg)	53	82	16	49	1.6%	1.98 [1.28, 3.05]	<del></del>
_iu 2017	58	111	33	109	2.6%	1.73 [1.23, 2.41]	
McDonnell 2018	15	46	7	45	0.6%	2.10 [0.94, 4.65]	<u>├</u>
Moon 2010	68	162	27	78	2.9%	1.21 [0.85, 1.73]	+
Mu 2018	157	314	136	308	10.8%	1.13 [0.96, 1.34]	+
NCT00394901 2006 (150 mg)	21	87	5	32	0.6%	1.54 [0.64, 3.75]	
NCT00394901 2006 (300 mg)	32	90	5	33	0.6%	2.35 [1.00, 5.51]	
NCT00394901 2006 (600 mg)	30	97	5	33	0.6%	2.04 [0.86, 4.83]	
NCT02215252 2014	12	46	7	45	0.6%	1.68 [0.73, 3.87]	
Raskin 2004	103	214	37	109	3.9%	1.42 [1.05, 1.91]	
Rauck 2012 (1200 mg)	31	62	14	30	1.5%	1.07 [0.68, 1.69]	
Rauck 2012 (2400 mg)	25	56	14	30	1.4%	0.96 [0.59, 1.55]	
Rauck 2012 (300 mg)	28	66	15	30	1.6%	0.85 [0.54, 1.34]	
Rauck 2012 (3600 mg)	66	116	14	30	1.8%	1.22 [0.81, 1.84]	
Rice 2001 (1800 mg)	37	115	8	55	0.9%	2.21 [1.11, 4.42]	
Rice 2001 (2400 mg)	37	108	8	56	0.8%	2.40 [1.20, 4.79]	
Richter 2005 (600 mg)	32	82	13	85	1.0%	2.55 [1.44, 4.51]	
Rosenstock 2004	30	76	10	70	0.8%	2.76 [1.46, 5.23]	
Rowbotham 1998	49	113	14	116	1.1%	3.59 [2.11, 6.13]	
Sabatowski 2004 (150 mg)	21	81	4	40	0.4%	2.59 [0.95, 7.05]	
Sabatowski 2004 (300 mg)	21	76	4	41	0.4%	2.83 [1.04, 7.70]	
Sandercock 2012 (Daily)	16	46	2	25	0.2%	4.35 [1.09, 17.40]	
Sandercock 2012 (Divided)	13	50	2	26	0.2%	3.38 [0.82, 13.86]	
Sang 2013	65	221	52	231	4.0%	1.31 [0.95, 1.79]	
Satoh 2011 (300 mg)	66	134	24	67	2.5%	1.38 [0.96, 1.98]	
Satoh 2011 (600 mg)	25	45	25	68	1.6%	1.51 [1.01, 2.27]	
	40	82	20	85	1.5%		
Sharma 2006 Smith 2014	40 49	82 98	20 45	85 93	1.5% 3.6%	2.07 [1.33, 3.23] 1.03 [0.77, 1.38]	$\perp$
Stacey 2008 (Fixed)	49 51	98 88	45 14	95 45	3.6% 1.5%	1.86 [1.16, 2.98]	[
	64	88 91	14 14	45 45			
Stacey 2008 (Flexed) Tolle 2008 (150 mg)	33	91	14 9	45 32	1.5%	2.26 [1.43, 3.56]	
	33	99	9		1.1%	1.19 [0.64, 2.20] 1.15 [0.62, 2.14]	
Folle 2008 (300 mg)			9 10	32	1.1%		
Folle 2008 (600 mg)	45	101		32	1.2%	1.43 [0.82, 2.49]	
Van-Seventer 2006 (150 mg)	34	87	5	31	0.6%	2.42 [1.04, 5.64]	·
Van-Seventer 2006 (300 mg)	40	98	5	31	0.6%	2.53 [1.10, 5.85]	
Van-Seventer 2006 (600 mg)	47	90	6	31	0.7%	2.70 [1.28, 5.68]	
/inik 2014 Mallaca 2010 (Dailu)	19	50	45	112	2.2%	0.95 [0.62, 1.44]	
Wallace 2010 (Daily)	49	134	18	66	1.9%	1.34 [0.85, 2.11]	
Wallace 2010 (Divided)	46	135	18	65	1.9%	1.23 [0.78, 1.94]	
Zhang 2013 (1200 mg)	57	107	13	32	1.6%	1.31 [0.83, 2.07]	
Zhang 2013 (2400 mg)	48	82	13	32	1.5%	1.44 [0.91, 2.28]	<u>–</u>
Zhang 2013 (3600 mg)	52	87	14	31	1.6%	1.32 [0.87, 2.02]	
Ziegler 2015 Subtetal (05% CI)	25	70	28	62	2.3%	0.79 [0.52, 1.20]	,
Subtotal (95% CI)		5735		3042	100.0%	1.49 [1.41, 1.58]	1
Γotal events Heterogeneity: Chi² = 116.95, α Γest for overall effect: Z = 13.5			1102 .); I <sup>2</sup> = 51	%			
Total (95% CI)		5735		3642	100.0%	1.49 [1.41, 1.58]	•
Total events	2609		1102				
Heterogeneity: $Chi^2 = 116.95$ , o		0.00001		%			0.01 0.1 1 10 1

# Figure 2.3: Anticonvulsants versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source

# Figure 2.4: Anticonvulsants versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by median risk of bias

Study or Subgroup	Anticonvu Events		Place Events		Weiaht	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M–H, Fixed, 95% Cl
2.4.1 Less than the median ris			2. 5113				
Arezzo 2008	40	82	20	85	1.5%	2.07 [1.33, 3.23]	
Baba 2020	38	85	37	88	2.8%	1.06 [0.76, 1.49]	
Backonja 1998	47	82	25	80	2.0%	1.83 [1.26, 2.67]	
Backonia 2011	26	82 47	15	54	2.0%		
						1.99 [1.21, 3.29]	
Dogra 2005	31	69	22	77	1.6%	1.57 [1.01, 2.44]	· · ·
Lesser 2004 (300 mg)	50	81	16	48	1.6%	1.85 [1.20, 2.86]	
Lesser 2004 (600 mg)	53	82	16	49	1.6%	1.98 [1.28, 3.05]	
Liu 2017	58	111	33	109	2.6%	1.73 [1.23, 2.41]	
McDonnell 2018	15	46	7	45	0.5%	2.10 [0.94, 4.65]	
Moon 2010	68	162	27	78	2.8%	1.21 [0.85, 1.73]	
Mu 2018	157	314	136	308	10.7%	1.13 [0.96, 1.34]	-
NCT02215252 2014	12	46	7	45	0.5%	1.68 [0.73, 3.87]	
Richter 2005 (600 mg)	32	82	13	85	1.0%	2.55 [1.44, 4.51]	<del></del>
Satoh 2011 (300 mg)	66	134	24	67	2.5%	1.38 [0.96, 1.98]	
Satoh 2011 (600 mg)	25	45	25	68	1.5%	1.51 [1.01, 2.27]	
Wallace 2010 (Daily)	49	134	18	66	1.9%	1.34 [0.85, 2.11]	+
Wallace 2010 (Divided)	46	135	18	65	1.9%	1.23 [0.78, 1.94]	+
Zhang 2013 (1200 mg)	57	107	13	32	1.6%	1.31 [0.83, 2.07]	+
Zhang 2013 (2400 mg)	48	82	13	32	1.5%	1.44 [0.91, 2.28]	
Zhang 2013 (3600 mg)	52	87	14	31	1.6%	1.32 [0.87, 2.02]	+
Ziegler 2015	25	70	28	62	2.3%	0.79 [0.52, 1.20]	-+
Subtotal (95% CI)		2083	-	1574	45.0%	1.41 [1.30, 1.54]	♦
Total events	995		527				
Heterogeneity: $Chi^2 = 35.50$ , df		$(02): 1^2 =$					
Test for overall effect: $Z = 8.14$							
		-/					
2.4.2 Greater than or equal to	the median	risk of	bias sco	ore			
Achar 2010	11	15	2	15	0.2%	5.50 [1.46, 20.71]	
Beydoun 2006 (1200 mg)	44	85	11	30	1.3%	1.41 [0.85, 2.36]	
Beydoun 2006 (1200 mg)	43	87	11	29	1.3%	1.30 [0.78, 2.17]	
Beydoun 2006 (600 mg)	30	83	11	30	1.3%	0.99 [0.57, 1.71]	
CTRI476G2301	22	71	24	70	1.9%	0.99 [0.56, 1.45]	
Dworkin 2003	56	89	24	84		2.52 [1.68, 3.77]	
					1.7%	• / •	
Freynhagen 2005 (Fixed)	88	132	12	32	1.5%	1.78 [1.12, 2.83]	
Freynhagen 2005 (Flexed)	83	141	12	33	1.5%	1.62 [1.01, 2.60]	
Guan 2011	130	206	53	102	5.5%	1.21 [0.98, 1.50]	
Huffman 2015	39	101	25	102	1.9%	1.58 [1.04, 2.40]	
NCT00394901 2006 (150 mg)	21	87	5	32	0.6%	1.54 [0.64, 3.75]	
NCT00394901 2006 (300 mg)	32	90	5	33	0.6%	2.35 [1.00, 5.51]	
NCT00394901 2006 (600 mg)	30	97	5	33	0.6%	2.04 [0.86, 4.83]	
Perez 2000	14	17	2	15	0.2%	6.18 [1.67, 22.86]	
Raskin 2004	103	214	37	109	3.8%	1.42 [1.05, 1.91]	
Rauck 2012 (1200 mg)	31	62	14	30	1.5%	1.07 [0.68, 1.69]	
Rauck 2012 (2400 mg)	25	56	14	30	1.4%	0.96 [0.59, 1.55]	_ <b>+</b> _
Rauck 2012 (300 mg)	28	66	15	30	1.6%	0.85 [0.54, 1.34]	
Rauck 2012 (3600 mg)	66	116	14	30	1.7%	1.22 [0.81, 1.84]	
Rice 2001 (1800 mg)	37	115	8	55	0.8%	2.21 [1.11, 4.42]	
Rice 2001 (2400 mg)	37	108	8	56	0.8%	2.40 [1.20, 4.79]	
Rosenstock 2004	30	76	10	70	0.8%	2.76 [1.46, 5.23]	
Rowbotham 1998	49	113	14	116	1.1%	3.59 [2.11, 6.13]	
Sabatowski 2004 (150 mg)	21	81	4	40	0.4%	2.59 [0.95, 7.05]	<u>├</u>
Sabatowski 2004 (300 mg)	21	76	4	41	0.4%	2.83 [1.04, 7.70]	
Sandercock 2012 (Daily)	16	46	2	25	0.2%	4.35 [1.09, 17.40]	
Sandercock 2012 (Divided)	13	50	2	26	0.2%	3.38 [0.82, 13.86]	
Sang 2013	65	221	52	231	3.9%	1.31 [0.95, 1.79]	<b>↓</b>
Shabbir 2011	64	70	14	70	1.1%	4.57 [2.85, 7.34]	
Sharma 2006	40	82	20	85	1.5%	2.07 [1.33, 3.23]	
Smith 2014	40	98	45	93	3.6%	1.03 [0.77, 1.38]	$\downarrow$
Stacev 2008 (Fixed)	49 51	98 88	43	45	1.4%	1.86 [1.16, 2.98]	
Stacey 2008 (Flexed) Stacey 2008 (Flexed)	64	88 91	14	45	1.4%	2.26 [1.43, 3.56]	
Tolle 2008 (150 mg)	33	91	9	43		1.19 [0.64, 2.20]	
Tolle 2008 (300 mg)					1.1%		
. 3,	32	99 101	9	32	1.1%	1.15 [0.62, 2.14]	
Tolle 2008 (600 mg)	45	101	10	32	1.2%	1.43 [0.82, 2.49]	
Van-Seventer 2006 (150 mg)	34	87	5	31	0.6%	2.42 [1.04, 5.64]	
Van-Seventer 2006 (300 mg)	40	98	5	31	0.6%	2.53 [1.10, 5.85]	
Van-Seventer 2006 (600 mg)	47	90	6	31	0.7%	2.70 [1.28, 5.68]	<del></del>
Vinik 2014	19	50	45	108	2.2%	0.91 [0.60, 1.39]	- <u>+</u> .
Subtotal (95% CI)		3754		2164	55.0%	1.64 [1.51, 1.77]	•
Total events	1703		593				
Heterogeneity: Chi <sup>2</sup> = 113.85, c Test for overall effect: Z = 12.4			); $I^2 = 6$	6%			
	_ ( 0.000			2720	100 00/	1 64 [1 45 1 62]	
Total (95% CI)	2000	5837	1.000	3138	100.0%	1.54 [1.45, 1.63]	'
Total events	2698		1120				, , l .
Heterogeneity: Chi <sup>2</sup> = 150.72, c			$I_{1}^{2} = 6$	υ%			0.01 0.1 1 10 1
Test for overall effect: Z = 14.7							

For each study, the risk of bias domain was scored (0=low risk, 1=unclear risk, 2=high risk) and a median was found among all the studies within each intervention. Studies were then divided into two categories: less than the median or greater than or equal to the median. (Higgins 2011)

Figure 2.5: Anticonvulsants versus control; Subgroup analysis: Proportion of patients with a
meaningful response to treatment, analyzed by neuropathic pain type

2.3.1 Diabetic Neuropathy	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Arezzo 2008	40	82	20	85	1.5%	2.07 [1.33, 3.23]	
Baba 2020	38	85	37	88	2.8%	1.06 [0.76, 1.49]	
Backonja 1998	47	82	25	80	2.0%	1.83 [1.26, 2.67]	
Beydoun 2006 (1200 mg)	44	85	11	30	1.3%	1.41 [0.85, 2.36]	+
Beydoun 2006 (1800 mg)	43	87	11	29	1.3%	1.30 [0.78, 2.17]	
Beydoun 2006 (600 mg)	30	83	11	30	1.3%	0.99 [0.57, 1.71]	
CTRI476G2301	22	71	24	70	1.9%	0.90 [0.56, 1.45]	
Dogra 2005	31	69	22	77	1.6%	1.57 [1.01, 2.44]	
Huffman 2015	39	101	25	102	1.9%	1.58 [1.04, 2.40]	
Lesser 2004 (300 mg)	50	81	16	48	1.6%	1.85 [1.20, 2.86]	
	53	82		40	1.6%		
Lesser 2004 (600 mg)			16			1.98 [1.28, 3.05]	
McDonnell 2018	15	46	7	45	0.5%	2.10 [0.94, 4.65]	
Mu 2018	157	314	136	308	10.7%	1.13 [0.96, 1.34]	T
NCT02215252 2014	12	46	7	45	0.5%	1.68 [0.73, 3.87]	
Perez 2000	14	17	2	15	0.2%	6.18 [1.67, 22.86]	
Raskin 2004	103	214	37	109	3.8%	1.42 [1.05, 1.91]	
Rauck 2012 (1200 mg)	31	62	14	30	1.5%	1.07 [0.68, 1.69]	
Rauck 2012 (2400 mg)	25	56	14	30	1.4%	0.96 [0.59, 1.55]	_ <del>_</del> _
Rauck 2012 (300 mg)	28	66	15	30	1.6%	0.85 [0.54, 1.34]	
Rauck 2012 (3600 mg)	66	116	14	30	1.7%	1.22 [0.81, 1.84]	
Richter 2005 (600 mg)	32	82	13	85	1.0%	2.55 [1.44, 4.51]	
Rosenstock 2004	30	76	10	70	0.8%	2.76 [1.46, 5.23]	
Sandercock 2012 (Daily)	16	46	2	25	0.2%	4.35 [1.09, 17.40]	
Sandercock 2012 (Divided)	13	50	2	26	0.2%	3.38 [0.82, 13.86]	<u> </u>
						1.38 [0.96, 1.98]	
Satoh 2011 (300 mg)	66	134	24	67	2.5%		L
Satoh 2011 (600 mg)	25	45	25	68	1.5%	1.51 [1.01, 2.27]	<b>—</b>
Shabbir 2011	64	70	14	70	1.1%	4.57 [2.85, 7.34]	
Sharma 2006	40	82	20	85	1.5%	2.07 [1.33, 3.23]	
Smith 2014	49	98	45	93	3.6%	1.03 [0.77, 1.38]	+
Tolle 2008 (150 mg)	33	99	9	32	1.1%	1.19 [0.64, 2.20]	- <del> -</del>
Tolle 2008 (300 mg)	32	99	9	32	1.1%	1.15 [0.62, 2.14]	_ <del></del>
Tolle 2008 (600 mg)	45	101	10	32	1.2%	1.43 [0.82, 2.49]	+
Vinik 2014	19	50	45	108	2.2%	0.91 [0.60, 1.39]	
Ziegler 2015	25	70	28	62	2.3%	0.79 [0.52, 1.20]	
Subtotal (95% CI)		2947		2185	60.8%	1.42 [1.32, 1.53]	•
Total events	1377		720				,
Heterogeneity: Chi <sup>2</sup> = 95.17, df		00001)					
Test for overall effect: Z = 9.55 (							
2.3.2 Postherpetic Neuralgia							
Achar 2010	11	15	2	15	0.2%	5.50 [1.46, 20.71]	
Backonja 2011	26	47	15	54	1.1%	1.99 [1.21, 3.29]	
Dworkin 2003	56	89	21	84	1.7%	2.52 [1.68, 3.77]	
Liu 2017	58	111	33	109	2.6%	1.73 [1.23, 2.41]	
Moon 2010	68	162	27	78	2.8%	1.21 [0.85, 1.73]	
NCT00394901 2006 (150 mg)	21	87	5	32	0.6%	1.54 [0.64, 3.75]	
NCT00394901 2006 (300 mg)	32	90	5	33	0.6%	2.35 [1.00, 5.51]	
NCT00394901 2006 (600 mg)	30	97	5	33	0.6%	2.04 [0.86, 4.83]	<u> </u>
Rice 2001 (1800 mg)	37	115	8	55	0.8%	2.21 [1.11, 4.42]	
Rice 2001 (2400 mg)	37	108	8	56	0.8%	2.40 [1.20, 4.79]	
Rowbotham 1998	49	113	14	116	1.1%	3.59 [2.11, 6.13]	
Sabatowski 2004 (150 mg)	21	81	4	40	0.4%	2.59 [0.95, 7.05]	
Sabatowski 2004 (300 mg)	21	76	4	41	0.4%	2.83 [1.04, 7.70]	
Sang 2013	65	221	52	231	3.9%	1.31 [0.95, 1.79]	<b>—</b>
Stacey 2008 (Fixed)	51	88	14	45	1.4%	1.86 [1.16, 2.98]	<del></del>
Stacey 2008 (Flexed)	64	91	14	45	1.5%	2.26 [1.43, 3.56]	
Van-Seventer 2006 (150 mg)	34	87	5	31	0.6%	2.42 [1.04, 5.64]	
Van-Seventer 2006 (300 mg)	40	98	5	31	0.6%	2.53 [1.10, 5.85]	<del></del>
Van-Seventer 2006 (600 mg)	47	90	6	31	0.7%	2.70 [1.28, 5.68]	
Wallace 2010 (Daily)	49	134	18	66	1.9%	1.34 [0.85, 2.11]	+
Wallace 2010 (Divided)	46	135	18	65	1.9%	1.23 [0.78, 1.94]	+
Zhang 2013 (1200 mg)	57	107	13	32	1.6%	1.31 [0.83, 2.07]	+
Zhang 2013 (2400 mg)	48	82	13	32	1.5%	1.44 [0.91, 2.28]	+
	52	87	14	31	1.6%	1.32 [0.87, 2.02]	<b>+</b>
	22	2411		1386	30.7%	1.81 [1.62, 2.01]	▲
Zhang 2013 (3600 mg)			222		/0		*
Zhang 2013 (3600 mg) Subtotal (95% Cl)	1020		~ / ~				
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events	1020 = 23 (P = 0	).04) <sup>.</sup> I <sup>2</sup> =	323 = 36%				
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df =	= 23 (P = 0)		323 = 36%				
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df Test for overall effect: Z = 10.92	= 23 (P = 0)		323 = 36%				
Zhang 2013 (3600 mg) Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia	= 23 (P = 0)	)01)	323 = 36%				
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df : Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia Subtotal (95% Cl)	= 23 (P = 0 2 (P < 0.000			0		Not estimable	
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df / Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia Subtotal (95% Cl)	= 23 (P = 0)	)01)	323 = 36% 0	0		Not estimable	
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia	= 23 (P = 0 2 (P < 0.000	)01)		0		Not estimable	
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia Subtotal (95% Cl) Total events	= 23 (P = 0 2 (P < 0.000 0	)01)		0		Not estimable	
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia Subtotal (95% Cl) Total events Heterogeneity: Not applicable Test for overall effect: Not applic	= 23 (P = 0 2 (P < 0.000 0	)01)		0		Not estimable	
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia Subtotal (95% Cl) Total events Heterogeneity: Not applicable Test for overall effect: Not applic	= 23 (P = 0 2 (P < 0.000 0	)01)		0		Not estimable	
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia Subtotal (95% Cl) Total events Heterogeneity: Not applicable Test for overall effect: Not applic 2.3.4 Mixed Population	= 23 (P = 0 2 (P < 0.000 0	)01)		0	1.5%		
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df - Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia Subtotal (95% Cl) Total events Heterogeneity: Not applicable Test for overall effect: Not applica 2.3.4 Mixed Population Freynhagen 2005 (Fixed)	= 23 (P = 0 2 (P < 0.000 0 cable 88	001) 0 132	0	32		1.78 [1.12, 2.83]	
Zhang 2013 (3600 mg) Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df - Test for overall effect: Z = 10.92 <b>2.3.3 Trigeminal Neuralgia</b> Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Not applic <b>2.3.4 Mixed Population</b> Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed)	= 23 (P = 0 2 (P < 0.000 0 cable 88 83	001) 0 132 141	0 12 12	32 33	1.5%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60]	
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df / Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia Subtotal (95% Cl) Total events Heterogeneity: Not applicable Test for overall effect: for	= 23 (P = 0 2 (P < 0.000 0 cable 88	001) 0 132 141 206	0	32 33 102	1.5% 5.5%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50]	  *•
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df - Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia Subtotal (95% Cl) Total events Heterogeneity: Not applicable Test for overall effect: Not applica 2.3.4 Mixed Population Freynhagen 2005 (Flexed) Guan 2011 Subtotal (95% Cl)	= 23 (P = 0 2 (P < 0.000 0 cable 88 83 130	001) 0 132 141	0 12 12 53	32 33	1.5%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60]	 
Zhang 2013 (3600 mg) Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df- Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Not applicable Total events	= 23 (P = 0 2 (P < 0.000 0 cable 88 83 130 301	001) 0 132 141 206 479	0 12 12 53 77	32 33 102	1.5% 5.5%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50]	 
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df / Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia Subtotal (95% Cl) Total events Heterogeneity: Not applicable Test for overall effect: Not applicable Test for overall effec	= 23 (P = 0) $(P < 0.000)$ $0$ $(P < 0.000)$ $= 88$ $83$ $130$ $301$ $= 2 (P = 0.2)$	001) 0 132 141 206 <b>479</b> 2); I <sup>2</sup> = 3	0 12 12 53 77	32 33 102	1.5% 5.5%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50]	 
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df / Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia Subtotal (95% Cl) Total events Heterogeneity: Not applicable Test for overall effect: Not applicable Test for overall effec	= 23 (P = 0) $(P < 0.000)$ $0$ $(P < 0.000)$ $= 88$ $83$ $130$ $301$ $= 2 (P = 0.2)$	001) 0 132 141 206 <b>479</b> 2); I <sup>2</sup> = 3	0 12 12 53 77	32 33 102	1.5% 5.5%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50]	 
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df / Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia Subtotal (95% Cl) Total events Heterogeneity: Not applicable Test for overall effect: Not applicable Terynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 2.99, df = Test for overall effect: Z = 3.49 (	= 23 (P = 0) $(P < 0.000)$ $0$ $(P < 0.000)$ $= 88$ $83$ $130$ $301$ $= 2 (P = 0.2)$	001) 0 132 141 206 <b>479</b> 2);   <sup>2</sup> = 3	0 12 12 53 77 3%	32 33 102 <b>167</b>	1.5% 5.5% <b>8.5%</b>	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.39 [1.15, 1.66]	 ►
Zhang 2013 (3600 mg) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 36.04, df Test for overall effect: Z = 10.92 2.3.3 Trigeminal Neuralgia Subtotal (95% Cl) Total events Heterogeneity: Not applicable Test for overall effect: Not applic 2.3.4 Mixed Population	= 23 (P = 0) $(P < 0.000)$ $0$ $(P < 0.000)$ $= 88$ $83$ $130$ $301$ $= 2 (P = 0.2)$	001) 0 132 141 206 <b>479</b> 2); I <sup>2</sup> = 3	0 12 12 53 77 3%	32 33 102 <b>167</b>	1.5% 5.5%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50]	•

Test for subgroup differences:  $Chi^2 = 14.34$ , df = 2 (P = 0.0008),  $I^2 = 86.0\%$ 

Study or Subgroup 2.1.1 Less than or equal to 15	Events	Total	Place Events		Weiaht	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% Cl
						,, 55/0 Cl	
Achar 2010	11	15	2	15	0.2%	5.50 [1.46, 20.71]	
Backonja 2011	26	47	15	54	1.1%	1.99 [1.21, 3.29]	
Beydoun 2006 (1200 mg)	44	85	11	30	1.3%	1.41 [0.85, 2.36]	
Beydoun 2006 (1200 mg) Beydoun 2006 (1800 mg)	44	87	11	29	1.3%	1.30 [0.78, 2.17]	
Beydoun 2006 (600 mg)	30	83	11	30	1.3%	0.99 [0.57, 1.71]	
CTRI476G2301	22	71	24	70	1.9%	0.90 [0.56, 1.45]	•
Dogra 2005	31	69	22	77	1.6%	1.57 [1.01, 2.44]	
Lesser 2004 (300 mg)	50	81	16	48	1.6%	1.85 [1.20, 2.86]	
Lesser 2004 (600 mg)	53	82	16	49	1.6%	1.98 [1.28, 3.05]	
McDonnell 2018	15	46	7	45	0.5%	2.10 [0.94, 4.65]	
NCT00394901 2006 (150 mg)	21	87	5	32	0.6%	1.54 [0.64, 3.75]	
NCT00394901 2006 (300 mg)	32	90	5	33	0.6%	2.35 [1.00, 5.51]	
NCT00394901 2006 (600 mg)	30	97	5	33	0.6%	2.04 [0.86, 4.83]	
NCT02215252 2014	12	46	7	45	0.5%	1.68 [0.73, 3.87]	
Perez 2000	14	17	2	15	0.2%	6.18 [1.67, 22.86]	
Rauck 2012 (1200 mg)	31	62	14	30	1.5%	1.07 [0.68, 1.69]	
Rauck 2012 (2400 mg)	25	56	14	30	1.4%	0.96 [0.59, 1.55]	
Rauck 2012 (300 mg)	28	66	15	30	1.6%	0.85 [0.54, 1.34]	
Rauck 2012 (3600 mg)	66	116	14	30	1.7%	1.22 [0.81, 1.84]	
Rosenstock 2004	30	76	10	70	0.8%	2.76 [1.46, 5.23]	
Sabatowski 2004 (150 mg)	21	81	4	40	0.4%	2.59 [0.95, 7.05]	
Sabatowski 2004 (300 mg)	21	76	4	41	0.4%	2.83 [1.04, 7.70]	· · · · · · · · · · · · · · · · · · ·
Sandercock 2012 (Daily)	16	46	2	25	0.4%	4.35 [1.09, 17.40]	
Sandercock 2012 (Daily)	13	50	2	26	0.2%	3.38 [0.82, 13.86]	<u> </u>
Satoh 2011 (600 mg)	25	45	25	68	1.5%	1.51 [1.01, 2.27]	
Shabbir 2011 (600 mg)	25 64	45 70	25 14	70	1.5%		
Shabbir 2011 Stacey 2008 (Fixed)						4.57 [2.85, 7.34]	
	51	88	14	45	1.4%	1.86 [1.16, 2.98]	
Stacey 2008 (Flexed)	64	91	14	45	1.5%	2.26 [1.43, 3.56]	
Tolle 2008 (150 mg)	33	99	9	32	1.1%	1.19 [0.64, 2.20]	
Tolle 2008 (300 mg)	32	99	9	32	1.1%	1.15 [0.62, 2.14]	
Tolle 2008 (600 mg)	45	101	10	32	1.2%	1.43 [0.82, 2.49]	
Van–Seventer 2006 (150 mg)	34	87	5	31	0.6%	2.42 [1.04, 5.64]	
Van-Seventer 2006 (300 mg)	40	98	5	31	0.6%	2.53 [1.10, 5.85]	
Van-Seventer 2006 (600 mg)	47	90	6	31	0.7%	2.70 [1.28, 5.68]	
Zhang 2013 (1200 mg)	57	107	13	32	1.6%	1.31 [0.83, 2.07]	
Zhang 2013 (2400 mg)	48	82	13	32	1.5%	1.44 [0.91, 2.28]	
Zhang 2013 (3600 mg)	52	87	14	31	1.6%	1.32 [0.87, 2.02]	+
Ziegler 2015	25	70	28	62	2.3%	0.79 [0.52, 1.20]	
Subtotal (95% CI)		2846		1501	40.4%	1.66 [1.51, 1.81]	•
Total events Heterogeneity: Chi <sup>2</sup> = 87.25. df	1302	00001)	417 $l^2 = 589$	%			
Total events Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 <b>2.1.2 Greater than 150 patien</b>	F = 37 (P < 0 3 (P < 0.000			%			
Heterogeneity: Chi <sup>2</sup> = 87.25, df Test for overall effect: Z = 10.9	F = 37 (P < 0 3 (P < 0.000			85	1.5%	2.07 [1.33, 3.23]	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Test for overall effect: Z = 10.9 2.1.2 Greater than 150 patien	<sup>E</sup> = 37 (P < 0 3 (P < 0.000 ts	01)	l <sup>2</sup> = 589		1.5% 2.8%	2.07 [1.33, 3.23] 1.06 [0.76, 1.49]	 
Heterogeneity: Chi <sup>2</sup> = 87.25, df Test for overall effect: Z = 10.9 <b>2.1.2 Greater than 150 patien</b> Arezzo 2008 Baba 2020	F = 37 (P < 0) 3 (P < 0.000) ts 40 38	01) 82 85	$I^2 = 589$ 20 37	85 88	2.8%	1.06 [0.76, 1.49]	 
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 <b>2.1.2 Greater than 150 patien</b> Arezzo 2008 Saba 2020 Backonja 1998	F = 37 (P < C) 3 (P < 0.000) ts 40 38 47	01) 82 85 82	l <sup>2</sup> = 589 20 37 25	85 88 80	2.8% 2.0%	1.06 [0.76, 1.49] 1.83 [1.26, 2.67]	 
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Baba 2020 Backonja 1998 Dworkin 2003	<sup>E</sup> = 37 (P < C 3 (P < 0.000 ts 40 38 47 56	01) 82 85 82 89	l <sup>2</sup> = 589 20 37 25 21	85 88 80 84	2.8% 2.0% 1.7%	1.06 [0.76, 1.49]	  
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Jaba 2020 Backonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed)	F = 37 (P < C) 3 (P < 0.000 ts 40 38 47 56 88	01) 82 85 82 89 132	I <sup>2</sup> = 589 20 37 25 21 12	85 88 80 84 32	2.8% 2.0% 1.7% 1.5%	1.06 [0.76, 1.49] 1.83 [1.26, 2.67] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83]	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Baba 2020 Backonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed)	F = 37 (P < C 3 (P < 0.000 ts 40 38 47 56 88 83	01) 82 85 82 89 132 141	<pre>I<sup>2</sup> = 589 20 37 25 21 12 12</pre>	85 88 80 84 32 33	2.8% 2.0% 1.7% 1.5% 1.5%	1.06 [0.76, 1.49] 1.83 [1.26, 2.67] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60]	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Baba 2020 Backonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) Guan 2011	= 37 (P < 0 3 (P < 0.000 ts 40 38 47 56 88 83 130	82 85 82 89 132 141 206	$I^{2} = 589$ 20 37 25 21 12 12 53	85 88 80 84 32 33 102	2.8% 2.0% 1.7% 1.5% 1.5% 5.5%	1.06 [0.76, 1.49] 1.83 [1.26, 2.67] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50]	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Test for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Sackonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) Guan 2011 Huffman 2015	F = 37 (P < 0 3 (P < 0.000 ts 40 38 47 56 88 83 130 39	82 85 82 89 132 141 206 101	20 37 25 21 12 12 53 25	85 88 80 84 32 33 102 102	2.8% 2.0% 1.7% 1.5% 1.5% 5.5% 1.9%	1.06 [0.76, 1.49] 1.83 [1.26, 2.67] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40]	      
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Saba 2020 Backonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) Guan 2011 Huffman 2015 Liu 2017	F = 37 (P < 0 3 (P < 0.000 ts 40 38 47 56 88 83 130 39 58	01) 82 85 82 89 132 141 206 101 111	<pre>l<sup>2</sup> = 585 20 37 25 21 12 12 53 25 33</pre>	85 88 80 84 32 33 102 102 102	2.8% 2.0% 1.7% 1.5% 1.5% 5.5% 1.9% 2.6%	1.06 (0.76, 1.49) 1.83 [1.26, 2.67] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41]	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Baba 2020 Backonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010	F = 37 (P < C 3 (P < 0.000 ts 40 38 47 56 88 83 130 39 58 68	01) 82 85 82 89 132 141 206 101 111 162	<pre>I<sup>2</sup> = 589 20 37 25 21 12 12 53 25 33 27</pre>	85 88 80 84 32 33 102 102 109 78	2.8% 2.0% 1.7% 1.5% 5.5% 1.9% 2.6% 2.8%	1.06 [0.76, 1.49] 1.83 [1.26, 2.67] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73]	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Baba 2020 Backonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018	F = 37 (P < C 3 (P < 0.000 ts 40 38 47 56 88 83 130 39 58 68 157	01) 82 85 82 89 132 141 206 101 111 162 314	<pre>I<sup>2</sup> = 588 200 37 25 21 12 12 12 53 25 33 27 136</pre>	85 88 80 84 32 33 102 102 109 78 308	2.8% 2.0% 1.7% 1.5% 5.5% 1.9% 2.6% 2.8% 10.7%	1.06 [0.76, 1.49] 1.83 [1.26, 2.67] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73] 1.13 [0.96, 1.34]	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Test for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Sackonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004	F = 37 (P < C 3 (P < 0.000) ts 40 38 47 56 88 83 130 39 58 68 68 157 103	01) 82 85 82 89 132 141 206 101 111 162 314 214	<pre>I<sup>2</sup> = 583 20 37 25 21 12 12 53 25 33 27 136 37</pre>	85 88 80 84 32 33 102 102 109 78 308 109	2.8% 2.0% 1.7% 1.5% 5.5% 1.9% 2.6% 2.8% 10.7% 3.8%	$\begin{array}{c} 1.06 & [0.76,  1.49] \\ 1.83 & [1.26, 2.67] \\ 2.52 & [1.68, 3.77] \\ 1.78 & [1.12, 2.83] \\ 1.62 & [1.01, 2.60] \\ 1.21 & [0.98, 1.50] \\ 1.58 & [1.04, 2.40] \\ 1.73 & [1.23, 2.41] \\ 1.21 & [0.85, 1.73] \\ 1.31 & [0.96, 1.34] \\ 1.42 & [1.05, 1.91] \end{array}$	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Baba 2020 Backonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (1800 mg)	F = 37 (P < C 3 (P < 0.000 ts 40 38 47 56 88 83 130 39 58 68 157 103 37	01) 82 85 82 89 132 141 206 101 111 162 314 214 115	<pre>I<sup>2</sup> = 583 20 37 25 21 12 12 53 25 33 27 136 37 8</pre>	85 88 80 84 32 33 102 102 109 78 308 109 55	2.8% 2.0% 1.7% 1.5% 5.5% 1.9% 2.6% 2.8% 10.7% 3.8% 0.8%	1.06 (0.76, 1.49) 1.83 (1.26, 2.67) 2.52 (1.68, 3.77) 1.78 (1.12, 2.83) 1.62 (1.01, 2.60) 1.21 (0.98, 1.50) 1.58 (1.04, 2.40) 1.73 (1.23, 2.41) 1.21 (0.85, 1.73) 1.13 (0.96, 1.34) 1.42 (1.05, 1.91) 2.21 (1.11, 4.42)	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Baba 2020 Backonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (1800 mg) Rice 2001 (2400 mg)	F = 37 (P < C 3 (P < 0.000 40 38 47 56 88 83 130 39 58 68 157 103 37 37 37	01) 82 85 82 89 132 141 206 101 111 162 314 214 115 108	I <sup>2</sup> = 585 20 37 25 21 12 12 53 325 33 27 136 37 8 8	85 88 80 84 32 33 102 102 109 78 308 109 55 56	2.8% 2.0% 1.7% 1.5% 5.5% 1.9% 2.6% 2.8% 10.7% 3.8% 0.8% 0.8%	1.06 [0.76, 1.49] 1.83 [1.26, 2.67] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73] 1.13 [0.96, 1.34] 1.42 [1.05, 1.91] 2.21 [1.11, 4.42] 2.40 [1.20, 4.79]	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Saba 2020 Sackonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (2400 mg) Richetr 2005 (600 mg)	F = 37 (P < C 3 (P < 0.000) ts 40 38 47 56 88 83 130 39 58 68 157 103 37 37 32	01) 82 85 82 89 132 141 206 101 111 162 314 214 115 108 82	<pre>I<sup>2</sup> = 585 20 37 25 21 12 12 12 12 33 25 33 27 136 37 8 8 13</pre>	85 88 80 84 32 102 109 78 308 109 55 56 85	2.8% 2.0% 1.7% 1.5% 5.5% 1.9% 2.6% 2.8% 10.7% 3.8% 0.8% 0.8% 1.0%	1.06 [0.76, 1.49] 1.83 [1.26, 2.67] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.73 [1.23, 2.41] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73] 1.13 [0.96, 1.34] 1.42 [1.05, 1.91] 2.21 [1.11, 4.42] 2.40 [1.20, 4.79] 2.55 [1.44, 4.51]	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Test for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Saba 2020 Sackonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (1800 mg) Richet 2005 (600 mg) Rowbotham 1998	F = 37 (P < C 3 (P < 0.000 ts 40 38 47 56 88 83 130 39 58 68 68 157 103 37 37 37 32 49	01) 82 85 82 89 132 141 206 101 111 162 314 214 115 108 82 113	I <sup>2</sup> = 585 20 37 25 21 12 25 325 33 27 136 37 8 8 13 14	85 88 80 84 32 33 102 109 78 308 109 55 56 85 116	2.8% 2.0% 1.7% 1.5% 5.5% 2.8% 10.7% 3.8% 0.8% 0.8% 0.8% 1.0% 1.1%	$\begin{array}{c} 1.06 & [0.76,  1.49] \\ 1.83 & [1.26, 2.67] \\ 2.52 & [1.68, 3.77] \\ 1.78 & [1.12, 2.83] \\ 1.62 & [1.01, 2.60] \\ 1.21 & [0.98, 1.50] \\ 1.58 & [1.04, 2.40] \\ 1.73 & [1.23, 2.41] \\ 1.21 & [0.85, 1.73] \\ 1.13 & [0.96, 1.34] \\ 1.42 & [1.05, 1.91] \\ 2.21 & [1.11, 4.42] \\ 2.40 & [1.20, 4.79] \\ 2.55 & [1.44, 4.51] \\ 3.59 & [2.11, 6.13] \end{array}$	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Saba 2020 Sackonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (2400 mg) Richetr 2005 (600 mg)	F = 37 (P < C 3 (P < 0.000) ts 40 38 47 56 88 83 130 39 58 68 157 103 37 37 32	01) 82 85 82 89 132 141 206 101 111 162 314 214 115 108 82	<pre>I<sup>2</sup> = 585 20 37 25 21 12 12 12 12 33 25 33 27 136 37 8 8 13</pre>	85 88 80 84 32 102 109 78 308 109 55 56 85	2.8% 2.0% 1.7% 1.5% 5.5% 1.9% 2.6% 2.8% 10.7% 3.8% 0.8% 0.8% 1.0%	1.06 [0.76, 1.49] 1.83 [1.26, 2.67] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.73 [1.23, 2.41] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73] 1.13 [0.96, 1.34] 1.42 [1.05, 1.91] 2.21 [1.11, 4.42] 2.40 [1.20, 4.79] 2.55 [1.44, 4.51]	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Test for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Saba 2020 Sackonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (1800 mg) Richet 2005 (600 mg) Rowbotham 1998	F = 37 (P < C 3 (P < 0.000 ts 40 38 47 56 88 83 130 39 58 68 68 157 103 37 37 37 32 49	01) 82 85 82 89 132 141 206 101 111 162 314 214 115 108 82 113	I <sup>2</sup> = 585 20 37 25 21 12 25 325 33 27 136 37 8 8 13 14	85 88 80 84 32 33 102 109 78 308 109 55 56 85 116	2.8% 2.0% 1.7% 1.5% 5.5% 2.8% 10.7% 3.8% 0.8% 0.8% 0.8% 1.0% 1.1%	$\begin{array}{c} 1.06 & [0.76,  1.49] \\ 1.83 & [1.26, 2.67] \\ 2.52 & [1.68, 3.77] \\ 1.78 & [1.12, 2.83] \\ 1.62 & [1.01, 2.60] \\ 1.21 & [0.98, 1.50] \\ 1.58 & [1.04, 2.40] \\ 1.73 & [1.23, 2.41] \\ 1.21 & [0.85, 1.73] \\ 1.13 & [0.96, 1.34] \\ 1.42 & [1.05, 1.91] \\ 2.21 & [1.11, 4.42] \\ 2.40 & [1.20, 4.79] \\ 2.55 & [1.44, 4.51] \\ 3.59 & [2.11, 6.13] \end{array}$	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Test for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Baba 2020 Backonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (1800 mg) Rice 2001 (1800 mg) Rice 2001 (2400 mg) Richer 2005 (600 mg) Rowbotham 1998 Sang 2013	F = 37 (P < C 3 (P < 0.000 ts 40 38 47 56 88 83 130 39 58 68 157 103 37 37 37 37 49 65	01) 82 85 82 89 132 141 206 101 111 162 314 214 115 108 82 113 221	I <sup>2</sup> = 585 20 37 25 21 12 12 53 25 33 25 33 25 33 27 136 37 8 8 13 14 52	85 88 80 84 32 33 102 109 78 308 109 55 6 85 116 231	2.8% 2.0% 1.7% 1.5% 5.5% 1.9% 2.6% 2.6% 2.6% 0.7% 3.8% 0.8% 0.8% 1.0%	$\begin{array}{c} 1.06 & [0.76,  1.49] \\ 1.83 & [1.26, 2.67] \\ 2.52 & [1.68, 3.77] \\ 1.78 & [1.12, 2.83] \\ 1.62 & [1.01, 2.60] \\ 1.21 & [0.98, 1.50] \\ 1.58 & [1.04, 2.40] \\ 1.73 & [1.23, 2.41] \\ 1.21 & [0.85, 1.73] \\ 1.13 & [0.96, 1.34] \\ 1.42 & [1.05, 1.91] \\ 2.21 & [1.11, 4.42] \\ 2.40 & [1.20, 4.79] \\ 2.55 & [1.44, 4.51] \\ 3.59 & [2.11, 6.13] \\ 1.31 & [0.95, 1.79] \end{array}$	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 <b>2.1.2 Greater than 150 patien</b> Arezzo 2008 Baba 2020 Backonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (1800 mg) Richer 2005 (600 mg) Rowbotham 1998 Sang 2013 Satoh 2011 (300 mg)	F = 37 (P < C 3 (P < 0.000 40 38 47 56 88 83 130 39 58 68 157 103 37 37 37 37 37 32 49 65 66	01) 82 85 82 89 132 141 206 101 111 162 314 214 115 108 82 113 221 134	I <sup>2</sup> = 583 20 37 25 21 12 12 12 12 12 12 53 33 27 136 37 136 37 8 8 8 13 14 52 24	85 88 80 84 32 102 109 78 308 109 55 56 85 56 85 5116 231 67	2.8% 2.0% 1.7% 1.5% 1.5% 2.6% 2.8% 10.7% 3.8% 0.8% 0.8% 1.0% 1.0% 3.9% 2.5%	$\begin{array}{c} 1.06 & [0.76,  1.49] \\ 1.83 & [1.26, 2.67] \\ 2.52 & [1.68, 3.77] \\ 1.78 & [1.12, 2.83] \\ 1.62 & [1.01, 2.60] \\ 1.21 & [0.98, 1.50] \\ 1.58 & [1.04, 2.40] \\ 1.73 & [1.23, 2.41] \\ 1.21 & [0.85, 1.73] \\ 1.13 & [0.96, 1.34] \\ 1.42 & [1.05, 1.91] \\ 2.21 & [1.11, 4.42] \\ 2.40 & [1.20, 4.79] \\ 2.55 & [1.44, 4.51] \\ 3.59 & [2.11, 6.13] \\ 1.31 & [0.96, 1.98] \\ 1.38 & [0.96, 1.98] \end{array}$	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Test for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Saba 2020 Sackonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (1800 mg) Richer 2005 (600 mg) Rowbotham 1998 Sang 2013 Satoh 2011 (300 mg) Sharma 2006	F = 37 (P < C 3 (P < 0.000) ts 40 38 47 56 88 83 130 39 58 68 157 103 37 37 37 32 49 65 66 40	01) 82 85 82 89 132 141 206 101 111 162 314 214 115 108 82 113 221 134 82	$I^2 = 589$ 200 377 225 33 25 33 25 33 25 33 25 33 25 33 25 33 25 33 25 33 25 33 25 33 25 24 4 20	85 88 80 84 32 33 102 109 78 308 109 55 56 85 116 231 67 85	2.8% 2.0% 1.7% 1.5% 5.5% 1.9% 2.6% 2.8% 10.7% 3.8% 0.8% 0.8% 1.0% 1.1% 3.9% 2.5%	$\begin{array}{c} 1.06 & [0.76,  1.49] \\ 1.83 & [1.26, 2.67] \\ 2.52 & [1.68, 3.77] \\ 1.78 & [1.12, 2.83] \\ 1.62 & [1.01, 2.60] \\ 1.21 & [0.98, 1.50] \\ 1.58 & [1.04, 2.40] \\ 1.73 & [1.23, 2.41] \\ 1.21 & [0.85, 1.73] \\ 1.31 & [0.96, 1.34] \\ 1.42 & [1.05, 1.91] \\ 2.21 & [1.11, 4.42] \\ 2.40 & [1.20, 4.79] \\ 2.55 & [1.44, 4.51] \\ 3.59 & [2.11, 6.13] \\ 1.31 & [0.95, 1.79] \\ 1.38 & [0.96, 1.98] \\ 2.07 & [1.33, 3.23] \end{array}$	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Test for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Baba 2020 Backonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (1800 mg) Rice 2001 (2400 mg) Richer 2005 (600 mg) Rowbotham 1998 Sang 2013 Satoh 2011 (300 mg) Sharma 2006 Smith 2014	F = 37 (P < C 3 (P < 0.000 40 38 47 56 88 83 130 39 58 68 157 103 37 37 37 32 49 65 66 65 66 40 49 19	01) 82 85 82 89 132 141 206 101 111 162 314 214 115 108 82 113 221 134 82 98 50	$I^2 = 589$ 200 377 255 21 122 122 53 255 33 257 1366 377 1366 377 1366 377 1362 37 252 24 202 45 24	85 88 80 84 33 102 109 55 56 85 116 231 67 85 93 108	2.8% 2.0% 1.7% 1.5% 5.5% 1.9% 2.6% 2.8% 10.7% 3.8% 0.8% 0.8% 0.8% 0.8% 1.0% 1.1% 3.9% 2.5% 3.6% 2.2%	$\begin{array}{c} 1.06 & [0.76,  1.49] \\ 1.83 & [1.26, 2.67] \\ 2.52 & [1.68, 3.77] \\ 1.78 & [1.12, 2.83] \\ 1.62 & [1.01, 2.60] \\ 1.21 & [0.98, 1.50] \\ 1.58 & [1.04, 2.40] \\ 1.73 & [1.23, 2.41] \\ 1.21 & [0.85, 1.73] \\ 1.13 & [0.96, 1.34] \\ 1.42 & [1.05, 1.91] \\ 2.21 & [1.11, 4.42] \\ 2.40 & [1.20, 4.79] \\ 2.55 & [1.44, 4.51] \\ 3.59 & [2.11, 6.13] \\ 1.31 & [0.95, 1.79] \\ 1.38 & [0.96, 1.98] \\ 2.07 & [1.33, 3.23] \\ 1.03 & [0.77, 1.38] \\ 0.91 & [0.60, 1.39] \end{array}$	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 <b>2.1.2 Greater than 150 patien</b> Arezzo 2008 Baba 2020 Backonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (2400 mg) Richet 2005 (600 mg) Rowbotham 1998 Sang 2013 Satoh 2011 (300 mg) Sharma 2006 Smith 2014 Vinik 2014 Vinik 2014 Viallace 2010 (Daily)	F = 37 (P < C 3 (P < 0.000 ts 40 38 47 56 88 83 130 39 58 68 157 103 37 37 37 37 37 32 49 65 66 40 49 19 49	01) 82 85 82 89 132 141 206 101 111 162 314 214 115 108 82 113 221 134 82 98 50 134	$I^2 = 589$ 20 37 25 21 12 12 53 325 33 25 33 27 136 37 8 8 13 14 52 24 20 45 45 18	85 88 80 84 33 102 109 78 308 55 56 85 109 231 67 85 93 108 66	$\begin{array}{c} 2.8\%\\ 2.0\%\\ 1.7\%\\ 1.5\%\\ 1.5\%\\ 1.5\%\\ 2.6\%\\ 2.8\%\\ 0.8\%\\ 0.8\%\\ 0.8\%\\ 1.1\%\\ 3.9\%\\ 2.5\%\\ 1.5\%\\ 3.6\%\\ 2.2\%\\ 1.9\%\\ \end{array}$	$\begin{array}{c} 1.06 & [0.76, 1.49]\\ 1.83 & [1.26, 2.67]\\ 2.52 & [1.68, 3.77]\\ 1.78 & [1.12, 2.83]\\ 1.62 & [1.01, 2.60]\\ 1.21 & [0.98, 1.50]\\ 1.58 & [1.04, 2.40]\\ 1.73 & [1.23, 2.41]\\ 1.21 & [0.85, 1.73]\\ 1.13 & [0.96, 1.34]\\ 1.42 & [1.05, 1.91]\\ 2.21 & [1.11, 4.42]\\ 2.40 & [1.20, 4.79]\\ 2.55 & [1.44, 4.51]\\ 3.59 & [2.11, 6.13]\\ 1.31 & [0.95, 1.79]\\ 1.38 & [0.96, 1.98]\\ 2.07 & [1.33, 3.23]\\ 1.03 & [0.77, 1.38]\\ 0.91 & [0.60, 1.39]\\ 1.34 & [0.85, 2.11]\\ \end{array}$	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Test for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Saba 2020 Sackonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (1800 mg) Richer 2005 (600 mg) Rowbotham 1998 Sang 2013 Satoh 2011 (300 mg) Sokohzam 1998 Sang 2013 Satoh 2011 (300 mg) Sharma 2006 Smith 2014 Vinik 2014 Vinik 2014 Viallace 2010 (Divided)	F = 37 (P < C 3 (P < 0.000 40 38 47 56 88 83 130 39 58 68 157 103 37 37 37 32 49 65 66 65 66 40 49 19	01) 82 85 82 141 206 101 111 162 314 115 108 82 113 221 134 82 98 50 134 135	$I^2 = 589$ 200 377 255 21 122 122 53 255 33 257 1366 377 1366 377 1366 377 1362 37 252 24 202 45 24	85 88 80 84 32 33 102 102 78 308 109 55 56 85 116 231 16 77 85 93 108 66 65	$\begin{array}{c} 2.8\%\\ 2.0\%\\ 1.7\%\\ 1.5\%\\ 1.5\%\\ 2.6\%\\ 2.8\%\\ 0.8\%\\ 0.8\%\\ 0.8\%\\ 1.0\%\\ 3.8\%\\ 0.8\%\\ 1.0\%\\ 3.9\%\\ 2.5\%\\ 1.6\%\\ 3.6\%\\ 2.2\%\\ 1.9\%\\ 1.9\%\\ \end{array}$	$\begin{array}{c} 1.06 & [0.76,  1.49]\\ 1.83 & [1.26, 2.67]\\ 2.52 & [1.68, 3.77]\\ 1.78 & [1.12, 2.83]\\ 1.62 & [1.01, 2.60]\\ 1.21 & [0.98, 1.50]\\ 1.58 & [1.04, 2.40]\\ 1.73 & [1.23, 2.41]\\ 1.21 & [0.85, 1.73]\\ 1.13 & [0.96, 1.34]\\ 1.42 & [1.05, 1.91]\\ 2.21 & [1.11, 4.42]\\ 2.40 & [1.20, 4.79]\\ 2.55 & [1.44, 4.51]\\ 3.59 & [2.11, 6.13]\\ 1.31 & [0.95, 1.79]\\ 1.38 & [0.96, 1.98]\\ 2.07 & [1.33, 3.23]\\ 1.03 & [0.77, 1.38]\\ 0.91 & [0.60, 1.39]\\ 1.34 & [0.85, 2.11]\\ 1.23 & [0.78, 1.94] \end{array}$	
Heterogeneity: Chi <sup>2</sup> = 87.25, di Test for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Baba 2020 Backonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (1800 mg) Rice 2001 (2400 mg) Statha 2014 Sombotham 1998 Sang 2013 Satoh 2011 (300 mg) Sharma 2006 Smith 2014 Vinik 2014 Vinik 2014 Vinik 2014 Vinik 2010 (Divided) Subtotal (95% CI)	F = 37 (P < C 3 (P < 0.000) 40 38 40 38 47 56 88 83 130 39 58 68 68 157 103 37 37 37 37 37 37 37 49 65 66 66 40 49 19 49 49	01) 82 85 82 89 132 141 206 101 111 162 314 214 115 108 82 113 221 134 82 98 50 134	$I^2 = 583$ 200 377 255 211 122 53 255 333 277 1366 377 136 378 137 138 138 137 138 138 138 138 138 138 138 138	85 88 80 84 33 102 109 78 308 55 56 85 109 231 67 85 93 108 66	$\begin{array}{c} 2.8\%\\ 2.0\%\\ 1.7\%\\ 1.5\%\\ 1.5\%\\ 1.5\%\\ 2.6\%\\ 2.8\%\\ 0.8\%\\ 0.8\%\\ 0.8\%\\ 1.1\%\\ 3.9\%\\ 2.5\%\\ 1.5\%\\ 3.6\%\\ 2.2\%\\ 1.9\%\\ \end{array}$	$\begin{array}{c} 1.06 & [0.76, 1.49]\\ 1.83 & [1.26, 2.67]\\ 2.52 & [1.68, 3.77]\\ 1.78 & [1.12, 2.83]\\ 1.62 & [1.01, 2.60]\\ 1.21 & [0.98, 1.50]\\ 1.58 & [1.04, 2.40]\\ 1.73 & [1.23, 2.41]\\ 1.21 & [0.85, 1.73]\\ 1.13 & [0.96, 1.34]\\ 1.42 & [1.05, 1.91]\\ 2.21 & [1.11, 4.42]\\ 2.40 & [1.20, 4.79]\\ 2.55 & [1.44, 4.51]\\ 3.59 & [2.11, 6.13]\\ 1.31 & [0.95, 1.79]\\ 1.38 & [0.96, 1.98]\\ 2.07 & [1.33, 3.23]\\ 1.03 & [0.77, 1.38]\\ 0.91 & [0.60, 1.39]\\ 1.34 & [0.85, 2.11]\\ \end{array}$	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Test for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Saba 2020 Sackonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (1800 mg) Richer 2005 (600 mg) Rowbotham 1998 Sang 2013 Satoh 2011 (300 mg) Sokohzam 1998 Sang 2013 Satoh 2011 (300 mg) Sharma 2006 Smith 2014 Vinik 2014 Vinik 2014 Viallace 2010 (Divided)	F = 37 (P < C 3 (P < 0.000) 40 38 47 56 88 83 130 39 58 68 157 103 37 37 37 37 37 32 49 65 66 40 49 19 49 46 1396 F = 22 (P < C	82 85 82 89 132 141 206 101 111 162 314 214 115 108 82 113 221 133 221 133 221 133 221 133 221 133 221 133 229 1	<pre>I<sup>2</sup> = 589 200 377 25 21 122 12 53 3 25 33 277 136 37 136 37 13 4 52 24 20 45 18 18 18 703</pre>	85 88 80 84 32 33 102 102 78 308 109 55 56 85 116 231 16 77 85 93 108 66 65	$\begin{array}{c} 2.8\%\\ 2.0\%\\ 1.7\%\\ 1.5\%\\ 1.5\%\\ 2.6\%\\ 2.8\%\\ 0.8\%\\ 0.8\%\\ 0.8\%\\ 1.0\%\\ 3.8\%\\ 0.8\%\\ 1.0\%\\ 3.9\%\\ 2.5\%\\ 1.6\%\\ 3.6\%\\ 2.2\%\\ 1.9\%\\ 1.9\%\\ \end{array}$	$\begin{array}{c} 1.06 & [0.76,  1.49]\\ 1.83 & [1.26, 2.67]\\ 2.52 & [1.68, 3.77]\\ 1.78 & [1.12, 2.83]\\ 1.62 & [1.01, 2.60]\\ 1.21 & [0.98, 1.50]\\ 1.58 & [1.04, 2.40]\\ 1.73 & [1.23, 2.41]\\ 1.21 & [0.85, 1.73]\\ 1.13 & [0.96, 1.34]\\ 1.42 & [1.05, 1.91]\\ 2.21 & [1.11, 4.42]\\ 2.40 & [1.20, 4.79]\\ 2.55 & [1.44, 4.51]\\ 3.59 & [2.11, 6.13]\\ 1.31 & [0.95, 1.79]\\ 1.38 & [0.96, 1.98]\\ 2.07 & [1.33, 3.23]\\ 1.03 & [0.77, 1.38]\\ 0.91 & [0.60, 1.39]\\ 1.34 & [0.85, 2.11]\\ 1.23 & [0.78, 1.94] \end{array}$	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 2.1.2 Greater than 150 patien Arezzo 2008 Baba 2020 Backonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (2400 mg) Richer 2005 (600 mg) Rowbotham 1998 Sang 2013 Satoh 2011 (300 mg) Sharma 2006 Smith 2014 Vinik 2014 Vinik 2014 Vallace 2010 (Daily) Malace 2010 (Divided) Subtotal (95% CI) Fotal (95% CI)	F = 37 (P < C  3 (P < 0.000)  13 (P < 0.000)  14 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P < 0.000)  15 (P	82 85 82 89 132 141 206 101 111 162 314 214 115 108 82 113 221 133 221 133 221 133 221 133 221 133 221 133 229 1	$I^2 = 583$ 200 377 253 211 122 533 255 333 277 136 377 136 377 136 377 136 377 136 377 136 377 136 377 136 377 136 377 241 255 138 255 138 255 138 255 138 255 138 255 138 255 138 255 138 255 138 255 138 255 138 255 138 255 138 255 138 257 136 377 256 377 256 377 256 377 256 377 256 377 256 377 256 377 256 377 256 377 256 377 256 377 257 136 377 257 136 377 277 136 377 277 136 377 277 136 377 277 136 377 274 274 274 274 274 274 274 2	85 88 80 84 32 102 109 78 308 109 55 56 85 116 231 67 85 93 108 66 65 2237	$\begin{array}{c} 2.8\%\\ 2.0\%\\ 1.7\%\\ 1.5\%\\ 1.5\%\\ 2.6\%\\ 2.8\%\\ 0.8\%\\ 0.8\%\\ 0.8\%\\ 1.0\%\\ 3.8\%\\ 0.8\%\\ 1.0\%\\ 3.9\%\\ 2.5\%\\ 1.6\%\\ 3.6\%\\ 2.2\%\\ 1.9\%\\ 1.9\%\\ \end{array}$	$\begin{array}{c} 1.06 & [0.76,  1.49]\\ 1.83 & [1.26, 2.67]\\ 2.52 & [1.68, 3.77]\\ 1.78 & [1.12, 2.83]\\ 1.62 & [1.01, 2.60]\\ 1.21 & [0.98, 1.50]\\ 1.58 & [1.04, 2.40]\\ 1.73 & [1.23, 2.41]\\ 1.21 & [0.85, 1.73]\\ 1.13 & [0.96, 1.34]\\ 1.42 & [1.05, 1.91]\\ 2.21 & [1.11, 4.42]\\ 2.40 & [1.20, 4.79]\\ 2.55 & [1.44, 4.51]\\ 3.59 & [2.11, 6.13]\\ 1.31 & [0.95, 1.79]\\ 1.38 & [0.96, 1.98]\\ 2.07 & [1.33, 3.23]\\ 1.03 & [0.77, 1.38]\\ 0.91 & [0.60, 1.39]\\ 1.34 & [0.85, 2.11]\\ 1.23 & [0.78, 1.94] \end{array}$	
Heterogeneity: Chi <sup>2</sup> = 87.25, df Fest for overall effect: Z = 10.9 <b>2.1.2 Greater than 150 patien</b> Arezzo 2008 Baba 2020 Backonja 1998 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Raskin 2004 Rice 2001 (1800 mg) Richter 2005 (600 mg) Rowbotham 1998 Sang 2013 Statoh 2011 (300 mg) Sharma 2006 Smith 2014 Vinik 2014 Wallace 2010 (Daily) Wallace 2010 (Daily) Mallace 2010 (Daily) Total events Heterogeneity: Chi <sup>2</sup> = 60.71, df Fest for overall effect: Z = 10.0	F = 37 (P < C 3 (P < 0.000) ts 40 38 47 56 88 83 130 39 58 68 68 157 103 37 37 37 37 32 49 65 66 40 49 19 49 46 5 5 66 60 40 49 9 5 8 5 6 6 6 6 6 5 6 6 6 6 5 6 6 6 6 6 5 6 6 6 6 5 6 6 6 6 6 5 6 6 6 6 7 7 7 7	01) 82 85 82 89 132 141 206 101 111 162 314 214 115 108 82 113 221 134 82 98 50 134 82 98 50 135 2991 .0001); I 01) 5837	$I^2 = 583$ 200 377 255 211 122 123 533 277 1366 377 8 8 8 13 14 52 244 200 45 45 18 18 18 27 18 18 18 20 24 24 25 25 25 21 27 25 25 25 27 25 27 27 25 27 25 27 27 25 27 25 27 27 25 27 27 25 27 27 25 27 27 25 27 27 25 27 27 25 27 27 26 27 27 26 27 27 26 27 27 26 27 27 26 27 27 26 27 27 26 27 27 26 27 27 26 27 27 26 27 27 26 27 27 26 27 27 26 27 27 27 26 27 27 27 26 27 27 26 27 27 26 27 27 27 26 27 27 26 27 27 27 26 27 27 27 26 27 27 26 27 27 26 27 27 26 27 27 26 27 27 26 27 27 27 26 27 27 26 26 27 27 26 26 27 27 26 26 27 27 26 26 27 27 26 26 27 27 26 26 27 27 26 26 26 27 27 26 26 27 27 26 26 26 27 26 26 26 26 27 26 26 27 26 26 27 26 26 26 26 26 26 26 26 26 26	85 88 80 102 109 78 308 85 56 65 231 16 231 67 85 93 108 66 65 2237 3738	2.8% 2.0% 1.7% 1.5% 5.5% 1.9% 2.6% 2.8% 0.8% 0.8% 0.8% 0.8% 1.0% 1.1% 3.9% 2.5% 1.5% 3.6% <b>59.6%</b>	$\begin{array}{c} 1.06 & [0.76,  1.49] \\ 1.83 & [1.26, 2.67] \\ 2.52 & [1.68, 3.77] \\ 1.78 & [1.12, 2.83] \\ 1.62 & [1.01, 2.60] \\ 1.21 & [0.98, 1.50] \\ 1.58 & [1.04, 2.40] \\ 1.73 & [1.23, 2.41] \\ 1.21 & [0.85, 1.73] \\ 1.13 & [0.96, 1.34] \\ 1.42 & [1.05, 1.91] \\ 2.21 & [1.11, 4.42] \\ 2.40 & [1.20, 4.79] \\ 2.55 & [1.44, 4.51] \\ 3.59 & [2.11, 6.13] \\ 1.31 & [0.95, 1.79] \\ 1.38 & [0.96, 1.98] \\ 2.07 & [1.33, 3.23] \\ 1.03 & [0.77, 1.38] \\ 0.91 & [0.60, 1.39] \\ 1.34 & [0.85, 2.11] \\ 1.23 & [0.78, 1.94] \\ 1.46 & [1.35, 1.57] \\ \end{array}$	

## Figure 2.6: Anticonvulsants versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size

## Anticonvulsants (Gabapentin)

Figure 3.1: Gabapentin versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater

	Gabape		Placel			Risk Ratio	Risk Ratio
Study or Subgroup						M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.8.1 Outcome data reporte		than o	r equal t	o 4 we	eks		
Backonja 2011	26	47	15	54	65.5%	1.99 [1.21, 3.29]	-∎-
Perez 2000	14	17	2	15	10.0%	6.18 [1.67, 22.86]	
Sandercock 2012 (Daily)	16	46	2	25	12.2%	4.35 [1.09, 17.40]	
Sandercock 2012 (Divided) Subtotal (95% CI)	13	50 160	2	26 <b>120</b>	12.3% <b>100.0%</b>	3.38 [0.82, 13.86] 2.87 [1.85, 4.44]	•
Total events	69		21				
Heterogeneity: $Chi^2 = 3.75$ , d	lf = 3 (P =	= 0.29);	$I^2 = 20\%$	5			
Test for overall effect: $Z = 4$ .	73 (P < 0	.00001)	)				
1.8.2 Outcome data reporte	d at grea	ter tha	n 4 weel	s to le	ess than	12 weeks	
Backonja 1998	47	82	25	80	15.8%	1.83 [1.26, 2.67]	
Rice 2001 (1800 mg)	37	115	8	55	6.8%	2.21 [1.11, 4.42]	— <b>-</b>
Rice 2001 (2400 mg)	37	108	8	56	6.6%	2.40 [1.20, 4.79]	
Rowbotham 1998	49	113	14	116	8.6%	3.59 [2.11, 6.13]	
Sang 2013	65	221	52	231	31.8%	1.31 [0.95, 1.79]	
Wallace 2010 (Daily)	49	134	18	66	15.1%	1.34 [0.85, 2.11]	
Wallace 2010 (Divided) <b>Subtotal (95% CI)</b>	46	135 <b>908</b>	18	65 <b>669</b>	15.2% <b>100.0%</b>	1.23 [0.78, 1.94] <b>1.71 [1.45, 2.03]</b>	
Total events	330		143				
Heterogeneity: $Chi^2 = 14.92$ ,	df = 6 (P	= 0.02	); $I^2 = 60$	1%			
Test for overall effect: $Z = 6.2$	23 (P < 0	.00001)					
1.8.3 Outcome data reporte	d at grea	ter tha	n or equ	al to 1	2 weeks		
Rauck 2012 (1200 mg)	31	62	14	30	15.9%	1.07 [0.68, 1.69]	
Rauck 2012 (2400 mg)	25	56	14	30	15.4%	0.96 [0.59, 1.55]	
Rauck 2012 (3600 mg)	66	116	14	30	18.7%	1.22 [0.81, 1.84]	
Zhang 2013 (1200 mg)	57	107	13	32	16.9%	1.31 [0.83, 2.07]	+
Zhang 2013 (2400 mg)	48	82	13	32	15.8%	1.44 [0.91, 2.28]	<b></b>
Zhang 2013 (3600 mg)	52	87	14	31	17.4%	1.32 [0.87, 2.02]	
Subtotal (95% CI)		510		185	100.0%	1.22 [1.02, 1.47]	◆
Total events	279		82				
Heterogeneity: $Chi^2 = 2.04$ , d			$1^{-} = 0\%$				
Test for overall effect: $Z = 2.2$	18 (P = 0)	.03)					
							6.01 0.1 1 10 10 Favours placebo Favours gabapentin
							ravours placebo ravours gabapentin

	Gabape	ntin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
1.7.1 Public Funding							
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not applicabl	le						
Test for overall effect: Not a	pplicable						
1.7.2 Industry Funding							
Backonja 1998	47	82	25	80	8.5%	1.83 [1.26, 2.67]	
Backonja 2011	26	47	15	54	4.7%	1.99 [1.21, 3.29]	——
Rauck 2012 (1200 mg)	31	62	14	30	6.3%	1.07 [0.68, 1.69]	+-
Rauck 2012 (2400 mg)	25	56	14	30	6.1%	0.96 [0.59, 1.55]	
Rauck 2012 (3600 mg)	66	116	14	30	7.5%	1.22 [0.81, 1.84]	
Rice 2001 (1800 mg)	37	115	8	55	3.6%	2.21 [1.11, 4.42]	
Rice 2001 (2400 mg)	37	108	8	56	3.5%	2.40 [1.20, 4.79]	
Rowbotham 1998	49	113	14	116	4.6%	3.59 [2.11, 6.13]	
Sandercock 2012 (Daily)	16	46	2	25	0.9%	4.35 [1.09, 17.40]	
Sandercock 2012 (Divided)	13	50	2	26	0.9%	3.38 [0.82, 13.86]	+
Sang 2013	65	221	52	231	17.1%	1.31 [0.95, 1.79]	
Wallace 2010 (Daily)	49	134	18	66	8.1%	1.34 [0.85, 2.11]	+
Wallace 2010 (Divided)	46	135	18	65	8.2%	1.23 [0.78, 1.94]	- <b>-</b>
Zhang 2013 (1200 mg)	57	107	13	32	6.7%	1.31 [0.83, 2.07]	+
Zhang 2013 (2400 mg)	48	82	13	32	6.3%	1.44 [0.91, 2.28]	
Zhang 2013 (3600 mg)	52	87	14	31	6.9%	1.32 [0.87, 2.02]	+
Subtotal (95% CI)		1561		959	100.0%	1.57 [1.39, 1.77]	♦
Fotal events	664		244				
Heterogeneity: Chi <sup>2</sup> = 28.74				48%			
Test for overall effect: $Z = 7$	.31 (P < 0	.00001	)				
Total (95% CI)		1561		959	100.0%	1.57 [1.39, 1.77]	•
Total events	664		244				
Heterogeneity: Chi <sup>2</sup> = 28.74	, df = 15	(P = 0.0)	()2); $I^2 = 4$	48%			0.01 0.1 1 10 10
Test for overall effect: $Z = 7$	.31 (P < 0	.00001	)				Favours placebo Favours gabapentin
lest for subgroup difference	s: Not an	olicable					ravours placebo ravours gabapentin

# Figure 3.2: Gabapentin versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source

Test for subgroup differences: Not applicable

	Gabape	ntin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.9.1 Diabetic Neuropathy							
Backonja 1998	47	82	25	80	8.4%	1.83 [1.26, 2.67]	
Perez 2000	14	17	2	15	0.7%	6.18 [1.67, 22.86]	
Rauck 2012 (1200 mg)	31	62	14	30	6.3%	1.07 [0.68, 1.69]	
Rauck 2012 (2400 mg)	25	56	14	30	6.1%	0.96 [0.59, 1.55]	
Rauck 2012 (3600 mg)	66	116	14	30	7.4%	1.22 [0.81, 1.84]	
Sandercock 2012 (Daily)	16	46	2	25	0.9%	4.35 [1.09, 17.40]	
Sandercock 2012 (Divided)	13	50	2	26	0.9%	3.38 [0.82, 13.86]	
Subtotal (95% CI)		429		236	30.7%	1.57 [1.28, 1.93]	
Total events	212		73				
Heterogeneity: $Chi^2 = 16.28$	df = 6 (P	P = 0.01	); $I^2 = 63$	3%			
Test for overall effect: $Z = 4$ .							
1.9.2 Postherpetic Neuralgi	a						
Backonja 2011	26	47	15	54	4.7%	1.99 [1.21, 3.29]	
Rice 2001 (1800 mg)	37	115	8	55	3.6%	2.21 [1.11, 4.42]	· · · · · · · · · · · · · · · · · · ·
Rice 2001 (2400 mg)	37	108	8	56	3.5%	2.40 [1.20, 4.79]	
Rowbotham 1998	49	113	14	116	4.6%	3.59 [2.11, 6.13]	
Sang 2013	65	221	52	231	17.0%	1.31 [0.95, 1.79]	+
Wallace 2010 (Daily)	49	134	18	66	8.0%	1.34 [0.85, 2.11]	
Wallace 2010 (Divided)	46	135	18	65	8.1%	1.23 [0.78, 1.94]	
Zhang 2013 (1200 mg)	57	107	13	32	6.7%	1.31 [0.83, 2.07]	
Zhang 2013 (2400 mg)	48	82	13	32	6.2%	1.44 [0.91, 2.28]	
Zhang 2013 (3600 mg)	52	87	14	31	6.9%	1.32 [0.87, 2.02]	
Subtotal (95% CI)		1149		738	69.3%	1.62 [1.40, 1.87]	•
Fotal events	466		173				
Heterogeneity: Chi <sup>2</sup> = 16.96	df = 9 (P	P = 0.05	5); $I^2 = 47$	7%			
Test for overall effect: $Z = 6$ .	40 (P < 0	.00001	)				
1.9.3 Trigeminal Neuralgia							
Subtotal (95% CI)		0		0		Not estimable	
Fotal events	0		0				
Heterogeneity: Not applicabl							
Fest for overall effect: Not a	oplicable						
Total (95% CI)		1578		074	100.0%	1 60 [1 42 1 81]	
, ,	6.70	1218	245	974	100.0%	1.60 [1.42, 1.81]	
Fotal events	678		246	-			
Heterogeneity: Chi <sup>2</sup> = 33.57 Fest for overall effect: Z = 7.				52%		-	0.5 0.7 1 1.5 2
	6U (P - 0	00001	1				Favours placebo Favours gabapentin

Figure 3.3: Gabapentin versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by neuropathic pain type

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.6.1 Less than or equal to	150 patie	ents					
Backonja 2011	26	47	15	54	4.7%	1.99 [1.21, 3.29]	_ <b>_</b>
Perez 2000	14	17	2	15	0.7%	6.18 [1.67, 22.86]	
Rauck 2012 (1200 mg)	31	62	14	30	6.3%	1.07 [0.68, 1.69]	
Rauck 2012 (2400 mg)	25	56	14	30	6.1%	0.96 [0.59, 1.55]	
Rauck 2012 (3600 mg)	66	116	14	30	7.4%	1.22 [0.81, 1.84]	
Sandercock 2012 (Daily)	16	46	2	25	0.9%	4.35 [1.09, 17.40]	
Sandercock 2012 (Divided)	13	50	2	26	0.9%	3.38 [0.82, 13.86]	
Zhang 2013 (1200 mg)	57	107	13	32	6.7%	1.31 [0.83, 2.07]	<b>+-</b>
Zhang 2013 (2400 mg)	48	82	13	32	6.2%	1.44 [0.91, 2.28]	
Zhang 2013 (3600 mg)	52	87	14	31	6.9%	1.32 [0.87, 2.02]	
Subtotal (95% CI)		670		305	46.7%	1.47 [1.25, 1.74]	•
Total events	348		103				
Heterogeneity: Chi <sup>2</sup> = 15.95	df = 9 (P	= 0.07	$(); I^2 = 44$	1%			
Test for overall effect: $Z = 4$	.51 (P < 0	00001	)				
1.6.2 Greater than 150 pat	ients						
		0.0	25	80	8.4%	1.83 [1.26, 2.67]	
Backonja 1998	47	82	25	00	0.470	1.65 [1.20, 2.07]	
	47 37	82 115	25	55	3.6%	2.21 [1.11, 4.42]	
Rice 2001 (1800 mg)							
Rice 2001 (1800 mg) Rice 2001 (2400 mg)	37	115	8	55	3.6%	2.21 [1.11, 4.42]	
Rice 2001 (1800 mg) Rice 2001 (2400 mg) Rowbotham 1998	37 37	115 108	8 8	55 56	3.6% 3.5%	2.21 [1.11, 4.42] 2.40 [1.20, 4.79]	
Rice 2001 (1800 mg) Rice 2001 (2400 mg) Rowbotham 1998 Sang 2013	37 37 49	115 108 113	8 8 14	55 56 116	3.6% 3.5% 4.6%	2.21 [1.11, 4.42] 2.40 [1.20, 4.79] 3.59 [2.11, 6.13]	
Rice 2001 (1800 mg) Rice 2001 (2400 mg) Rowbotham 1998 Sang 2013 Wallace 2010 (Daily) Wallace 2010 (Divided)	37 37 49 65	115 108 113 221 134 135	8 8 14 52	55 56 116 231 66 65	3.6% 3.5% 4.6% 17.0% 8.0% 8.1%	2.21 [1.11, 4.42] 2.40 [1.20, 4.79] 3.59 [2.11, 6.13] 1.31 [0.95, 1.79] 1.34 [0.85, 2.11] 1.23 [0.78, 1.94]	
Rice 2001 (1800 mg) Rice 2001 (2400 mg) Rowbotham 1998 Sang 2013 Wallace 2010 (Daily) Wallace 2010 (Divided)	37 37 49 65 49	115 108 113 221 134	8 8 14 52 18	55 56 116 231 66	3.6% 3.5% 4.6% 17.0% 8.0%	2.21 [1.11, 4.42] 2.40 [1.20, 4.79] 3.59 [2.11, 6.13] 1.31 [0.95, 1.79] 1.34 [0.85, 2.11]	
Rice 2001 (1800 mg) Rice 2001 (2400 mg) Rowbotham 1998 Sang 2013 Wallace 2010 (Daily) Wallace 2010 (Divided) Subtotal (95% CI)	37 37 49 65 49	115 108 113 221 134 135	8 8 14 52 18	55 56 116 231 66 65	3.6% 3.5% 4.6% 17.0% 8.0% 8.1%	2.21 [1.11, 4.42] 2.40 [1.20, 4.79] 3.59 [2.11, 6.13] 1.31 [0.95, 1.79] 1.34 [0.85, 2.11] 1.23 [0.78, 1.94]	
Rice 2001 (1800 mg) Rice 2001 (2400 mg) Rowbotham 1998 Sang 2013 Wallace 2010 (Daily) Wallace 2010 (Divided) Subtotal (95% Cl) Total events	37 37 49 65 49 46 330	115 108 113 221 134 135 <b>908</b>	8 14 52 18 18 143	55 56 116 231 66 65 <b>669</b>	3.6% 3.5% 4.6% 17.0% 8.0% 8.1%	2.21 [1.11, 4.42] 2.40 [1.20, 4.79] 3.59 [2.11, 6.13] 1.31 [0.95, 1.79] 1.34 [0.85, 2.11] 1.23 [0.78, 1.94]	
Rice 2001 (1800 mg) Rice 2001 (2400 mg) Rowbotham 1998 Sang 2013 Wallace 2010 (Daily) Wallace 2010 (Divided) Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 14.92	37 37 49 65 49 46 330 2, df = 6 (P	115 108 113 221 134 135 <b>908</b> = 0.02	8 8 14 52 18 18 18 2); I <sup>2</sup> = 60	55 56 116 231 66 65 <b>669</b>	3.6% 3.5% 4.6% 17.0% 8.0% 8.1%	2.21 [1.11, 4.42] 2.40 [1.20, 4.79] 3.59 [2.11, 6.13] 1.31 [0.95, 1.79] 1.34 [0.85, 2.11] 1.23 [0.78, 1.94]	• • •
Backonja 1998 Rice 2001 (1800 mg) Rice 2001 (2400 mg) Rowbotham 1998 Sang 2013 Wallace 2010 (Daily) Wallace 2010 (Divided) <b>Subtotal (95% CI)</b> Total events Heterogeneity: Chi <sup>2</sup> = 14.92 Test for overall effect: Z = 6 <b>Total (95% CI)</b>	37 37 49 65 49 46 330 2, df = 6 (P	115 108 113 221 134 135 <b>908</b> = 0.02	8 8 14 52 18 18 18 2); I <sup>2</sup> = 60	55 56 116 231 66 65 <b>669</b> %	3.6% 3.5% 4.6% 17.0% 8.0% 8.1%	2.21 [1.11, 4.42] 2.40 [1.20, 4.79] 3.59 [2.11, 6.13] 1.31 [0.95, 1.79] 1.34 [0.85, 2.11] 1.23 [0.78, 1.94]	
Rice 2001 (1800 mg) Rice 2001 (2400 mg) Rowbotham 1998 Sang 2013 Wallace 2010 (Daily) Wallace 2010 (Divided) Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = 14.92 Fest for overall effect: Z = 6 Total (95% CI)	37 37 49 65 49 46 330 2, df = 6 (P	115 108 113 221 134 135 <b>908</b> = 0.02 .00001	8 8 14 52 18 18 18 2); I <sup>2</sup> = 60	55 56 116 231 66 65 <b>669</b> %	3.6% 3.5% 4.6% 17.0% 8.0% 8.1% 53.3%	2.21 [1.11, 4.42] 2.40 [1.20, 4.79] 3.59 [2.11, 6.13] 1.31 [0.95, 1.79] 1.34 [0.85, 2.11] 1.23 [0.78, 1.94] <b>1.71 [1.45, 2.03</b> ]	• •
Rice 2001 (1800 mg) Rice 2001 (2400 mg) Rowbotham 1998 Sang 2013 Wallace 2010 (Daily) Wallace 2010 (Divided) <b>Subtotal (95% CI)</b> Total events Heterogeneity: Chi <sup>2</sup> = 14.92 Test for overall effect: Z = 6	37 37 49 65 49 46 330 46 2, df = 6 (P 23 (P < 0	115 108 113 221 134 135 <b>908</b> = 0.02 00001 <b>1578</b>	$88 14 52 18 18 143 (1); I^2 = 60(1)246$	55 56 116 231 66 65 <b>669</b> % <b>974</b>	3.6% 3.5% 4.6% 17.0% 8.0% 8.1% 53.3%	2.21 [1.11, 4.42] 2.40 [1.20, 4.79] 3.59 [2.11, 6.13] 1.31 [0.95, 1.79] 1.34 [0.85, 2.11] 1.23 [0.78, 1.94] <b>1.71 [1.45, 2.03</b> ]	• •

# Figure 3.4: Gabapentin versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size

#### **Anticonvulsants (Oxcarbazepine)**

Figure 4.1: Oxcarbazepine versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater

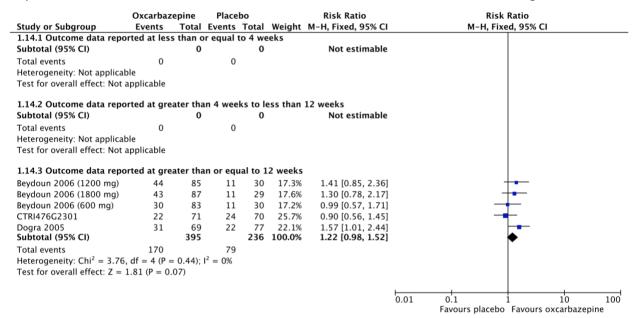


Figure 4.2: Oxcarbazepine versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source

	Oxcarbaz	epine	Place	00		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
1.26.1 Public Funding							
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not applical	ble						
Test for overall effect: Not	applicable						
1.26.2 Industry Funding							
Beydoun 2006 (1200 mg)	44	85	11	30	17.3%	1.41 [0.85, 2.36]	+ <b>-</b> -
Beydoun 2006 (1800 mg)	43	87	11	29	17.6%	1.30 [0.78, 2.17]	- <b>+</b>
Beydoun 2006 (600 mg)	30	83	11	30	17.2%	0.99 [0.57, 1.71]	_ <b>+</b> _
CTRI476G2301	22	71	24	70	25.7%	0.90 [0.56, 1.45]	
Dogra 2005	31	69	22	77	22.1%	1.57 [1.01, 2.44]	
Subtotal (95% CI)		395		236	100.0%	1.22 [0.98, 1.52]	◆
Total events	170		79				
Heterogeneity: Chi <sup>2</sup> = 3.76	, df = 4 (P =	0.44);	$l^2 = 0\%$				
Test for overall effect: Z =	1.81 (P = 0.)	07)					
Total (95% CI)		395		236	100.0%	1.22 [0.98, 1.52]	◆
Total events Heterogeneity: Chi <sup>2</sup> = 3.76 Test for overall effect: Z = Test for subgroup difference	1.81 (P = 0.	07)	79 $I^2 = 0\%$				0.01 0.1 1 10 100 Favours placebo Favours oxcarbazepine

Figure 4.3: Oxcarbazepine versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by neuropathic pain type

	Oxcarbaz	zepine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
1.27.1 Diabetic Neuropath	ıy						
Beydoun 2006 (1200 mg)	44	85	11	30	17.3%	1.41 [0.85, 2.36]	+
Beydoun 2006 (1800 mg)	43	87	11	29	17.6%	1.30 [0.78, 2.17]	+ <b>-</b>
Beydoun 2006 (600 mg)	30	83	11	30	17.2%	0.99 [0.57, 1.71]	<b>_</b>
CTRI476G2301	22	71	24	70	25.7%	0.90 [0.56, 1.45]	
Dogra 2005	31	69	22	77	22.1%	1.57 [1.01, 2.44]	
Subtotal (95% CI)		395		236	100.0%	1.22 [0.98, 1.52]	◆
Total events	170		79				
Heterogeneity: Chi <sup>2</sup> = 3.76	, df = 4 (P =	= 0.44);	$I^2 = 0\%$				
Test for overall effect: Z =	1.81 (P = 0	.07)					
1.27.2 Postherpetic Neura	laia						
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not applical			•				
Test for overall effect: Not							
1.27.3 Trigeminal Neural	nia						
Subtotal (95% CI)	, ici	0		0		Not estimable	
Total events	0	•	0	•		not estimable	
Heterogeneity: Not applical	-		0				
Test for overall effect: Not							
resciol overall effect. Not	applicable						
Total (95% CI)		395		236	100.0%	1.22 [0.98, 1.52]	◆
Total events	170		79				
Heterogeneity: Chi <sup>2</sup> = 3.76	df = 4 (P =	= 0.44);	$l^2 = 0\%$				
Test for overall effect: Z =							0.01 0.1 1 10 100 Favours placebo Favours oxcarbazepine
Test for subgroup difference	ces: Not app	olicable					ravours placebo Favours oxcarbazepine
subgroup afferen							

Figure 4.4: Oxcarbazepine versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size

	Oxcarbaz	epine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.28.1 Less than or equal	to 150 pati	ents					
Beydoun 2006 (1200 mg)	44	85	11	30	17.3%	1.41 [0.85, 2.36]	+
Beydoun 2006 (1800 mg)	43	87	11	29	17.6%	1.30 [0.78, 2.17]	- <b>+</b>
Beydoun 2006 (600 mg)	30	83	11	30	17.2%	0.99 [0.57, 1.71]	_ <b>+</b> _
CTRI476G2301	22	71	24	70	25.7%	0.90 [0.56, 1.45]	
Dogra 2005 <b>Subtotal (95% CI)</b>	31	69 <b>395</b>	22	77 236	22.1% <b>100.0%</b>		<b>→</b>
Total events	170		79				
Heterogeneity: $Chi^2 = 3.76$ ,	df = 4 (P =	0 44)	$l^2 = 0\%$				
Test for overall effect: $Z = 1$							
1.28.2 Greater than 150 pa	atients						
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not applicab	ole						
Test for overall effect: Not a	applicable						
Total (95% CI)		395		236	100.0%	1.22 [0.98, 1.52]	•
Total events	170		79				
Heterogeneity: $Chi^2 = 3.76$ ,	df = 4 (P =	0.44);	$ ^2 = 0\%$				
Test for overall effect: $Z = 1$							
Test for subgroup differenc							Favours placebo Favours oxcarbazepine

## Anticonvulsants (Pregabalin)

Figure 5.1: Pregabalin versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater

	Pregab		Place			Risk Ratio	Risk Ratio
Study or Subgroup						M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.3.1 Outcome data reported a	at less tha	n or ea	ual to 4	week	s		
McDonnell 2018	15	46	7	45	13.8%	2.10 [0.94, 4.65]	
NCT02215252 2014	12	46	7	45	13.8%	1.68 [0.73, 3.87]	
Stacey 2008 (Fixed)	51	88	14	45	36.0%	1.86 [1.16, 2.98]	
Stacey 2008 (Flexed)	64	91	14	45	36.4%	2.26 [1.43, 3.56]	
Subtotal (95% CI)		271		180	100.0%	2.01 [1.52, 2.68]	•
Total events	142		42				
Heterogeneity: $Chi^2 = 0.55$ , df =	= 3 (P = 0)	91); I <sup>2</sup>	= 0%				
Test for overall effect: $Z = 4.83$							
1.3.2 Outcome data reported a	at greater	than 4	weeks t	o less	than 12	weeks	
Achar 2010	11	15	2	15	0.4%	5.50 [1.46, 20.71]	
Baba 2020	38	85	37	88	7.1%	1.06 [0.76, 1.49]	+-
Dworkin 2003	56	89	21	84	4.2%	2.52 [1.68, 3.77]	
Guan 2011	130	206	53	102	13.9%	1.21 [0.98, 1.50]	-
Huffman 2015	39	101	25	102	4.9%	1.58 [1.04, 2.40]	
Lesser 2004 (300 mg)	50	81	16	48	3.9%	1.85 [1.20, 2.86]	
Lesser 2004 (600 mg)	53	82	16	49	3.9%	1.98 [1.28, 3.05]	
Liu 2017	58	111	33	109	6.5%	1.73 [1.23, 2.41]	
Moon 2010	68	162	27	78	7.2%	1.21 [0.85, 1.73]	
Mu 2018	157	314	136	308	27.0%	1.13 [0.96, 1.34]	-
Richter 2005 (600 mg)	32	82	13	85	2.5%	2.55 [1.44, 4.51]	
Rosenstock 2004	30	76	10	70	2.0%	2.76 [1.46, 5.23]	
Sabatowski 2004 (150 mg)	21	81	4	40	1.1%	2.59 [0.95, 7.05]	
Sabatowski 2004 (130 mg)	21	76	4	40	1.0%	2.83 [1.04, 7.70]	
Shabbir 2011	64	70	14	70	2.8%		
Vinik 2014	19	50	45	108	5.6%	4.57 [2.85, 7.34] 0.91 [0.60, 1.39]	
	25	70					
Ziegler 2015 Subtotal (95% CI)	25	1751	28	62	5.8% 100.0%	0.79 [0.52, 1.20] 1.51 [1.38, 1.65]	
	070	17.51	40.4	1433	100.0%	1.51 [1.56, 1.65]	
Total events	872		484				
L	10 10	0 000		0.00/			
Heterogeneity: $Chi^2 = 78.71$ , df				80%			
Heterogeneity: $Chi^2 = 78.71$ , df Test for overall effect: Z = 9.15				80%			
Test for overall effect: Z = 9.15 1.3.3 Outcome data reported a	(P < 0.00) at greater	001) than o	)1); I <sup>2</sup> =	o 12 v			
Test for overall effect: Z = 9.15 1.3.3 Outcome data reported a Arezzo 2008	(P < 0.00) at greater 40	001) than o 82	)1); I <sup>2</sup> =	<b>to 12 v</b> 85	6.9%	2.07 [1.33, 3.23]	-
Test for overall effect: Z = 9.15 1.3.3 Outcome data reported a Arezzo 2008 Freynhagen 2005 (Fixed)	(P < 0.000 at greater 40 88	001) than o 82 132	(1); I <sup>2</sup> =	<b>to 12 v</b> 85 32	6.9% 6.8%	1.78 [1.12, 2.83]	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed)	(P < 0.00) at greater 40 88 83	001) than o 82 132 141	(1); I <sup>2</sup> =	85 32 33	6.9% 6.8% 6.8%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60]	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg)	(P < 0.000 at greater 40 88 83 21	001) than o 82 132 141 87	01); I <sup>2</sup> = r equal t 20 12 12 5	85 32 33 32	6.9% 6.8% 6.8% 2.6%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75]	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg)	(P < 0.000 at greater 40 88 83 21 32	001) than o 82 132 141 87 90	(1);   <sup>2</sup> = <b>r equal</b> 1 20 12 12 5 5	85 32 33 32 33 32 33	6.9% 6.8% 6.8% 2.6%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75] 2.35 [1.00, 5.51]	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg)	(P < 0.000 at greater 40 88 83 21 32 30	001) than o 82 132 141 87 90 97	(1);   <sup>2</sup> = <b>r equal</b> 1 20 12 12 5 5 5	85 32 33 32 33 32 33 33	6.9% 6.8% 6.8% 2.6% 2.6%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75] 2.35 [1.00, 5.51] 2.04 [0.86, 4.83]	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Rauck 2012 (300 mg)	(P < 0.00) at greater 40 88 83 21 32 30 28	001) than o 82 132 141 87 90 97 66	()1); I <sup>2</sup> = r equal 1 20 12 12 5 5 5 15	85 32 33 32 33 32 33 33 33 30	6.9% 6.8% 6.8% 2.6% 2.6% 2.6% 7.2%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75] 2.35 [1.00, 5.51] 2.04 [0.86, 4.83] 0.85 [0.54, 1.34]	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (600 mg) NCT00394901 2006 (600 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg)	(P < 0.00) at greater 40 88 83 21 32 30 28 66	than o 82 132 141 87 90 97 66 134	()1); I <sup>2</sup> = r equal 1 20 12 12 5 5 5 5 15 24	85 32 33 32 33 33 33 30 67	6.9% 6.8% 2.6% 2.6% 2.6% 7.2% 11.2%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75] 2.35 [1.00, 5.51] 2.04 [0.86, 4.83] 0.85 [0.54, 1.34] 1.38 [0.96, 1.98]	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (600 mg) NCT00394901 2006 (600 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (600 mg)	(P < 0.000 at greater 40 88 83 21 32 30 28 66 25	001) than o 82 132 141 87 90 97 66 134 45	()1); $l^2 =$ r equal t 20 12 12 5 5 5 15 24 25	85 32 33 32 33 33 30 67 68	6.9% 6.8% 2.6% 2.6% 7.2% 11.2% 7.0%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75] 2.35 [1.00, 5.51] 2.04 [0.86, 4.83] 0.85 [0.54, 1.34] 1.38 [0.96, 1.98] 1.51 [1.01, 2.27]	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (600 mg) NCT00394901 2006 (600 mg) Rauck 2012 (300 mg) Satoh 2011 (600 mg) Sharma 2006	(P < 0.000 <b>at greater</b> 40 88 83 21 32 30 28 66 25 40	001) than o 82 132 141 87 90 97 66 134 45 82	(1);   <sup>2</sup> = r equal 1 20 12 12 12 5 5 5 15 24 25 20	85 32 33 32 33 33 30 67 68 85	6.9% 6.8% 2.6% 2.6% 7.2% 11.2% 7.0% 6.9%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75] 2.35 [1.00, 5.51] 2.04 [0.86, 4.83] 0.85 [0.54, 1.34] 1.38 [0.96, 1.98] 1.51 [1.01, 2.27] 2.07 [1.33, 3.23]	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (600 mg) Sharma 2006 Smith 2014	(P < 0.000 at greater 40 88 83 21 32 30 28 66 25 40 49	001) than o 82 132 141 87 90 97 66 134 45 82 98	01); I <sup>2</sup> = r equal f 20 12 12 5 5 5 5 5 5 5 5 5 5 5 24 25 20 45	<b>12 v</b> 85 32 33 32 33 33 30 67 68 85 93	6.9% 6.8% 2.6% 2.6% 7.2% 11.2% 7.0% 6.9% 16.2%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75] 2.35 [1.00, 5.51] 2.04 [0.86, 4.83] 0.85 [0.54, 1.34] 1.38 [0.96, 1.98] 1.51 [1.01, 2.27]	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (600 mg) NCT00394901 2006 (600 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (600 mg) Sharma 2006 Smith 2014 Tolle 2008 (150 mg)	(P < 0.000 at greater 40 88 83 21 32 30 28 66 25 40 49 33	001) than o 82 132 141 87 90 97 66 134 45 82 98 99	01);   <sup>2</sup> = r equal f 20 12 5 5 5 5 5 5 24 25 20 45 9	<b>12 v</b> 85 32 33 32 33 33 30 67 68 85 93 32	6.9% 6.8% 2.6% 2.6% 7.2% 11.2% 6.9% 16.2% 4.8%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75] 2.35 [1.00, 5.51] 2.04 [0.86, 4.83] 0.85 [0.54, 1.34] 1.38 [0.96, 1.98] 1.51 [1.01, 2.27] 2.07 [1.33, 3.23]	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (600 mg) Sharma 2006 Smith 2014	(P < 0.000 at greater 40 88 83 21 32 30 28 66 25 40 49	001) than o 82 132 141 87 90 97 66 134 45 82 98	01); I <sup>2</sup> = r equal f 20 12 12 5 5 5 5 5 5 5 5 5 5 5 24 25 20 45	<b>12 v</b> 85 32 33 32 33 33 30 67 68 85 93	6.9% 6.8% 2.6% 2.6% 7.2% 11.2% 7.0% 6.9% 16.2%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75] 2.35 [1.00, 5.51] 2.04 [0.86, 4.83] 0.85 [0.54, 1.34] 1.38 [0.96, 1.98] 1.51 [1.01, 2.27] 2.07 [1.33, 3.23] 1.03 [0.77, 1.38]	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (600 mg) NCT00394901 2006 (600 mg) Rauck 2012 (300 mg) Satoh 2011 (300 mg) Satoh 2011 (600 mg) Sharma 2006 Smith 2014 Tolle 2008 (150 mg)	(P < 0.000 at greater 40 88 83 21 32 30 28 66 25 40 49 33	001) than o 82 132 141 87 90 97 66 134 45 82 98 99	01);   <sup>2</sup> = r equal f 20 12 5 5 5 5 5 5 24 25 20 45 9	<b>12 v</b> 85 32 33 32 33 33 30 67 68 85 93 32	6.9% 6.8% 2.6% 2.6% 7.2% 11.2% 6.9% 16.2% 4.8%	$\begin{array}{c} 1.78 \ [1.12, 2.83] \\ 1.62 \ [1.01, 2.60] \\ 1.54 \ [0.64, 3.75] \\ 2.35 \ [1.00, 5.51] \\ 2.04 \ [0.86, 4.83] \\ 0.85 \ [0.54, 1.34] \\ 1.38 \ [0.96, 1.98] \\ 1.51 \ [1.01, 2.27] \\ 2.07 \ [1.33, 3.23] \\ 1.03 \ [0.77, 1.38] \\ 1.19 \ [0.64, 2.20] \end{array}$	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) NCT00394901 2006 (150 mg) NCT00394901 2006 (300 mg) NCT00394901 2006 (600 mg) Rauck 2012 (300 mg) Satoh 2011 (600 mg) Sharma 2006 Smith 2014 Tolle 2008 (150 mg) Tolle 2008 (300 mg)	(P < 0.000 at greater 40 88 83 21 32 30 28 66 25 40 49 33 32	001) than o 82 132 141 87 90 97 66 134 45 82 98 99 99	01); I <sup>2</sup> = r equal t 12 12 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	85 32 33 32 33 33 30 67 68 85 93 32 32	6.9% 6.8% 2.6% 2.6% 7.2% 7.2% 6.9% 16.2% 4.8%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75] 2.04 [0.86, 4.83] 0.85 [0.54, 1.34] 1.38 [0.96, 1.98] 1.51 [1.01, 2.27] 2.07 [1.33, 3.23] 1.03 [0.77, 1.38] 1.19 [0.64, 2.20] 1.15 [0.62, 2.14]	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008           Freynhagen 2005 (Fixed)           Freynhagen 2005 (Flexed)           NCT00394901 2006 (150 mg)           NCT00394901 2006 (300 mg)           NCT00394901 2006 (600 mg)           Rauck 2012 (300 mg)           Satoh 2011 (300 mg)           Satoh 2011 (600 mg)           Smith 2014           Tolle 2008 (300 mg)           Tolle 2008 (600 mg)	(P < 0.000 at greater 40 88 83 21 322 30 28 66 255 40 49 33 322 45	001) than o 82 132 141 87 90 97 66 134 45 82 98 99 99 101	(1); i <sup>2</sup> = r equal t 20 12 12 12 5 5 5 15 24 25 20 45 9 9 10	85 32 33 32 33 30 67 68 85 93 32 32 32 32	6.9% 6.8% 2.6% 2.6% 7.2% 11.2% 7.0% 6.9% 16.2% 4.8% 5.3%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75] 2.35 [1.00, 5.51] 2.04 [0.86, 4.83] 0.85 [0.54, 1.34] 1.38 [0.96, 1.98] 1.51 [1.01, 2.27] 2.07 [1.33, 3.23] 1.03 [0.77, 1.38] 1.19 [0.64, 2.20] 1.15 [0.62, 2.14] 1.43 [0.82, 2.49]	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008           Freynhagen 2005 (Fixed)           Freynhagen 2005 (Flexed)           NCT00394901 2006 (150 mg)           NCT00394901 2006 (600 mg)           Rauck 2012 (300 mg)           Satoh 2011 (600 mg)           Satoh 2011 (600 mg)           Sharma 2006           Smith 2014           Folle 2008 (150 mg)           Tolle 2008 (600 mg)           Van-Seventer 2006 (150 mg)	(P < 0.000 at greater 40 88 83 21 32 30 28 66 25 40 49 33 32 45 45 34	001) than o 82 132 141 87 90 97 66 134 45 82 98 99 99 99 101 87	(1); i <sup>2</sup> = r equal 1 20 12 12 12 5 5 5 15 24 25 20 45 9 9 10 5	85 32 33 33 33 30 67 68 85 93 32 32 32 32 31 31 31	6.9% 6.8% 2.6% 2.6% 7.2% 11.2% 7.0% 6.9% 16.2% 4.8% 4.8% 5.3% 2.6%	$\begin{array}{c} 1.78 \ [1.12, 2.83]\\ 1.62 \ [1.01, 2.60]\\ 1.54 \ [0.64, 3.75]\\ 2.35 \ [1.00, 5.51]\\ 2.04 \ [0.86, 4.83]\\ 0.85 \ [0.54, 1.34]\\ 1.38 \ [0.96, 1.98]\\ 1.51 \ [1.01, 2.27]\\ 2.07 \ [1.33, 3.23]\\ 1.03 \ [0.77, 1.38]\\ 1.19 \ [0.64, 2.20]\\ 1.15 \ [0.62, 2.14]\\ 1.43 \ [0.82, 2.49]\\ 2.42 \ [1.04, 5.64] \end{array}$	
Fest for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008         Freynhagen 2005 (Fixed)         Freynhagen 2005 (Flexed)         NCT00394901 2006 (150 mg)         NCT00394901 2006 (300 mg)         NCT00394901 2006 (300 mg)         NCT00394901 2006 (300 mg)         Satoh 2011 (300 mg)         Satoh 2011 (600 mg)         Sharma 2006         Smith 2014         Tolle 2008 (150 mg)         Tolle 2008 (500 mg)         Van-Seventer 2006 (150 mg)         Van-Seventer 2006 (300 mg)	(P < 0.000 at greater 40 88 83 21 32 30 28 66 25 40 49 33 32 45 5 34 40 47	001) than o 82 132 141 87 90 97 66 134 45 82 99 99 101 87 98 90	(1); i <sup>2</sup> = r equal t 20 12 12 5 5 5 5 15 24 25 20 45 9 9 10 5 5 6	85 32 33 33 33 30 67 68 85 93 32 32 32 32 31 31 31	6.9% 6.8% 2.6% 2.6% 7.2% 11.2% 7.0% 6.9% 16.2% 4.8% 5.3% 2.6% 2.7% 3.1%	$\begin{array}{c} 1.78 \ [1.12, 2.83]\\ 1.62 \ [1.01, 2.60]\\ 1.54 \ [0.64, 3.75]\\ 2.35 \ [1.00, 5.51]\\ 2.04 \ [0.86, 4.83]\\ 0.85 \ [0.54, 1.34]\\ 1.38 \ [0.96, 1.98]\\ 1.51 \ [1.01, 2.27]\\ 2.07 \ [1.33, 3.23]\\ 1.03 \ [0.77, 1.38]\\ 1.19 \ [0.64, 2.20]\\ 1.15 \ [0.62, 2.14]\\ 1.43 \ [0.82, 2.49]\\ 2.42 \ [1.04, 5.64]\\ 2.53 \ [1.10, 5.85]\\ 2.70 \ [1.28, 5.68] \end{array}$	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008         Freynhagen 2005 (Fixed)         Freynhagen 2005 (Fixed)         VCT00394901 2006 (150 mg)         NCT00394901 2006 (600 mg)         Rauck 2012 (300 mg)         Satoh 2011 (600 mg)         Sharma 2006         Smith 2014         Tolle 2008 (150 mg)         Tolle 2008 (300 mg)         Tolle 2008 (300 mg)         Yan-Seventer 2006 (150 mg)         Van-Seventer 2006 (300 mg)         Van-Seventer 2006 (600 mg)         Subtotal (95% CI)         Total events	(P < 0.000 at greater 40 88 83 211 32 30 28 66 62 55 40 49 33 32 45 34 40 47 733	001) than o 82 132 141 87 90 97 66 134 45 82 98 99 101 87 98 90 1628	D1); I <sup>2</sup> = r equal t 20 12 12 5 5 5 5 24 25 20 40 40 5 6 232	80 12 v 85 32 33 32 33 30 67 68 85 93 32 32 32 32 31 31 31 780	6.9% 6.8% 2.6% 2.6% 7.2% 11.2% 7.0% 6.9% 16.2% 4.8% 5.3% 2.6% 2.7% 3.1%	$\begin{array}{c} 1.78 \ [1.12, 2.83]\\ 1.62 \ [1.01, 2.60]\\ 1.54 \ [0.64, 3.75]\\ 2.35 \ [1.00, 5.51]\\ 2.04 \ [0.86, 4.83]\\ 0.85 \ [0.54, 1.34]\\ 1.38 \ [0.96, 1.98]\\ 1.51 \ [1.01, 2.27]\\ 2.07 \ [1.33, 3.23]\\ 1.03 \ [0.77, 1.38]\\ 1.19 \ [0.64, 2.20]\\ 1.15 \ [0.62, 2.14]\\ 1.43 \ [0.82, 2.49]\\ 2.42 \ [1.04, 5.64]\\ 2.53 \ [1.10, 5.85]\\ 2.70 \ [1.28, 5.68] \end{array}$	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008         Freynhagen 2005 (Fixed)         Freynhagen 2005 (Flexed)         NCT00394901 2006 (150 mg)         NCT00394901 2006 (600 mg)         Rauck 2012 (300 mg)         Satoh 2011 (600 mg)         Satoh 2011 (600 mg)         Folle 2008 (150 mg)         Tolle 2008 (150 mg)         Tolle 2008 (000 mg)         Van-Seventer 2006 (150 mg)         Van-Seventer 2006 (300 mg)         Van-Seventer 2006 (300 mg)         Van-Seventer 2006 (150 mg)         Van-Seventer 2006 (300 mg)	(P < 0.000 at greater 40 88 83 211 32 30 28 66 66 25 40 49 33 322 45 34 40 47 733 = 16 (P =	001) than o 82 132 141 87 90 97 66 134 45 82 99 99 101 87 99 101 87 90 101 0.05);	D1); I <sup>2</sup> = r equal t 20 12 12 5 5 5 5 24 25 20 40 40 5 6 232	80 12 v 85 32 33 32 33 30 67 68 85 93 32 32 32 32 31 31 31 780	6.9% 6.8% 2.6% 2.6% 7.2% 11.2% 7.0% 6.9% 16.2% 4.8% 5.3% 2.6% 2.7% 3.1%	$\begin{array}{c} 1.78 \ [1.12, 2.83]\\ 1.62 \ [1.01, 2.60]\\ 1.54 \ [0.64, 3.75]\\ 2.35 \ [1.00, 5.51]\\ 2.04 \ [0.86, 4.83]\\ 0.85 \ [0.54, 1.34]\\ 1.38 \ [0.96, 1.98]\\ 1.51 \ [1.01, 2.27]\\ 2.07 \ [1.33, 3.23]\\ 1.03 \ [0.77, 1.38]\\ 1.19 \ [0.64, 2.20]\\ 1.15 \ [0.62, 2.14]\\ 1.43 \ [0.82, 2.49]\\ 2.42 \ [1.04, 5.64]\\ 2.53 \ [1.10, 5.85]\\ 2.70 \ [1.28, 5.68] \end{array}$	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008         Freynhagen 2005 (Fixed)         Freynhagen 2005 (Fixed)         VCT00394901 2006 (150 mg)         NCT00394901 2006 (600 mg)         Rauck 2012 (300 mg)         Satoh 2011 (600 mg)         Sharma 2006         Smith 2014         Tolle 2008 (150 mg)         Tolle 2008 (300 mg)         Tolle 2008 (300 mg)         Yan-Seventer 2006 (150 mg)         Van-Seventer 2006 (300 mg)         Van-Seventer 2006 (600 mg)         Subtotal (95% CI)         Total events	(P < 0.000 at greater 40 88 83 211 32 30 28 66 66 25 40 49 33 322 45 34 40 47 733 = 16 (P =	001) than o 82 132 141 87 90 97 66 134 45 82 99 99 101 87 99 101 87 90 101 0.05);	D1); I <sup>2</sup> = r equal t 20 12 12 5 5 5 5 24 25 20 40 40 5 6 232	80 12 v 85 32 33 32 33 30 67 68 85 93 32 32 32 32 31 31 31 780	6.9% 6.8% 2.6% 2.6% 7.2% 11.2% 7.0% 6.9% 16.2% 4.8% 5.3% 2.6% 2.7% 3.1%	$\begin{array}{c} 1.78 \ [1.12, 2.83]\\ 1.62 \ [1.01, 2.60]\\ 1.54 \ [0.64, 3.75]\\ 2.35 \ [1.00, 5.51]\\ 2.04 \ [0.86, 4.83]\\ 0.85 \ [0.54, 1.34]\\ 1.38 \ [0.96, 1.98]\\ 1.51 \ [1.01, 2.27]\\ 2.07 \ [1.33, 3.23]\\ 1.03 \ [0.77, 1.38]\\ 1.19 \ [0.64, 2.20]\\ 1.15 \ [0.62, 2.14]\\ 1.43 \ [0.82, 2.49]\\ 2.42 \ [1.04, 5.64]\\ 2.53 \ [1.10, 5.85]\\ 2.70 \ [1.28, 5.68] \end{array}$	
Test for overall effect: Z = 9.15 <b>1.3.3 Outcome data reported a</b> Arezzo 2008         Freynhagen 2005 (Fixed)         Freynhagen 2005 (Flexed)         NCT00394901 2006 (150 mg)         NCT00394901 2006 (600 mg)         Rauck 2012 (300 mg)         Satoh 2011 (600 mg)         Satoh 2011 (600 mg)         Folle 2008 (150 mg)         Tolle 2008 (150 mg)         Tolle 2008 (000 mg)         Van-Seventer 2006 (150 mg)         Van-Seventer 2006 (300 mg)         Van-Seventer 2006 (300 mg)         Van-Seventer 2006 (150 mg)         Van-Seventer 2006 (300 mg)         Van-Seventer 2006 (500 mg)         Van-Seventer 2006 (300 mg)         Van-Seventer 2006 (300 mg)         Van-Seventer 2006 (300 mg)         Van-Seventer 2006 (500 mg)         Van-Seventer 2006 (300 mg)	(P < 0.000 at greater 40 88 83 211 32 30 28 66 66 25 40 49 33 322 45 34 40 47 733 = 16 (P =	001) than o 82 132 141 87 90 97 66 134 45 82 99 99 101 87 99 101 87 90 101 0.05);	D1); I <sup>2</sup> = r equal t 20 12 12 5 5 5 5 24 25 20 40 40 5 6 232	80 12 v 85 32 33 32 33 30 67 68 85 93 32 32 32 32 31 31 31 780	6.9% 6.8% 2.6% 2.6% 7.2% 11.2% 7.0% 6.9% 16.2% 4.8% 5.3% 2.6% 2.7% 3.1%	1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.54 [0.64, 3.75] 2.04 [0.86, 4.83] 0.85 [0.54, 1.34] 1.38 [0.96, 1.98] 1.51 [1.01, 2.27] 2.07 [1.33, 3.23] 1.03 [0.77, 1.38] 1.19 [0.64, 2.20] 1.15 [0.62, 2.14] 1.43 [0.82, 2.49] 2.42 [1.04, 5.64] 2.53 [1.10, 5.85] 2.70 [1.28, 5.68] 1.56 [1.38, 1.77]	

Figure 5.2: Pregabalin versus control; Subgroup analysis: Proportion of patients with a
meaningful response to treatment, analyzed by study funding source

·	Pregat		Place		Waladas	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Iotal	Events	Total	weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
L.5.1 Public Funding		0		0		Net estimable	
Subtotal (95% CI)		0		0		Not estimable	
Fotal events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not appli	cable						
1.5.2 Industry Funding							
Arezzo 2008	40	82	20	85	2.4%	2.07 [1.33, 3.23]	
Baba 2020	38	85	37	88	4.4%	1.06 [0.76, 1.49]	+
Dworkin 2003	56	89	21	84	2.6%	2.52 [1.68, 3.77]	
reynhagen 2005 (Fixed)	88	132	12	32	2.3%	1.78 [1.12, 2.83]	
reynhagen 2005 (Flexed)	83	141	12	33	2.3%	1.62 [1.01, 2.60]	
Guan 2011	130	206	53	102	8.5%	1.21 [0.98, 1.50]	-
Huffman 2015	39	101	25	102	3.0%	1.58 [1.04, 2.40]	
esser 2004 (300 mg)	50	81	16	48	2.4%	1.85 [1.20, 2.86]	
esser 2004 (600 mg)	53	82	16	49	2.4%	1.98 [1.28, 3.05]	
iu 2017	58	111	33	109	4.0%	1.73 [1.23, 2.41]	
AcDonnell 2018	15	46	7	45	0.9%	2.10 [0.94, 4.65]	L
Moon 2010	68	162	27	78	4.4%	1.21 [0.85, 1.73]	+
Mu 2018	157	314	136	308	16.6%	1.13 [0.96, 1.34]	-
NCT00394901 2006 (150 mg)	21	87	5	32	0.9%	1.54 [0.64, 3.75]	
NCT00394901 2006 (300 mg)	32	90	5	33	0.9%	2.35 [1.00, 5.51]	
VCT00394901 2006 (600 mg)	30	97	5	33	0.9%	2.04 [0.86, 4.83]	
NCT02215252 2014	12	46	7	45	0.9%	1.68 [0.73, 3.87]	
Rauck 2012 (300 mg)	28	66	15	30	2.5%	0.85 [0.54, 1.34]	
Richter 2005 (600 mg)	32	82	13	85	1.5%	2.55 [1.44, 4.51]	
Rosenstock 2004	30	76	10	70	1.3%	2.76 [1.46, 5.23]	
Sabatowski 2004 (150 mg)	21	81	4	40	0.6%	2.59 [0.95, 7.05]	
Sabatowski 2004 (300 mg)	21	76	4	41	0.6%	2.83 [1.04, 7.70]	
Satoh 2011 (300 mg)	66	134	24	67	3.9%	1.38 [0.96, 1.98]	
Satoh 2011 (600 mg)	25	45	25	68	2.4%	1.51 [1.01, 2.27]	
Sharma 2006	40	82	20	85	2.4%	2.07 [1.33, 3.23]	
Smith 2014	49	98	45	93	5.6%	1.03 [0.77, 1.38]	+
Stacey 2008 (Fixed)	51	88	14	45	2.2%	1.86 [1.16, 2.98]	
Stacey 2008 (Flexed)	64	91	14	45	2.3%	2.26 [1.43, 3.56]	
Tolle 2008 (150 mg)	33	99	9	32	1.6%	1.19 [0.64, 2.20]	
Folle 2008 (300 mg)	32	99	9	32	1.6%	1.15 [0.62, 2.14]	
Folle 2008 (600 mg)	45	101	10	32	1.8%	1.43 [0.82, 2.49]	
/an-Seventer 2006 (150 mg)	34	87	5	31	0.9%	2.42 [1.04, 5.64]	
/an-Seventer 2006 (300 mg)	40	98	5	31	0.9%	2.53 [1.10, 5.85]	
/an-Seventer 2006 (600 mg)	40	90	6	31	1.1%	2.70 [1.28, 5.68]	
/inik 2014	19	50	45	108	3.4%	0.91 [0.60, 1.39]	
Ziegler 2015	25	70	28	62	3.6%	0.79 [0.52, 1.20]	-+
Subtotal (95% CI)	23	3565	20		100.0%	1.50 [1.39, 1.61]	
Total events	1672		742				
Heterogeneity: Chi <sup>2</sup> = 83.21, df		0.000		5.8%			
Test for overall effect: $Z = 11.12$			01), 1 =	50%			
Fotal (95% CI)		3565		2334	100.0%	1.50 [1.39, 1.61]	•
Total events	1672	5505	742	2001	200.070	1.50 [1.55, 1.01]	
Heterogeneity: Chi <sup>2</sup> = 83.21, df		0 000		5.80/			
		0.000	V1/, I =	10/0			0.01 0.1 1 10

Figure 5.3: Pregabalin versus control; Su	<pre>ubgroup analysis: </pre>	Proportion of	patients with a
meaningful response to treatment, anal	yzed by neuropat	hic pain type	

tudy or Subgroup	Pregab		Place		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% Cl
.2.1 Diabetic Neuropathy	Events	Total	events	rotal	weight	m-n, rixeu, 95% Cl	
rezzo 2008	40	82	20	85	2 20/	2.07 [1.33, 3.23]	
		82 85			2.3%		
aba 2020	38		37	88	4.3%	1.06 [0.76, 1.49]	
luffman 2015	39	101	25	102	2.9%	1.58 [1.04, 2.40]	
esser 2004 (300 mg)	50	81	16	48	2.4%	1.85 [1.20, 2.86]	
esser 2004 (600 mg)	53	82	16	49	2.4%	1.98 [1.28, 3.05]	
CDonnell 2018	15	46	7	45	0.8%	2.10 [0.94, 4.65]	
1u 2018	157	314	136	308	16.2%	1.13 [0.96, 1.34]	
ICT02215252 2014	12	46	7	45	0.8%	1.68 [0.73, 3.87]	
auck 2012 (300 mg)	28	66	15	30	2.4%	0.85 [0.54, 1.34]	
ichter 2005 (600 mg)	32	82	13	85	1.5%	2.55 [1.44, 4.51]	
osenstock 2004	30	76	10	70	1.2%	2.76 [1.46, 5.23]	
atoh 2011 (300 mg)	66	134	24	67	3.8%	1.38 [0.96, 1.98]	
atoh 2011 (600 mg)	25	45	25	68	2.4%	1.51 [1.01, 2.27]	
habbir 2011	64	70	14	70	1.7%	4.57 [2.85, 7.34]	
harma 2006	40	82	20	85	2.3%	2.07 [1.33, 3.23]	
mith 2014	49	98	45	93	5.5%	1.03 [0.77, 1.38]	+
olle 2008 (150 mg)	33	99	9	32	1.6%	1.19 [0.64, 2.20]	
olle 2008 (300 mg)	32	99	9	32	1.6%	1.15 [0.62, 2.14]	
olle 2008 (600 mg)	45	101	10	32	1.8%	1.43 [0.82, 2.49]	
/inik 2014	19	50	45	108	3.4%	0.91 [0.60, 1.39]	
liegler 2015	25	70	28	62	3.4%	0.79 [0.52, 1.20]	
ubtotal (95% CI)	25	<b>1909</b>	28	1604	64.9%	<b>1.43 [1.31, 1.56]</b>	
	000	1909	531	1004	04.9%	1.45 [1.51, 1.50]	•
otal events	892		531	====			
leterogeneity: Chi <sup>2</sup> = 74.86, df rest for overall effect: Z = 8.20			01); 1- =	73%			
.2.2 Postherpetic Neuralgia							
char 2010	11	15	2	15	0.2%	5.50 [1.46, 20.71]	· · · · · · · · · · · · · · · · · · ·
workin 2003	56	89	21	84	2.6%	2.52 [1.68, 3.77]	
iu 2017	58	111	33	109	3.9%	1.73 [1.23, 2.41]	
1oon 2010	68	162	27	78	4.3%	1.21 [0.85, 1.73]	+
ICT00394901 2006 (150 mg)	21	87	5	32	0.9%	1.54 [0.64, 3.75]	
ICT00394901 2006 (300 mg)	32	90	5	33	0.9%	2.35 [1.00, 5.51]	
ICT00394901 2006 (600 mg)	30	97	5	33	0.9%	2.04 [0.86, 4.83]	
abatowski 2004 (150 mg)	21	81	4	40	0.6%	2.59 [0.95, 7.05]	
abatowski 2004 (300 mg)	21	76	4	41	0.6%	2.83 [1.04, 7.70]	
tacey 2008 (Fixed)	51	88	14	45	2.2%	1.86 [1.16, 2.98]	
tacey 2008 (Flexed)	64	91	14	45	2.2%	2.26 [1.43, 3.56]	
		87					
(an-Seventer 2006 (150 mg)	34		5	31	0.9%	2.42 [1.04, 5.64]	
(an-Seventer 2006 (300 mg)	40	98	5	31	0.9%	2.53 [1.10, 5.85]	
an-Seventer 2006 (600 mg)	47	90	6	31	1.1%	2.70 [1.28, 5.68]	
ubtotal (95% CI)		1262		648	22.1%	2.02 [1.73, 2.35]	♥
otal events	554		150				
leterogeneity: Chi <sup>2</sup> = 14.64, df			$l^2 = 11\%$	6			
test for overall effect: $Z = 8.96$	(P < 0.00	001)					
2.3 Trigeminal Neuralgia ubtotal (95% CI)		0		0		Not estimable	
otal events	0	5	0	2			
leterogeneity: Not applicable	5		5				
est for overall effect: Not appli	icable						
.2.4 Mixed Population							
reynhagen 2005 (Fixed)	88	132	12	32	2.3%	1.78 [1.12, 2.83]	<del></del>
reynhagen 2005 (Flexed)	83	141	12	33	2.3%	1.62 [1.01, 2.60]	
Guan 2011 ubtotal (95% CI)	130	206 <b>479</b>	53	102 <b>167</b>	8.4% 1 <b>3.0%</b>	1.21 [0.98, 1.50] 1.39 [1.15, 1.66]	<b>•</b>
otal events	301		77				•
leterogeneity: $Chi^2 = 2.99$ , df = fest for overall effect: Z = 3.49	= 2 (P = 0)						
otal (95% CI)		3650		2419	100.0%	1.56 [1.45, 1.67]	•
otal events	1747		758				
	IF _ 27 (D	< 0.00	001) 12 -	- 67%			
leterogeneity: Chi <sup>2</sup> = 111.21, c	r = 27 (r)	< 0.00	001), I -	- 0770			0.01 0.1 1 10 1

Figure 5.4: Pregabalin versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size

	Pregab		Place		Walate	Risk Ratio	Risk Ratio
Study or Subgroup			Events	Total	weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
1.4.1 Less than or equal to 15	•		-				
Achar 2010	11	15	2	15	0.2%	5.50 [1.46, 20.71]	· · · · · ·
esser 2004 (300 mg)	50	81	16	48	2.3%	1.85 [1.20, 2.86]	
esser 2004 (600 mg)	53	82	16	49	2.3%	1.98 [1.28, 3.05]	
AcDonnell 2018	15	46	7	45	0.8%	2.10 [0.94, 4.65]	
NCT00394901 2006 (150 mg)	21	87	5	32	0.8%	1.54 [0.64, 3.75]	
NCT00394901 2006 (300 mg)	32	90	5	33	0.8%	2.35 [1.00, 5.51]	
NCT00394901 2006 (600 mg)	30	97	5	33	0.9%	2.04 [0.86, 4.83]	
NCT02215252 2014	12	46	7	45	0.8%	1.68 [0.73, 3.87]	
Rauck 2012 (300 mg)	28	66	15	30	2.4%	0.85 [0.54, 1.34]	
Rosenstock 2004	30	76	10	70	1.2%	2.76 [1.46, 5.23]	
Sabatowski 2004 (150 mg)	21	81	4	40	0.6%	2.59 [0.95, 7.05]	
Sabatowski 2004 (300 mg)	21	76	4	41	0.6%	2.83 [1.04, 7.70]	
Satoh 2011 (300 mg)	66	134	24	67	3.6%	1.38 [0.96, 1.98]	
Satoh 2011 (600 mg)	25	45	25	68	2.3%	1.51 [1.01, 2.27]	
Shabbir 2011	64	70	14	70	1.6%	4.57 [2.85, 7.34]	
Stacey 2008 (Fixed)	51	88	14	45	2.1%	1.86 [1.16, 2.98]	_ <del></del>
stacey 2008 (Flexed)	64	91	14	45	2.1%	2.26 [1.43, 3.56]	
Tolle 2008 (150 mg)	33	99	9	32	1.6%	1.19 [0.64, 2.20]	
Tolle 2008 (300 mg)	32	99	9	32	1.6%	1.15 [0.62, 2.14]	
Гolle 2008 (600 mg)	45	101	10	32	1.7%	1.43 [0.82, 2.49]	
/an-Seventer 2006 (150 mg)	34	87	5	31	0.8%	2.42 [1.04, 5.64]	
/an-Seventer 2006 (300 mg)	40	98	5	31	0.9%	2.53 [1.10, 5.85]	
/an-Seventer 2006 (600 mg)	47	90	6	31	1.0%	2.70 [1.28, 5.68]	
liegler 2015	25	70	28	62	3.4%	0.79 [0.52, 1.20]	
Subtotal (95% CI)		1915		1027	36.4%	1.84 [1.63, 2.06]	•
Test for overall effect: Z = 10.2		0001)					
1.4.2 Greater than 150 batien	ts						
		0.0	20	0.5			
Arezzo 2008	40	82	20	85	2.2%	2.07 [1.33, 3.23]	
Arezzo 2008 Baba 2020	40 38	85	37	88	4.1%	1.06 [0.76, 1.49]	+
Arezzo 2008 Baba 2020 Dworkin 2003	40 38 56	85 89	37 21	88 84	4.1% 2.5%	1.06 [0.76, 1.49] 2.52 [1.68, 3.77]	+
Arezzo 2008 Baba 2020 Dworkin 2003 Freynhagen 2005 (Fixed)	40 38 56 88	85 89 132	37 21 12	88 84 32	4.1% 2.5% 2.2%	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83]	+
Arezzo 2008 Baba 2020 Oworkin 2003 reynhagen 2005 (Fixed) reynhagen 2005 (Flexed)	40 38 56 88 83	85 89 132 141	37 21 12 12	88 84 32 33	4.1% 2.5% 2.2% 2.2%	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60]	
Arezzo 2008 Baba 2020 Oworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) Guan 2011	40 38 56 88 83 130	85 89 132 141 206	37 21 12 12 53	88 84 32 33 102	4.1% 2.5% 2.2% 2.2% 8.1%	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50]	
Arezzo 2008 Jaba 2020 Oworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) Juan 2011 Huffman 2015	40 38 56 88 83 130 39	85 89 132 141 206 101	37 21 12 12 53 25	88 84 32 33 102 102	4.1% 2.5% 2.2% 2.2% 8.1% 2.8%	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40]	
Arezzo 2008 Baba 2020 Oworkin 2003 Freynhagen 2005 (Fixed) Guan 2011 Juffman 2015 iu 2017	40 38 56 88 83 130 39 58	85 89 132 141 206 101 111	37 21 12 53 25 33	88 84 32 33 102 102 109	4.1% 2.5% 2.2% 2.2% 8.1% 2.8% 3.8%	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41]	
Arezzo 2008 Baba 2020 Dworkin 2003 reynhagen 2005 (Fixed) Guan 2011 Luffman 2015 Lu 2017 Moon 2010	40 38 56 88 130 39 58 68	85 89 132 141 206 101 111 162	37 21 12 53 25 33 27	88 84 32 33 102 102 109 78	4.1% 2.5% 2.2% 2.2% 8.1% 2.8% 3.8% 4.2%	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73]	
Arezzo 2008 Baba 2020 Dworkin 2003 reynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018	40 38 56 88 130 39 58 68 157	85 89 132 141 206 101 111 162 314	37 21 12 53 25 33 27 136	88 84 32 33 102 102 109 78 308	4.1% 2.5% 2.2% 8.1% 2.8% 3.8% 4.2% 15.7%	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73] 1.13 [0.96, 1.34]	
Arezzo 2008 Baba 2020 Dworkin 2003 reynhagen 2005 (Fixed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Richter 2005 (600 mg)	40 38 56 88 130 39 58 68 157 32	85 89 132 141 206 101 111 162 314 82	37 21 12 53 25 33 27 136 13	88 84 32 33 102 102 109 78 308 85	4.1% 2.5% 2.2% 8.1% 2.8% 3.8% 4.2% 15.7% 1.5%	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73] 1.13 [0.96, 1.34] 2.55 [1.44, 4.51]	
Arezzo 2008 Jaba 2020 Oworkin 2003 (reynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) Juan 2011 Huffman 2015 Jui 2017 Moon 2010 Au 2018 Lichter 2005 (600 mg) Jatoh 2011 (300 mg)	40 38 56 88 130 39 58 68 157 32 66	85 89 132 141 206 101 111 162 314 82 134	37 21 12 53 25 33 27 136 13 24	88 84 32 33 102 102 109 78 308 85 67	4.1% 2.5% 2.2% 8.1% 2.8% 3.8% 4.2% 15.7% 1.5% 3.6%	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73] 1.13 [0.96, 1.34] 2.55 [1.44, 4.51] 1.38 [0.96, 1.98]	
Arezzo 2008 Baba 2020 Oworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Richter 2005 (600 mg) Gatoh 2011 (300 mg) Gharma 2006	40 38 56 88 130 39 58 68 157 32 66 40	85 89 132 141 206 101 111 162 314 82 134 82	37 21 12 53 25 33 27 136 13 24 20	88 84 32 33 102 102 109 78 308 85 67 85	4.1% 2.5% 2.2% 8.1% 2.8% 3.8% 4.2% 15.7% 1.5% 3.6% 2.2%	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73] 1.13 [0.96, 1.34] 2.55 [1.44, 4.51] 1.38 [0.96, 1.98] 2.07 [1.33, 3.23]	
Arezzo 2008 Baba 2020 Dworkin 2003 Freynhagen 2005 (Fixed) Guan 2011 Auffman 2015 Liu 2017 Moon 2010 Mu 2018 Richter 2005 (600 mg) Statoh 2011 (300 mg) Sharma 2006 Smith 2014	40 38 56 88 130 39 58 68 157 32 66 40 49	85 89 132 141 206 101 111 162 314 82 134 82 98	37 21 12 53 25 33 27 136 13 24 20 45	88 84 32 33 102 109 78 308 85 67 85 93	4.1% 2.5% 2.2% 8.1% 2.8% 3.8% 4.2% 1.5% 3.6% 2.2% 5.3%	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73] 1.13 [0.96, 1.34] 2.55 [1.44, 4.51] 1.38 [0.96, 1.98] 2.07 [1.33, 3.23] 1.03 [0.77, 1.38]	
Arezzo 2008 Baba 2020 Dworkin 2003 (reynhagen 2005 (Fixed)) Guan 2011 (uffman 2015 Ju 2017 Moon 2010 Au 2018 Richter 2005 (600 mg) Jatoh 2011 (300 mg) Jharma 2006 Jimith 2014	40 38 56 88 130 39 58 68 157 32 66 40	85 89 132 141 206 101 111 162 314 82 134 82	37 21 12 53 25 33 27 136 13 24 20	88 84 32 33 102 102 109 78 308 85 67 85	4.1% 2.5% 2.2% 8.1% 2.8% 3.8% 4.2% 15.7% 1.5% 3.6% 2.2%	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73] 1.13 [0.96, 1.34] 2.55 [1.44, 4.51] 1.38 [0.96, 1.98] 2.07 [1.33, 3.23]	
Arezzo 2008 Baba 2020 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) Juan 2011 Huffman 2015 Ju 2017 Moon 2010 Mu 2018 Bichter 2005 (600 mg) Biatoh 2011 (300 mg) Biatoh 2014 Juint 2014 Juint 2014 Juint 2014 Juint 2014 Juint 2014 Jotal events Heterogeneity: Chi <sup>2</sup> = 40.43, df	40 38 56 83 130 39 58 68 157 32 66 40 49 19 963 f = 14 (P =	85 89 132 141 206 101 111 162 314 82 134 82 98 50 <b>1869</b>	37 21 12 53 25 33 27 136 13 24 20 45 45 523	88 84 32 33 102 109 78 308 85 67 85 93 108 1459	4.1% 2.5% 2.2% 8.1% 2.8% 3.8% 4.2% 15.7% 3.6% 2.2% 5.3% 3.2%	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73] 1.13 [0.96, 1.34] 2.55 [1.44, 4.51] 1.38 [0.96, 1.98] 2.07 [1.33, 3.23] 1.03 [0.77, 1.38] 0.91 [0.60, 1.39]	
Arezzo 2008 Baba 2020 Oworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) Guan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Richter 2005 (600 mg) Gatoh 2011 (300 mg) Gharma 2006	40 38 56 83 130 39 58 68 157 32 66 40 49 19 963 f = 14 (P =	85 89 132 141 206 101 111 162 314 82 134 82 98 50 <b>1869</b>	37 21 12 53 25 33 27 136 13 24 20 45 45 523	88 84 32 33 102 102 102 78 308 85 67 85 93 108 1459	4.1% 2.5% 2.2% 8.1% 2.8% 3.8% 4.2% 15.7% 3.6% 2.2% 5.3% 3.2%	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73] 1.13 [0.96, 1.34] 2.55 [1.44, 4.51] 1.38 [0.96, 1.98] 2.07 [1.33, 3.23] 1.03 [0.77, 1.38] 0.91 [0.60, 1.39]	
Arezzo 2008 Baba 2020 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) Juan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Richter 2005 (600 mg) Batoh 2011 (300 mg) Batoh 2011 (300 mg) Batoh 2014 (Jinik 2014 Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = 40.43, df Fest for overall effect: Z = 7.59 Fotal (95% CI)	40 38 56 88 83 130 39 58 68 68 68 68 40 49 19 963 f = 14 (P = 0 (P < 0.00	85 89 132 141 206 101 111 162 314 82 134 82 98 50 <b>1869</b> = 0.000 001)	37 21 12 53 25 33 27 136 13 24 20 20 45 45 45 223 2);   <sup>2</sup> = 6	88 84 32 33 102 102 102 78 308 85 67 85 93 108 1459	4.1% 2.5% 2.2% 8.1% 2.8% 3.8% 4.2% 15.7% 1.5% 3.6% 2.2% 5.3% 3.2% <b>63.6%</b>	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73] 1.13 [0.96, 1.34] 2.55 [1.44, 4.51] 1.38 [0.96, 1.98] 2.07 [1.33, 3.23] 1.03 [0.77, 1.38] 0.91 [0.60, 1.39] <b>1.38 [1.27, 1.51]</b>	
vezzo 2008 aba 2020 workin 2003 reynhagen 2005 (Fixed) reynhagen 2005 (Fixed) iuan 2011 luffman 2015 iu 2017 doon 2010 du 2018 ichter 2005 (600 mg) atoh 2011 (300 mg) harma 2006 mith 2014 ubtotal (95% CI) otal events leterogeneity: Chi <sup>2</sup> = 40.43, df est for overall effect: Z = 7.59 <b>Total (95% CI)</b> otal events	40 38 56 88 83 130 39 58 68 157 32 66 40 49 19 963 f = 14 (P = (P < 0.00 1813	85 89 132 141 206 101 111 162 314 82 134 82 98 50 <b>1869</b> ■ 0.000 001) <b>3784</b>	$\begin{array}{c} 37\\ 21\\ 12\\ 12\\ 53\\ 25\\ 33\\ 27\\ 136\\ 13\\ 24\\ 20\\ 45\\ 45\\ 523\\ 2); \  ^2 = 6\\ 782 \end{array}$	88 84 32 33 102 109 78 308 85 67 85 93 108 1459 55% 2486	4.1% 2.5% 2.2% 8.1% 2.8% 3.8% 4.2% 15.7% 1.5% 3.6% 2.2% 5.3% 3.2% <b>63.6%</b>	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73] 1.13 [0.96, 1.34] 2.55 [1.44, 4.51] 1.38 [0.96, 1.98] 2.07 [1.33, 3.23] 1.03 [0.77, 1.38] 0.91 [0.60, 1.39] <b>1.38 [1.27, 1.51]</b>	
Arezzo 2008 Baba 2020 Dworkin 2003 Freynhagen 2005 (Fixed) Freynhagen 2005 (Flexed) Suan 2011 Huffman 2015 Liu 2017 Moon 2010 Mu 2018 Richter 2005 (600 mg) Batoh 2011 (300 mg) Bharma 2006 Bmith 2014 Jinik 2014 Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = 40.43, df Fest for overall effect: Z = 7.59	40 38 56 88 83 130 39 58 68 157 32 66 40 49 19 963 f = 14 (P = (P < 0.00 1813 df = 38 (P	85 89 132 141 206 101 111 162 314 82 134 82 98 50 <b>1869</b> = 0.000 001) <b>3784</b> < 0.000	$\begin{array}{c} 37\\ 21\\ 12\\ 12\\ 53\\ 25\\ 33\\ 27\\ 136\\ 13\\ 24\\ 20\\ 45\\ 45\\ 523\\ 2); \  ^2 = 6\\ 782 \end{array}$	88 84 32 33 102 109 78 308 85 67 85 93 108 1459 55% 2486	4.1% 2.5% 2.2% 8.1% 2.8% 3.8% 4.2% 15.7% 1.5% 3.6% 2.2% 5.3% 3.2% <b>63.6%</b>	1.06 [0.76, 1.49] 2.52 [1.68, 3.77] 1.78 [1.12, 2.83] 1.62 [1.01, 2.60] 1.21 [0.98, 1.50] 1.58 [1.04, 2.40] 1.73 [1.23, 2.41] 1.21 [0.85, 1.73] 1.13 [0.96, 1.34] 2.55 [1.44, 4.51] 1.38 [0.96, 1.98] 2.07 [1.33, 3.23] 1.03 [0.77, 1.38] 0.91 [0.60, 1.39] <b>1.38 [1.27, 1.51]</b>	0.01 0.1 1 10 10 Favours placebo Favours pregabalin

#### **Anticonvulsants (Topiramate)**

Figure 6.1: Topiramate versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater

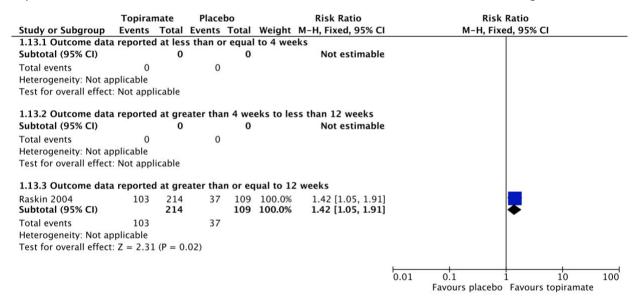
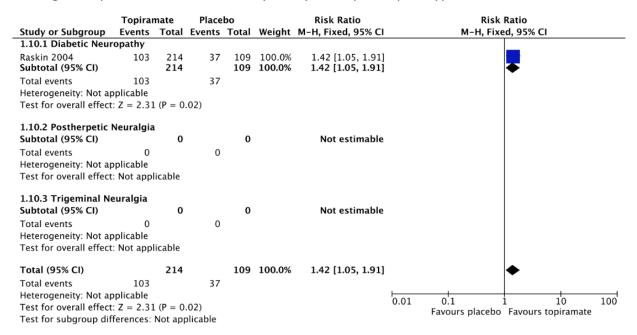


Figure 6.2: Topiramate versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source

	Topirar	nate	Place	bo		<b>Risk Ratio</b>		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M–H, Fixe	ed, 95% CI	
1.11.1 Public Fundin	g									
Subtotal (95% CI)		0		0		Not estimable				
Total events	0		0							
Heterogeneity: Not ap	plicable									
Test for overall effect:	Not appl	icable								
1.11.2 Industry Fund	ling									
Raskin 2004	103	214	37	109	100.0%	1.42 [1.05, 1.91]				
Subtotal (95% CI)		214		109	100.0%	1.42 [1.05, 1.91]			◆	
Total events	103		37							
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 2.31	(P = 0)	.02)							
Total (95% CI)		214		109	100.0%	1.42 [1.05, 1.91]			◆	
Total events	103		37							
Heterogeneity: Not ap	plicable						0.01	0.1	1 10	100
Test for overall effect:	Z = 2.31	(P = 0)	.02)				0.01		Favours topiramate	100
Test for subgroup diff	ferences:	Not app	olicable					ravours placebo	ravours topramate	

Figure 6.3: Topiramate versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by neuropathic pain type



## Figure 6.4: Topiramate versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size

	Topirar	nate	Place	bo		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95	% CI
1.12.1 Less than or e	qual to 1	50 pat	ients						
Subtotal (95% CI)		0		0		Not estimable			
Total events	0		0						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Not appl	icable							
1.12.2 Greater than 1	L50 patie	nts							
Raskin 2004	103	214	37	109	100.0%	1.42 [1.05, 1.91]			
Subtotal (95% CI)		214		109	100.0%	1.42 [1.05, 1.91]		●	
Total events	103		37						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 2.31	(P = 0)	.02)						
Total (95% CI)		214		109	100.0%	1.42 [1.05, 1.91]		•	
Total events	103		37						
Heterogeneity: Not ap	plicable								10 100
Test for overall effect:	Z = 2.31	(P = 0)	.02)				0.01	0.1 1 Favours placebo Favo	10 100 100
Test for subgroup diff	erences:	Not app	olicable					ravours placebo ravo	urs tophainate

#### Opioids

Figure 7.1: Opioids versus control; Outcome: Proportion of patients with a meaningful response to treatment

	Opioi	ids	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Freeman 2007	90	160	57	153	28.7%	1.51 [1.18, 1.93]	+
Hanna 2008	72	169	51	169	25.1%	1.41 [1.06, 1.88]	
Jensen 2006	37	82	20	77	10.2%	1.74 [1.11, 2.71]	
NCT01124617 2010	29	60	13	31	8.5%	1.15 [0.71, 1.88]	- <b>-</b>
Simpson 2016	46	93	38	93	18.7%	1.21 [0.88, 1.67]	
Zin 2010	15	29	19	33	8.8%	0.90 [0.57, 1.42]	
Total (95% CI)		593		556	100.0%	1.37 [1.19, 1.57]	•
Total events	289		198				
Heterogeneity: Chi <sup>2</sup> =	6.04, df	= 5 (P =	= 0.30); I	$ ^2 = 172$	6		0.01 0.1 1 10 100
Test for overall effect:	Z = 4.43	8 (P < 0	.00001)				Favours placebo Favours opioids

Figure 7.2: Opioids versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater

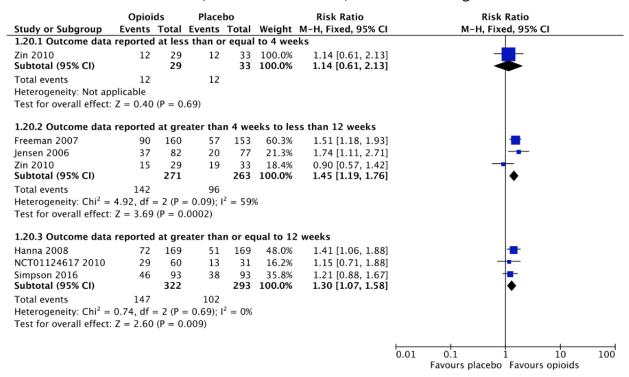


Figure 7.3: Opioids versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source

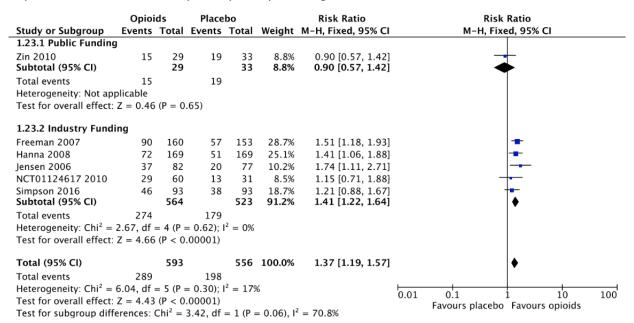


Figure 7.4: Opioids versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by median risk of bias

	Opioi	ds	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M–H, Fixed, 95% Cl
1.22.1 Less than the	median r	isk of	bias sco	re				
Hanna 2008	72	169	51	169	25.1%	1.41 [1.06, 1.88]		
Jensen 2006	37	82	20	77	10.2%	1.74 [1.11, 2.71]		
Zin 2010	15	29	19	33	8.8%	0.90 [0.57, 1.42]		-
Subtotal (95% CI)		280		279	44.1%	1.38 [1.12, 1.72]		◆
Total events	124		90					
Heterogeneity: Chi <sup>2</sup> =	4.44, df	= 2 (P =	= 0.11); I	$ ^2 = 55\%$	%			
Test for overall effect:	Z = 2.97	(P=0)	.003)					
1.22.2 Greater than o	r equal t	o the r	nedian r	isk of l	bias scor	e		
Freeman 2007	90	160	57	153	28.7%	1.51 [1.18, 1.93]		-
NCT01124617 2010	29	60	13	31	8.5%	1.15 [0.71, 1.88]		
Simpson 2016	46	93	38	93	18.7%	1.21 [0.88, 1.67]		+=
Subtotal (95% CI)		313		277	55.9%	1.36 [1.13, 1.62]		◆
Total events	165		108					
Heterogeneity: Chi <sup>2</sup> =	1.64, df	= 2 (P =	= 0.44); I	$ ^2 = 0\%$				
Test for overall effect:	Z = 3.29	(P = 0	.0010)					
Total (95% CI)		593		556	100.0%	1.37 [1.19, 1.57]		•
Total events	289		198					
Heterogeneity: Chi <sup>2</sup> =	6.04, df	= 5 (P =	= 0.30); I	$ ^2 = 179$	%		0.01	0.1 1 10 100
Test for overall effect:	Z = 4.43	(P < 0	.00001)				0.01	Favours placebo Favours opioids
Test for subgroup diff	oroncos:	Chi <sup>2</sup> -	0.02 df	_ 1 (D	0.00	2 00/		ravours placebo ravours opiolus

For each study, the risk of bias domain was scored (0=low risk, 1=unclear risk, 2=high risk) and a median was found among all the studies within each intervention. Studies were then divided into two categories: less than the median or greater than or equal to the median. (Higgins 2011)

	Opioi	ds	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.24.1 Diabetic Neuro	opathy						
Freeman 2007	90	160	57	153	28.7%	1.51 [1.18, 1.93]	-
Hanna 2008	72	169	51	169	25.1%	1.41 [1.06, 1.88]	-
Jensen 2006	37	82	20	77	10.2%	1.74 [1.11, 2.71]	
Simpson 2016	46	93	38	93	18.7%	1.21 [0.88, 1.67]	+
Subtotal (95% CI)		504		492	82.8%	1.44 [1.24, 1.68]	♦
Total events	245		166				
Heterogeneity: Chi <sup>2</sup> =	1.97, df	= 3 (P =	= 0.58);	$ ^2 = 0\%$			
Test for overall effect:	Z = 4.69	(P < 0	.00001)				
1.24.2 Postherpetic N	leuralgia						
Subtotal (95% CI)	2	0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not appl	icable					
1.24.3 Trigeminal Ne	uralgia						
Subtotal (95% CI)	<b>,</b>	0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap			-				
Test for overall effect:		icable					
1.24.4 Mixed Populat	ion						
NCT01124617 2010	29	60	13	31	8.5%	1.15 [0.71, 1.88]	_ <b>_</b>
Zin 2010	15	29	19		8.8%	0.90 [0.57, 1.42]	_ <b>_</b>
Subtotal (95% CI)	10	89	20	64	17.2%	1.02 [0.73, 1.43]	
Total events	44		32				Ī
Heterogeneity: Chi <sup>2</sup> =	0.54, df	= 1 (P =	= 0.46):	$ ^2 = 0\%$			
Test for overall effect:	Z = 0.13	(P = 0	.89)				
Total (95% CI)		593		556	100.0%	1.37 [1.19, 1.57]	•
Total events	289		198				
Heterogeneity: $Chi^2 =$		= 5 (P =		$ ^2 = 179$	6		
Test for overall effect:	, ,				-		0.01 0.1 1 10 10 Favours placebo Favours opioids
		·· · · ·	3.30, df				

Figure 7.5: Opioids versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by neuropathic pain type

Figure 7.6: Opioids versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size

	Opioid	s	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
1.21.1 Less than or e	qual to 15	50 pat	ients				
NCT01124617 2010	29	60	13	31	8.5%	1.15 [0.71, 1.88]	- <b>-</b>
Zin 2010	15	29	19	33	8.8%	0.90 [0.57, 1.42]	
Subtotal (95% CI)		89		64	17.2%	1.02 [0.73, 1.43]	<b>•</b>
Total events	44		32				
Heterogeneity: Chi <sup>2</sup> =	0.54, df =	: 1 (P =	= 0.46); I	$^{2} = 0\%$			
Test for overall effect:	Z = 0.13	(P=0.	.89)				
1.21.2 Greater than 1	150 patien	ts					
Freeman 2007	90	160	57	153	28.7%	1.51 [1.18, 1.93]	-
Hanna 2008	72	169	51	169	25.1%	1.41 [1.06, 1.88]	+
Jensen 2006	37	82	20	77	10.2%	1.74 [1.11, 2.71]	
Simpson 2016	46	93	38	93	18.7%	1.21 [0.88, 1.67]	<b>+-</b> -
Subtotal (95% CI)		504		492	82.8%	1.44 [1.24, 1.68]	◆
Total events	245		166				
Heterogeneity: Chi <sup>2</sup> =	1.97, df =	: 3 (P =	= 0.58); l	$^{2} = 0\%$			
Test for overall effect:	Z = 4.69	(P < 0.	.00001)				
Total (95% CI)		593		556	100.0%	1.37 [1.19, 1.57]	•
Total events	289		198				
Heterogeneity: Chi <sup>2</sup> =	6.04, df =	5 (P =	= 0.30); I	$^{2} = 179$	6		0.01 0.1 1 10 100
Test for overall effect:	Z = 4.43	(P < 0.	.00001)				Favours placebo Favours opioids
Test for subgroup diff	erences: C	$hi^2 = 3$	3.30, df =	= 1 (P =	= 0.07), l <sup>2</sup>	$^{2} = 69.7\%$	ravours placebo ravours opiolus

## Rubefacients (Capsaicin)

Figure 8.1: Rubefacients versus control; Outcome: Proportion of patients with a meaningful response to treatment

	Rubefa	cient	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Backonja 2008	91	205	69	197	18.3%	1.27 [0.99, 1.62]	-
Bernstein 1989	9	16	1	16	0.3%	9.00 [1.29, 63.02]	· · · · · · · · · · · · · · · · · · ·
Capsaicin Study Group 1992	52	138	44	139	11.4%	1.19 [0.86, 1.65]	
Irving 2011	100	212	71	204	18.8%	1.36 [1.07, 1.72]	+
Moon 2017 (cream)	6	16	0	4	0.2%	3.82 [0.26, 56.78]	
Moon 2017a (low dose)	3	16	1	5	0.4%	0.94 [0.12, 7.13]	
Moon 2017b (high dose)	1	14	0	5	0.2%	1.20 [0.06, 25.53]	
Simpson 2017	76	186	58	183	15.2%	1.29 [0.98, 1.70]	-
Tandan 1992	7	11	2	11	0.5%	3.50 [0.92, 13.24]	
Vinik 2015	107	157	32	77	11.1%	1.64 [1.23, 2.18]	-
Vinik 2015a	105	156	32	78	11.1%	1.64 [1.23, 2.19]	-
Watson 1993	28	74	14	69	3.8%	1.86 [1.07, 3.24]	
Webster 2010	50	102	26	53	8.9%	1.00 [0.71, 1.40]	+
Total (95% CI)		1303		1041	100.0%	1.40 [1.26, 1.55]	•
Total events	635		350				
Heterogeneity: $Chi^2 = 15.19$ ,	df = 12 (P	= 0.23	); $I^2 = 21$	%			0.01 0.1 1 10 100
Test for overall effect: $Z = 6.3$	7 (P < 0.0	00001)					Favours control Favours rubefacients

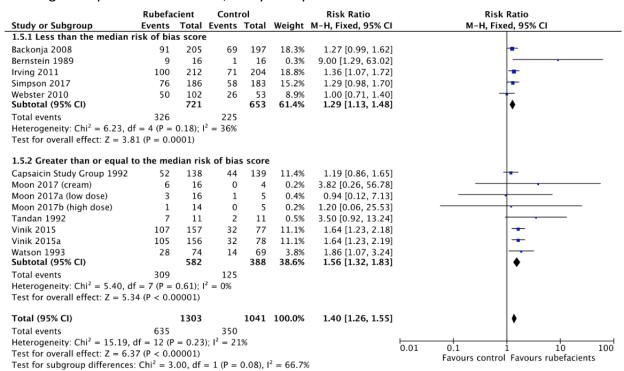
Figure 8.2: Rubefacients versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater

tudy or Subgroup						M-H, Fixed, 95% CI	M–H, Fixed, 95% CI
.8.1 Outcome data reported			-				
ernstein 1989	7	16	3	16	18.2%	2.33 [0.73, 7.45]	
Vatson 1993	20	74	13	69	81.8%	1.43 [0.77, 2.66]	
ubtotal (95% CI)		90		85	100.0%	1.60 [0.93, 2.75]	-
otal events	27		16				
leterogeneity: Chi <sup>2</sup> = 0.53, di			$^{2} = 0\%$				
est for overall effect: Z = 1.7	'0 (P = 0.0)	9)					
.8.2 Outcome data reported	l at greate	er than	4 weeks	to les	s than 12	2 weeks	
ackonja 2008	87	205	63	197	24.8%	1.33 [1.02, 1.72]	-
Sernstein 1989	9	16	1	16	0.4%	9.00 [1.29, 63.02]	
Capsaicin Study Group 1992	52	138	44	139	16.9%	1.19 [0.86, 1.65]	+ <b>-</b> -
rving 2011	98	212	69	204	27.1%	1.37 [1.07, 1.74]	-
Aoon 2017 (cream)	6	16	0	4	0.3%	3.82 [0.26, 56.78]	
/loon 2017a (low dose)	3	16	1	5	0.6%	0.94 [0.12, 7.13]	
/loon 2017b (high dose)	1	14	0	5	0.3%	1.20 [0.06, 25.53]	
impson 2017	74	186	60	183	23.3%	1.21 [0.92, 1.59]	
andan 1992	7	11	2	11	0.8%	3.50 [0.92, 13.24]	
Vatson 1993	28	74	14	69	5.6%	1.86 [1.07, 3.24]	
ubtotal (95% CI)		888		833	100.0%	1.37 [1.20, 1.56]	•
otal events	365		254				
leterogeneity: Chi <sup>2</sup> = 8.93, di	f = 9 (P =	0.44); I	$^{2} = 0\%$				
est for overall effect: $Z = 4.7$	7 (P < 0.0	0001)					
.8.3 Outcome data reported	l at greate	er than	or equa	to 12	weeks		
lackonja 2008	91	205	69	197	21.9%	1.27 [0.99, 1.62]	-
rving 2011	100	212	71	204	22.5%	1.36 [1.07, 1.72]	-
impson 2017	76	186	58	183	18.2%	1.29 [0.98, 1.70]	
/inik 2015	107	157	32	77	13.4%	1.64 [1.23, 2.18]	-
/inik 2015a	105	156	32	78	13.3%	1.64 [1.23, 2.19]	
Vebster 2010	50	102	26	53	10.7%	1.00 [0.71, 1.40]	+
ubtotal (95% CI)		1018		792	100.0%	1.36 [1.22, 1.52]	•
otal events	529		288				
leterogeneity: Chi <sup>2</sup> = 6.94, di			$^{2} = 28\%$				
est for overall effect: $Z = 5.4$	6 (P < 0.0	0001)					

Figure 8.3: Rubefacients versus control; Subgroup analysis: Proportion of patients with a
meaningful response to treatment, analyzed by study funding source

	Rubefa	cient	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.9.1 Public Funding							
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not app	licable						
1.9.2 Industry Funding							
Backonja 2008	91	205	69	197	18.3%	1.27 [0.99, 1.62]	-
Bernstein 1989	9	16	1	16	0.3%	9.00 [1.29, 63.02]	
Capsaicin Study Group 1992	52	138	44	139	11.4%	1.19 [0.86, 1.65]	+
Irving 2011	100	212	71	204	18.8%	1.36 [1.07, 1.72]	-
Moon 2017 (cream)	6	16	0	4	0.2%	3.82 [0.26, 56.78]	
Moon 2017a (low dose)	3	16	1	5	0.4%	0.94 [0.12, 7.13]	
Moon 2017b (high dose)	1	14	0	5	0.2%	1.20 [0.06, 25.53]	
Simpson 2017	76	186	58	183	15.2%	1.29 [0.98, 1.70]	-
Tandan 1992	7	11	2	11	0.5%	3.50 [0.92, 13.24]	
Vinik 2015	107	157	32	77	11.1%	1.64 [1.23, 2.18]	
Vinik 2015a	105	156	32	78	11.1%	1.64 [1.23, 2.19]	
Watson 1993	28	74	14	69	3.8%	1.86 [1.07, 3.24]	
Webster 2010	50	102	26	53	8.9%	1.00 [0.71, 1.40]	<del></del>
Subtotal (95% CI)		1303		1041	100.0%	1.40 [1.26, 1.55]	•
Total events	635		350				
Heterogeneity: $Chi^2 = 15.19$ , d			); $I^2 = 21$	.%			
Test for overall effect: $Z = 6.3$	7 (P < 0.0	0001)					
Total (95% CI)		1303		1041	100.0%	1.40 [1.26, 1.55]	•
Total events	635		350				
Heterogeneity: $Chi^2 = 15.19$ , d	df = 12 (P	= 0.23	); $I^2 = 21$	%			0.01 0.1 1 10 1
Test for overall effect: $Z = 6.3$	7 (P < 0.0	0001)					Favours control Favours rubefacients
Test for subgroup differences:	Not appl	icable					avours control ravours rubelacients

Figure 8.4: Rubefacients versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by median risk of bias



For each study, the risk of bias domain was scored (0=low risk, 1=unclear risk, 2=high risk) and a median was found

among all the studies within each intervention. Studies were then divided into two categories: less than the median or greater than or equal to the median. (Higgins 2011)

Figure 8.5: Rubefacients versus control; Subgroup analysis: Proportion of patients with a
meaningful response to treatment, analyzed by neuropathic pain type

	Rubefa		Cont			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.10.1 Diabetic Neuropathy							
Capsaicin Study Group 1992	52	138	44	139	11.4%	1.19 [0.86, 1.65]	<b>+-</b>
Simpson 2017	76	186	58	183	15.2%	1.29 [0.98, 1.70]	-
Tandan 1992	7	11	2	11	0.5%	3.50 [0.92, 13.24]	· · · · ·
Vinik 2015	107	157	32	77	11.1%	1.64 [1.23, 2.18]	-
Vinik 2015a	105	156	32	78	11.1%	1.64 [1.23, 2.19]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)		648		488	49.3%	1.45 [1.25, 1.67]	♦
Total events	347		168				
Heterogeneity: Chi <sup>2</sup> = 5.23, df	<sup>2</sup> = 4 (P =	0.26); I	$^{2} = 23\%$				
Test for overall effect: $Z = 5.0$	2 (P < 0.0	0001)					
1.10.2 Postherpetic Neuralgi	a						
Backonja 2008	91	205	69	197	18.3%	1.27 [0.99, 1.62]	-
Bernstein 1989	9	16	1	16	0.3%	9.00 [1.29, 63.02]	
Irving 2011	100	212	71	204	18.8%	1.36 [1.07, 1.72]	-
Moon 2017 (cream)	6	16	0	4	0.2%	3.82 [0.26, 56.78]	
Moon 2017a (low dose)	3	16	1	5	0.4%	0.94 [0.12, 7.13]	
Moon 2017b (high dose)	1	14	0	5	0.2%	1.20 [0.06, 25.53]	
Watson 1993	28	74	14	69	3.8%	1.86 [1.07, 3.24]	
Webster 2010	50	102	26	53	8.9%	1.00 [0.71, 1.40]	+
Subtotal (95% CI)		655		553	50.7%	1.34 [1.16, 1.55]	◆
Total events	288		182				
Heterogeneity: Chi <sup>2</sup> = 8.90, df			$^{2} = 21\%$				
Test for overall effect: Z = 3.9	8 (P < 0.0	0001)					
1.10.3 Trigeminal Neuralgia							
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not app	licable						
Total (95% CI)		1303		1041	100.0%	1.40 [1.26, 1.55]	•
Total events	635		350				
Heterogeneity: Chi <sup>2</sup> = 15.19, o	df = 12 (P)	= 0.23	); $I^2 = 21$	%			0.01 0.1 1 10 10
Test for overall effect: $Z = 6.3$	7 (P < 0.0	00001)					0.01 0.1 1 10 10 Favours control Favours rubefacients
Test for subgroup differences	Ch:2 0	F1 df	1 (D	0.40	2 00/		ravours control ravours ruberacients

	Rubefa	cient	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
1.20.1 Frequent Application	(Creams/	Low Do	se Patch	ıes)			
Bernstein 1989	9	16	1	16	0.3%	9.00 [1.29, 63.02]	· · · · · · · · · · · · · · · · · · ·
Capsaicin Study Group 1992	52	138	44	139	11.4%	1.19 [0.86, 1.65]	
Moon 2017 (cream)	6	16	0	4	0.2%	3.82 [0.26, 56.78]	
Moon 2017a (low dose)	3	16	1	5	0.4%	0.94 [0.12, 7.13]	
Moon 2017b (high dose)	1	14	0	5	0.2%	1.20 [0.06, 25.53]	
Fandan 1992	7	11	2	11	0.5%	3.50 [0.92, 13.24]	
Vatson 1993	28	74	14	69	3.8%	1.86 [1.07, 3.24]	
Subtotal (95% CI)		285		249	16.7%	1.56 [1.20, 2.03]	•
Fotal events	106		62				
leterogeneity: Chi <sup>2</sup> = 8.29, d	f = 6 (P =	0.22); l <sup>2</sup>	2 = 28%				
Test for overall effect: $Z = 3.3$	80 (P = 0.0)	010)					
1.20.2 Less Frequent Applic	ation (Hig	h Poten	cy Patcł	nes)			
Backonja 2008	91	205	. 69	197	18.3%	1.27 [0.99, 1.62]	
rving 2011	100	212	71	204	18.8%	1.36 [1.07, 1.72]	
Simpson 2017	76	186	58	183	15.2%	1.29 [0.98, 1.70]	-
/inik 2015	107	157	32	77	11.1%	1.64 [1.23, 2.18]	-
/inik 2015a	105	156	32	78	11.1%	1.64 [1.23, 2.19]	
Vebster 2010	50	102	26	53	8.9%	1.00 [0.71, 1.40]	
Subtotal (95% CI)		1018		792	83.3%	1.36 [1.22, 1.52]	•
Fotal events	529		288				
Heterogeneity: Chi <sup>2</sup> = 6.94, d	f = 5 (P =	0.23); l <sup>2</sup>	2 = 28%				
Test for overall effect: $Z = 5.4$	16 (P < 0.0	0001)					
Fotal (95% CI)		1303		1041	100.0%	1.40 [1.26, 1.55]	•
Fotal events	635		350			- / -	
Heterogeneity: $Chi^2 = 15.19$ ,		= 0.23		%			H H
Test for overall effect: $Z = 6.3$			,				0.01 0.1 1 10 1
Test for subgroup differences			1 (5		2 00/		Favours control Favours rubefacients

Figure 8.6: Rubefacients versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by drug type

# Figure 8.7: Rubefacients versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size

Events					Risk Ratio	
Licito	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
50 patier	ts					
9	16	1	16	0.3%	9.00 [1.29, 63.02]	
6	16	0	4	0.2%	3.82 [0.26, 56.78]	
3	16	1	5	0.4%	0.94 [0.12, 7.13]	
1	14	0	5	0.2%	1.20 [0.06, 25.53]	
7	11	2	11	0.5%	3.50 [0.92, 13.24]	
28	74	14	69	3.8%	1.86 [1.07, 3.24]	
	147		110	5.3%	2.35 [1.49, 3.73]	•
54		18				
f = 5 (P =	0.56); I	$^{2} = 0\%$				
5 (P = 0.0)	003)					
nts						
91	205	69	197	18.3%	1.27 [0.99, 1.62]	-
52	138	44	139	11.4%	1.19 [0.86, 1.65]	<b>+-</b>
100	212	71	204	18.8%	1.36 [1.07, 1.72]	
76	186	58	183	15.2%	1.29 [0.98, 1.70]	
107	157	32	77	11.1%	1.64 [1.23, 2.18]	-
105	156	32	78	11.1%	1.64 [1.23, 2.19]	
50		26				<u>+</u> .
	1156		931	94.7%	1.34 [1.21, 1.49]	•
		332				
		$^{2} = 20\%$				
8 (P < 0.0	0001)					
	1303		1041	100.0%	1.40 [1.26, 1.55]	•
635		350				· · · · · · · · · · · · · · · · · · ·
	= 0.23		%			· · · · · · · · · · · · · · · · · · ·
		,, - 21	.70			0.01 0.1 1 10 10
	,	– 1 (P –	0 0 2) 1	$^{2} - 81.79$	4	Favours control Favours rubefacients
	$\begin{array}{c} 6\\ 3\\ 1\\ 7\\ 28\\ 54\\ 5=5 \ (P=0.0\\ 0\\ 107\\ 105\\ 50\\ 581\\ f=6 \ (P=8\\ 8 \ (P<0.0\\ 635\\ 0\\ f=12 \ (P<0.0\\ 0\\ 7 \ (P<0.0\\ 0\\ 7 \ (P<0.0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0$	$\begin{array}{c} 6 & 16 \\ 3 & 16 \\ 1 & 14 \\ 7 & 11 \\ 28 & 74 \\ 54 \\ 5 & (P = 0.56); 1 \\ 5 & (P = 0.0003) \\ \\ \text{mts} \\ \begin{array}{c} 91 & 205 \\ 52 & 138 \\ 100 & 212 \\ 76 & 186 \\ 107 & 157 \\ 105 & 156 \\ 50 & 102 \\ 1156 \\ 581 \\ \hline 586 \\ 8 & (P < 0.0001) \\ \end{array}$	$\begin{array}{cccccccc} 6 & 16 & 0 \\ 3 & 16 & 1 \\ 1 & 14 & 0 \\ 7 & 11 & 2 \\ 28 & 74 & 14 \\ 147 & & & \\ 54 & & 18 \\ \hline 5 & (P = 0.56); \ l^2 = 0\% \\ 5 & (P = 0.0003) & & \\ \hline 5 & (P = 0.0003) & & \\ \hline 147 & & & \\ 91 & 205 & 69 \\ 52 & 138 & 44 \\ 100 & 212 & 71 \\ 76 & 186 & 32 \\ 100 & 212 & 71 \\ 76 & 186 & 32 \\ 107 & 157 & 32 \\ 105 & 156 & 32 \\ 50 & 102 & 26 \\ \hline 1156 & & \\ 581 & & & 332 \\ \hline 5 & 581 & & & 332 \\ \hline 5 & 581 & & & & 332 \\ \hline 5 & 581 & & & & & \\ 107 & 157 & 32 \\ 105 & 156 & 32 \\ 50 & 102 & 26 \\ \hline 1156 & & & & \\ \hline 581 & & & & & & \\ 581 & & & & & & \\ 581 & & & & & & & \\ 581 & & & & & & & \\ 581 & & & & & & & \\ 581 & & & & & & & \\ 581 & & & & & & & \\ \hline 581 & & & & & & & \\ 583 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 7 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 7 & & & & & & & \\ \hline 6 & & & & & & & \\ \hline 7 & & & & & & & \\ \hline 7 & & & & & \\ 7 & & & & & & \\ \hline 7 & & & & & \\ \hline 7 & & & & & & \\ 7 & & & & & & \\ \hline 7 & & & & & \\ 7 & & & & & \\ 7 & & & & &$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

## SNRIs

Figure 9.1: SNRIs versus control; Outcome: Proportion of patients with a meaningful response to treatment.

	1	Place	00		Risk Ratio	Risk Ratio
Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
30	63	8	22	2.5%	1.31 [0.71, 2.41]	
47	86	8	22	2.7%	1.50 [0.84, 2.70]	+
51	99	8	22	2.7%	1.42 [0.79, 2.54]	+
31	68	9	23	2.8%	1.17 [0.66, 2.06]	- <del> -</del>
74	106	67	109	13.8%	1.14 [0.94, 1.38]	+
127	202	94	202	19.6%	1.35 [1.13, 1.62]	<b>T</b>
46	115	10	38	3.1%	1.52 [0.85, 2.71]	
55	114	10	38	3.1%	1.83 [1.04, 3.23]	
57	113	9	39	2.8%	2.19 [1.20, 3.99]	
79	116	25	58	7.0%	1.58 [1.15, 2.18]	-
74	116	25	58	7.0%	1.48 [1.07, 2.05]	
31	82	14	40	3.9%	1.08 [0.65, 1.79]	+-
46	82	14	41	3.9%	1.64 [1.03, 2.62]	<b>⊢</b>
72	114	22	54	6.2%	1.55 [1.09, 2.20]	
77	112	23	54	6.5%	1.61 [1.16, 2.25]	
47	85	29	84	6.1%	1.60 [1.13, 2.28]	
51	86	30	83	6.4%	1.64 [1.17, 2.29]	-
	1759		987	100.0%	1.45 [1.33, 1.59]	•
995		405				
13.12, d	f = 16	(P = 0.60)	5); I <sup>2</sup> =	0%		0.01 0.1 1 10 10
Z = 8.42	1 (P < 0	).00001)				0.01 0.1 1 10 10 Favours Placebo Favours SNRIs
	30 47 51 31 74 127 46 55 57 79 74 31 46 72 77 47 51 995 13.12, d	30 63 47 86 51 99 31 68 74 106 127 202 46 115 55 114 55 113 79 116 74 116 31 82 46 82 72 114 77 112 47 85 51 86 <b>1759</b> 995 13.12, df = 16	30         63         8           47         86         8           51         99         8           31         68         9           74         106         67           127         202         94           46         115         10           55         114         10           57         113         9           79         116         25           74         116         25           31         82         14           46         82         14           46         82         14           46         82         14           72         114         22           77         112         23           47         85         29           51         86         30           1759         995         405           13.12, df = 16 (P = 0.60         64	30       63       8       22         47       86       8       22         51       99       8       22         31       68       9       23         74       106       67       109         127       202       94       202         46       115       10       38         57       113       9       39         79       116       25       58         74       116       25       58         74       116       25       58         31       82       14       40         46       82       14       41         72       114       22       54         77       112       23       54         47       85       29       84         51       86       30       83         1759       987       995       405	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

Figure 9.2: SNRIs versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater

Study or Subgroup	SNR Events		Placek Events		Weight	Risk Ratio M–H, Fixed, 95% CI		Risk Ratio M-H, Fixed, 95% Cl
1.22.1 Outcome data	reported	d at less	s than o	r equa	l to 4 wee			
Subtotal (95% CI)		0		0		Not estimable		
Total events	0		0					
Heterogeneity: Not ap								
Test for overall effect:	Not appl	licable						
1.22.2 Outcome data	reported	d at gre	ater tha	n 4 we	eks to les	s than 12 weeks		
Rowbotham 2005	31	82	14	40	50.2%	1.08 [0.65, 1.79]		
Rowbotham 2005a	46	82	14	41	49.8%	1.64 [1.03, 2.62]		- <b>-</b> -
Subtotal (95% CI)		164		81	100.0%	1.36 [0.97, 1.91]		•
Total events	77		28					
Heterogeneity: Chi <sup>2</sup> =	,			$^{2} = 30$	%			
Test for overall effect:	Z = 1.77	P = 0.	08)					
1.22.3 Outcome data	reported	d at gre	ater tha	n or e	qual to 12	weeks		
Allen 2014	30	63	8	22	2.7%	1.31 [0.71, 2.41]		+
Allen 2014a	47	86	8	22	2.9%	1.50 [0.84, 2.70]		<b>—</b>
Allen 2014b	51	99	8	22	3.0%	1.42 [0.79, 2.54]		+
Allen 2014c	31	68	9	23	3.0%	1.17 [0.66, 2.06]		- <b>-</b>
Gao 2010	74	106	67	109	15.0%	1.14 [0.94, 1.38]		-
Gao 2014	127	202	94	202	21.3%	1.35 [1.13, 1.62]		+
Goldstein 2005	46	115	10	38	3.4%	1.52 [0.85, 2.71]		<b>—</b>
Goldstein 2005a	55	114	10	38	3.4%	1.83 [1.04, 3.23]		
Goldstein 2005b	57	113	9	39	3.0%	2.19 [1.20, 3.99]		
Raskin 2005	79	116	25	58	7.5%	1.58 [1.15, 2.18]		
Raskin 2005a	74	116	25	58	7.5%	1.48 [1.07, 2.05]		
Wernicke 2006	72	114	22	54	6.8%	1.55 [1.09, 2.20]		
Wernicke 2006a	77	112	23	54	7.0%	1.61 [1.16, 2.25]		-
Yasuda 2011	47	85	29	84	6.6%	1.60 [1.13, 2.28]		
Yasuda 2011a	51	86	30	83	6.9%	1.64 [1.17, 2.29]		
Subtotal (95% CI)		1595		906	100.0%	1.46 [1.34, 1.60]		♦
Total events	918	-	377					
Heterogeneity: Chi <sup>2</sup> =				); I <sup>2</sup> =	0%			
Test for overall effect:	Z = 8.26	5 (P < 0.	00001)					
							0.01	
							0.01	Favours placebo Favours SNRIs

Figure 9.3: SNRIs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source

	SNR		Place			Risk Ratio	Risk Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
1.26.1 Public Fundin	ig						
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not a							
Test for overall effect	: Not app	licable					
1.26.2 Industry Fund	ding						
Allen 2014	30	63	8	22	2.5%	1.31 [0.71, 2.41]	
Allen 2014a	47	86	8	22	2.7%	1.50 [0.84, 2.70]	
Allen 2014b	51	99	8	22	2.7%	1.42 [0.79, 2.54]	+
Allen 2014c	31	68	9	23	2.8%	1.17 [0.66, 2.06]	
Gao 2010	74	106	67	109	13.8%	1.14 [0.94, 1.38]	-
Gao 2014	127	202	94	202	19.6%	1.35 [1.13, 1.62]	+
Goldstein 2005	46	115	10	38	3.1%	1.52 [0.85, 2.71]	
Goldstein 2005a	55	114	10	38	3.1%	1.83 [1.04, 3.23]	
Goldstein 2005b	57	113	9	39	2.8%	2.19 [1.20, 3.99]	
Raskin 2005	79	116	25	58	7.0%	1.58 [1.15, 2.18]	
Raskin 2005a	74	116	25	58	7.0%	1.48 [1.07, 2.05]	
Rowbotham 2005	31	82	14	40	3.9%	1.08 [0.65, 1.79]	
Rowbotham 2005a	46	82	14	41	3.9%	1.64 [1.03, 2.62]	
Wernicke 2006	72	114	22	54	6.2%	1.55 [1.09, 2.20]	
Wernicke 2006a	77	112	23	54	6.5%	1.61 [1.16, 2.25]	
Yasuda 2011	47	85	29	84	6.1%	1.60 [1.13, 2.28]	
Yasuda 2011a	51	86	30	83	6.4%		
Subtotal (95% CI)		1759		987	100.0%	1.45 [1.33, 1.59]	♦
Total events	995		405				
Heterogeneity: Chi <sup>2</sup> =					0%		
Test for overall effect	z = 8.42	1 (P < 0	).00001)				
Total (95% CI)		1759		987	100.0%	1.45 [1.33, 1.59]	•
Total events	995		405				
Heterogeneity: Chi <sup>2</sup> =	= 13.12, d	lf = 16	(P = 0.6)	6); I <sup>2</sup> =	0%		0.01 0.1 1 10 1
Test for overall effect	: Z = 8.4	1 (P < 0	).00001)				Favours Placebo Favours SNRIs
Test for subgroup dif	ferences:	Not ap	plicable				ravouis riacebo ravouis SINNIS

	SNR	1	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
1.4.2 Less than the	median ri	sk of b	ias scor	e			
Allen 2014	30	63	8	22	2.5%	1.31 [0.71, 2.41]	- <b>-</b>
Allen 2014a	47	86	8	22	2.7%	1.50 [0.84, 2.70]	+
Allen 2014b	51	99	8	22	2.7%	1.42 [0.79, 2.54]	+
Allen 2014c	31	68	9	23	2.8%	1.17 [0.66, 2.06]	-+
Goldstein 2005	46	115	10	38	3.1%	1.52 [0.85, 2.71]	
Goldstein 2005a	55	114	10	38	3.1%	1.83 [1.04, 3.23]	
Goldstein 2005b	57	113	9	39	2.8%	2.19 [1.20, 3.99]	
Raskin 2005	79	116	25	58	7.0%	1.58 [1.15, 2.18]	
Raskin 2005a	74	116	25	58	7.0%	1.48 [1.07, 2.05]	
Wernicke 2006	72	114	22	54	6.2%	1.55 [1.09, 2.20]	
Wernicke 2006a	77	112	23	54	6.5%	1.61 [1.16, 2.25]	-
Subtotal (95% CI)		1116		428	46.3%	1.56 [1.37, 1.79]	•
Total events	619		157				
Heterogeneity: Chi <sup>2</sup> =	= 3.12. df	= 10 (	P = 0.98	$ I^2 = 0$	%		
Test for overall effect	t: Z = 6.50	) (P < 0	.00001)				
1.4.3 Greater than o	r equal to	the m	edian ri	sk of b	ias score		
	<b>r equal to</b> 74	<b>the m</b> 106	edian ri 67	<b>sk of b</b> 109	<b>ias score</b> 13.8%	1.14 [0.94, 1.38]	-
Gao 2010							-
Gao 2010 Gao 2014	74	106	67	109	13.8%	1.14 [0.94, 1.38]	-
Gao 2010 Gao 2014 Rowbotham 2005	74 127	106 202	67 94	109 202	13.8% 19.6%	1.14 [0.94, 1.38] 1.35 [1.13, 1.62]	*
Gao 2010 Gao 2014 Rowbotham 2005 Rowbotham 2005a	74 127 31	106 202 82	67 94 14	109 202 40	13.8% 19.6% 3.9%	1.14 [0.94, 1.38] 1.35 [1.13, 1.62] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62]	-
Gao 2010 Gao 2014 Rowbotham 2005 Rowbotham 2005a Yasuda 2011	74 127 31 46	106 202 82 82	67 94 14 14	109 202 40 41	13.8% 19.6% 3.9% 3.9%	1.14 [0.94, 1.38] 1.35 [1.13, 1.62] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62] 1.60 [1.13, 2.28]	• • •
Gao 2010 Gao 2014 Rowbotham 2005 Rowbotham 2005a Yasuda 2011 Yasuda 2011a	74 127 31 46 47	106 202 82 82 85	67 94 14 14 29	109 202 40 41 84	13.8% 19.6% 3.9% 3.9% 6.1%	1.14 [0.94, 1.38] 1.35 [1.13, 1.62] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62]	<b>■</b> <b>■</b> <b>■</b> <b>■</b> <b>■</b> <b>■</b> <b>■</b> <b>■</b>
Gao 2010 Gao 2014 Rowbotham 2005 Rowbotham 2005a Yasuda 2011 Yasuda 2011a <b>Subtotal (95% CI)</b>	74 127 31 46 47	106 202 82 82 85 85	67 94 14 14 29	109 202 40 41 84 83	13.8% 19.6% 3.9% 3.9% 6.1% 6.4%	1.14 [0.94, 1.38] 1.35 [1.13, 1.62] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62] 1.60 [1.13, 2.28] 1.64 [1.17, 2.29]	* * * *
Gao 2010 Gao 2014 Rowbotham 2005 Rowbotham 2005a Yasuda 2011 Yasuda 2011a <b>Subtotal (95% CI)</b> Total events	74 127 31 46 47 51 376	106 202 82 82 85 86 <b>643</b>	67 94 14 14 29 30 248	109 202 40 41 84 83 <b>559</b>	13.8% 19.6% 3.9% 3.9% 6.1% 6.4% <b>53.7%</b>	1.14 [0.94, 1.38] 1.35 [1.13, 1.62] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62] 1.60 [1.13, 2.28] 1.64 [1.17, 2.29]	* * 
1.4.3 Greater than o Gao 2010 Gao 2014 Rowbotham 2005 Rowbotham 2005a Yasuda 2011 Yasuda 2011a Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect	74 127 31 46 47 51 376 = 6.77, df	106 202 82 82 85 86 <b>643</b> = 5 (P	67 94 14 14 29 30 248 = 0.24);	109 202 40 41 84 83 <b>559</b>	13.8% 19.6% 3.9% 3.9% 6.1% 6.4% <b>53.7%</b>	1.14 [0.94, 1.38] 1.35 [1.13, 1.62] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62] 1.60 [1.13, 2.28] 1.64 [1.17, 2.29]	* * * *
Gao 2010 Gao 2014 Rowbotham 2005 Rowbotham 2005a Yasuda 2011 Yasuda 2011a <b>Subtotal (95% CI)</b> Total events Heterogeneity: Chi <sup>2</sup> =	74 127 31 46 47 51 376 = 6.77, df	106 202 82 82 85 86 <b>643</b> = 5 (P	67 94 14 14 29 30 248 = 0.24);	109 202 40 41 84 83 <b>559</b>	13.8% 19.6% 3.9% 3.9% 6.1% 6.4% <b>53.7%</b>	1.14 [0.94, 1.38] 1.35 [1.13, 1.62] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62] 1.60 [1.13, 2.28] 1.64 [1.17, 2.29]	* * * *
Gao 2010 Gao 2014 Rowbotham 2005 Rowbotham 2005a Yasuda 2011 Yasuda 2011a <b>Subtotal (95% CI)</b> Total events	74 127 31 46 47 51 376 = 6.77, df	106 202 82 82 85 86 <b>643</b> = 5 (P	67 94 14 14 29 30 248 = 0.24);	$109  202  40  41  84  83  559  I^2 = 26$	13.8% 19.6% 3.9% 3.9% 6.1% 6.4% <b>53.7%</b>	1.14 [0.94, 1.38] 1.35 [1.13, 1.62] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62] 1.60 [1.13, 2.28] 1.64 [1.17, 2.29]	* * * *
Gao 2010 Gao 2014 Rowbotham 2005 Rowbotham 2005a Yasuda 2011 Yasuda 2011a <b>Subtotal (95% CI)</b> Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect	74 127 31 46 47 51 376 = 6.77, df	106 202 82 85 86 <b>643</b> = 5 (P 4 (P < 0	67 94 14 14 29 30 248 = 0.24);	$109  202  40  41  84  83  559  I^2 = 26$	13.8% 19.6% 3.9% 6.1% 6.4% 53.7%	1.14 [0.94, 1.38] 1.35 [1.13, 1.62] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62] 1.60 [1.13, 2.28] 1.64 [1.17, 2.29] <b>1.36 [1.21, 1.52]</b>	• • •
Gao 2010 Gao 2014 Rowbotham 2005 Rowbotham 2005a Yasuda 2011 Yasuda 2011a <b>Subtotal (95% CI)</b> Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect <b>Total (95% CI)</b> Total events	74 127 31 46 47 51 376 = 6.77, df t: Z = 5.34 995	106 202 82 85 86 643 = 5 (P 4 (P < C 1759	67 94 14 14 29 30 248 = 0.24); 0.00001) 405	$109202404184559 ^2 = 26987$	13.8% 19.6% 3.9% 3.9% 6.1% 6.4% 53.7%	1.14 [0.94, 1.38] 1.35 [1.13, 1.62] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62] 1.60 [1.13, 2.28] 1.64 [1.17, 2.29] <b>1.36 [1.21, 1.52]</b>	
Gao 2010 Gao 2014 Rowbotham 2005 Rowbotham 2005a Yasuda 2011 Yasuda 2011a <b>Subtotal (95% CI)</b> Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect <b>Total (95% CI)</b>	74 127 31 46 47 51 376 = 6.77, df t: Z = 5.34 995 = 13.12, d	106 202 82 85 86 <b>643</b> = 5 (P 4 (P < C <b>1759</b> f = 16	67 94 14 14 29 30 248 = 0.24); 0.00001) 405 (P = 0.66	$109202404184559 ^2 = 26987$	13.8% 19.6% 3.9% 3.9% 6.1% 6.4% 53.7%	1.14 [0.94, 1.38] 1.35 [1.13, 1.62] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62] 1.60 [1.13, 2.28] 1.64 [1.17, 2.29] <b>1.36 [1.21, 1.52]</b>	0.01 0.1 1 10 1 Favours Placebo Favours SNRIs

Figure 9.4: SNRIs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by median risk of bias

For each study, the risk of bias domain was scored (0=low risk, 1=unclear risk, 2=high risk) and a median was found among all the studies within each intervention. Studies were then divided into two categories: less than the median or greater than or equal to the median. (Higgins 2011)

	SNR		Place			Risk Ratio	Risk Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.27.1 Diabetic Neur	opathy						
Allen 2014	30	63	8	22	2.5%	1.31 [0.71, 2.41]	
Allen 2014a	47	86	8	22	2.7%	1.50 [0.84, 2.70]	+
Allen 2014b	51	99	8	22	2.7%	1.42 [0.79, 2.54]	
Allen 2014c	31	68	9	23	2.8%	1.17 [0.66, 2.06]	
Gao 2010	74	106	67	109	13.8%	1.14 [0.94, 1.38]	-
Gao 2014	127	202	94	202	19.6%	1.35 [1.13, 1.62]	+
Goldstein 2005	46	115	10	38	3.1%	1.52 [0.85, 2.71]	<b>—</b>
Goldstein 2005a	55	114	10	38	3.1%	1.83 [1.04, 3.23]	
Goldstein 2005b	57	113	9	39	2.8%	2.19 [1.20, 3.99]	
Raskin 2005	79	116	25	58	7.0%	1.58 [1.15, 2.18]	
Raskin 2005a	74	116	25	58	7.0%	1.48 [1.07, 2.05]	
Rowbotham 2005	31	82	14	40	3.9%	1.08 [0.65, 1.79]	_ <b>_</b>
Rowbotham 2005a	46	82	14	41	3.9%	1.64 [1.03, 2.62]	_ <b>_</b> _
Wernicke 2006	72	114	22	54	6.2%	1.55 [1.09, 2.20]	
Wernicke 2006a	77	112	23	54	6.5%	1.61 [1.16, 2.25]	
Yasuda 2011	47	85	29	84	6.1%	1.60 [1.13, 2.28]	- <b>-</b> -
Yasuda 2011a	51	86	30	83	6.4%	1.64 [1.17, 2.29]	
Subtotal (95% CI)		1759		987	100.0%	1.45 [1.33, 1.59]	♦
Total events	995		405				
Heterogeneity: Chi <sup>2</sup> =	13.12, d	f = 16	(P = 0.66)	5); $I^2 =$	0%		
Test for overall effect:	Z = 8.41	L (P < 0	.00001)				
1.27.2 Postherpetic N	Neuralgia	ı					
Subtotal (95% CI)	•	0		0		Not estimable	
, ,	0		0	0		Not estimable	
Total events	-		0	0		Not estimable	
, , ,	plicable	0	0	0		Not estimable	
Total events Heterogeneity: Not ap	plicable Not app	0	0	0		Not estimable	
Total events Heterogeneity: Not ap Test for overall effect:	plicable Not app	0	0	0		Not estimable Not estimable	
Total events Heterogeneity: Not ap Test for overall effect: 1.27.3 Trigeminal Ne Subtotal (95% CI)	plicable Not app	<b>0</b> licable	0	_			
Total events Heterogeneity: Not ap Test for overall effect: 1.27.3 Trigeminal Ne Subtotal (95% CI) Total events	plicable : Not app euralgia 0	<b>0</b> licable	_	_			
Total events Heterogeneity: Not ap Test for overall effect: 1.27.3 Trigeminal Ne Subtotal (95% CI)	plicable Not app euralgia 0 plicable	0 licable 0	_	_			
Total events Heterogeneity: Not ap Test for overall effect: <b>1.27.3 Trigeminal Ne</b> <b>Subtotal (95% CI)</b> Total events Heterogeneity: Not ap Test for overall effect:	plicable Not app euralgia 0 plicable	0 licable 0	_	0	100.0%	Not estimable	
Total events Heterogeneity: Not ap Test for overall effect: <b>1.27.3 Trigeminal Ne</b> <b>Subtotal (95% CI)</b> Total events Heterogeneity: Not ap Test for overall effect: <b>Total (95% CI)</b>	oplicable : Not app euralgia 0 oplicable : Not app	0 licable 0 licable	0	0	100.0%		•
Total events Heterogeneity: Not ap Test for overall effect: <b>1.27.3 Trigeminal Ne</b> <b>Subtotal (95% Cl)</b> Total events Heterogeneity: Not ap Test for overall effect: <b>Total (95% Cl)</b> Total events	pplicable : Not app euralgia 0 pplicable : Not app 995	0 licable 0 licable 1759	0	0 987		Not estimable	
Total events Heterogeneity: Not ap Test for overall effect: <b>1.27.3 Trigeminal Ne</b> <b>Subtotal (95% CI)</b> Total events Heterogeneity: Not ap Test for overall effect: <b>Total (95% CI)</b>	pplicable Not app euralgia 0 pplicable Not app 995 13.12, d	0 licable licable 1759 f = 16	0 405 (P = 0.66	0 987		Not estimable	0.01 0.1 1 10 10 Favours Placebo Favours SNRIs

Figure 9.5: SNRIs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by neuropathic pain type

	SNR		Place			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.28.1 Duloxetine							
Gao 2010	74	106	67	109	13.8%	1.14 [0.94, 1.38]	-
Gao 2014	127	202	94	202	19.6%	1.35 [1.13, 1.62]	+
Goldstein 2005	46	115	10	38	3.1%	1.52 [0.85, 2.71]	
Goldstein 2005a	55	114	10	38	3.1%	1.83 [1.04, 3.23]	
Goldstein 2005b	57	113	9	39	2.8%	2.19 [1.20, 3.99]	
Raskin 2005	79	116	25	58	7.0%	1.58 [1.15, 2.18]	
Raskin 2005a	74	116	25	58	7.0%	1.48 [1.07, 2.05]	
Wernicke 2006	72	114	22	54	6.2%	1.55 [1.09, 2.20]	
Vernicke 2006a	77	112	23	54	6.5%	1.61 [1.16, 2.25]	
Yasuda 2011	47	85	29	84	6.1%	1.60 [1.13, 2.28]	
Yasuda 2011a	51	86	30	83	6.4%	1.64 [1.17, 2.29]	
Subtotal (95% CI)		1279		817	81.5%	1.48 [1.34, 1.62]	♦
Total events	759		344				
Heterogeneity: Chi <sup>2</sup> =	= 11.23, d	lf = 10	(P = 0.34)	4); $I^2 =$	11%		
Fest for overall effect	t: $Z = 8.09$	9 (P < 0	).00001)				
1.28.2 Venlafaxine/	Desvenla	favine					
	Destenia	avine					
	30	63	8	22	2.5%	1.31 [0.71, 2.41]	
Allen 2014			8 8	22 22	2.5% 2.7%	1.31 [0.71, 2.41] 1.50 [0.84, 2.70]	+
Allen 2014 Allen 2014a	30	63				• • •	
Allen 2014 Allen 2014a Allen 2014b	30 47	63 86	8	22	2.7%	1.50 [0.84, 2.70]	
Allen 2014 Allen 2014a Allen 2014b Allen 2014c	30 47 51	63 86 99	8 8	22 22	2.7% 2.7%	1.50 [0.84, 2.70] 1.42 [0.79, 2.54]	
Allen 2014 Allen 2014a Allen 2014b Allen 2014c Rowbotham 2005	30 47 51 31	63 86 99 68	8 8 9	22 22 23	2.7% 2.7% 2.8%	1.50 [0.84, 2.70] 1.42 [0.79, 2.54] 1.17 [0.66, 2.06]	
Allen 2014 Allen 2014a Allen 2014b Allen 2014c Rowbotham 2005 Rowbotham 2005a	30 47 51 31 31	63 86 99 68 82	8 8 9 14	22 22 23 40	2.7% 2.7% 2.8% 3.9%	1.50 [0.84, 2.70] 1.42 [0.79, 2.54] 1.17 [0.66, 2.06] 1.08 [0.65, 1.79]	
Allen 2014 Allen 2014a Allen 2014b Allen 2014c Rowbotham 2005 Rowbotham 2005a <b>Subtotal (95% CI)</b>	30 47 51 31 31	63 86 99 68 82 82	8 8 9 14	22 22 23 40 41	2.7% 2.7% 2.8% 3.9% 3.9%	1.50 [0.84, 2.70] 1.42 [0.79, 2.54] 1.17 [0.66, 2.06] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62]	•
Allen 2014 Allen 2014a Allen 2014b Allen 2014c Rowbotham 2005 Rowbotham 2005a <b>Subtotal (95% CI)</b> Fotal events	30 47 51 31 31 46 236	63 86 99 68 82 82 <b>82</b> <b>480</b>	8 9 14 14	22 22 23 40 41 <b>170</b>	2.7% 2.7% 2.8% 3.9% 3.9% <b>18.5%</b>	1.50 [0.84, 2.70] 1.42 [0.79, 2.54] 1.17 [0.66, 2.06] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62]	+
Allen 2014 Allen 2014a Allen 2014b Allen 2014c Rowbotham 2005 Rowbotham 2005a <b>Subtotal (95% CI)</b> Fotal events Heterogeneity: Chi <sup>2</sup> =	30 47 51 31 31 46 236 = 1.85, df	63 86 99 68 82 82 <b>480</b> = 5 (P	8 9 14 14 61 = 0.87);	22 22 23 40 41 <b>170</b>	2.7% 2.7% 2.8% 3.9% 3.9% <b>18.5%</b>	1.50 [0.84, 2.70] 1.42 [0.79, 2.54] 1.17 [0.66, 2.06] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62]	•
Allen 2014 Allen 2014a Allen 2014b Allen 2014c Rowbotham 2005 Rowbotham 2005a <b>Subtotal (95% CI)</b> Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect	30 47 51 31 31 46 236 = 1.85, df	63 86 99 68 82 82 <b>480</b> = 5 (P	8 9 14 14 61 = 0.87);	$22 \\ 22 \\ 23 \\ 40 \\ 41 \\ 170 \\ 1^2 = 0\%$	2.7% 2.7% 2.8% 3.9% 3.9% <b>18.5%</b>	1.50 [0.84, 2.70] 1.42 [0.79, 2.54] 1.17 [0.66, 2.06] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62]	+
Allen 2014 Allen 2014a Allen 2014b Allen 2014c Rowbotham 2005a <b>Subtotal (95% Cl)</b> Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect <b>Fotal (95% Cl)</b>	30 47 51 31 31 46 236 = 1.85, df	63 86 99 68 82 <b>480</b> = 5 (P 6 (P = 0	8 9 14 14 61 = 0.87);	$22 \\ 22 \\ 23 \\ 40 \\ 41 \\ 170 \\ 1^2 = 0\%$	2.7% 2.7% 2.8% 3.9% 3.9% <b>18.5%</b>	1.50 [0.84, 2.70] 1.42 [0.79, 2.54] 1.17 [0.66, 2.06] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62] <b>1.35 [1.08, 1.69]</b>	•
Allen 2014 Allen 2014a Allen 2014b Allen 2014c Rowbotham 2005 <b>Subtotal (95% CI)</b> Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect <b>Total (95% CI)</b> Total events Heterogeneity: Chi <sup>2</sup>	30 47 51 31 46 236 = 1.85, df t: Z = 2.66	63 86 99 68 82 82 480 = 5 (P 6 (P = 0 1759	8 9 14 14 61 = 0.87); 0.008) 405	$22 \\ 22 \\ 23 \\ 40 \\ 41 \\ 170 \\  ^2 = 0\% \\ 987$	2.7% 2.7% 2.8% 3.9% 3.9% 18.5%	1.50 [0.84, 2.70] 1.42 [0.79, 2.54] 1.17 [0.66, 2.06] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62] <b>1.35 [1.08, 1.69]</b>	
Allen 2014 Allen 2014a Allen 2014b Allen 2014c Rowbotham 2005a Gobotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect Fotal (95% CI) Fotal events	30 47 51 31 46 236 = 1.85, df t: Z = 2.66 995 = 13.12, d	63 86 99 68 82 <b>480</b> = 5 (P 5 (P = 0 <b>1759</b> If = 16	8 8 9 14 14 61 = 0.87); 0.008) 405 (P = 0.66	$22 \\ 22 \\ 23 \\ 40 \\ 41 \\ 170 \\  ^2 = 0\% \\ 987$	2.7% 2.7% 2.8% 3.9% 3.9% 18.5%	1.50 [0.84, 2.70] 1.42 [0.79, 2.54] 1.17 [0.66, 2.06] 1.08 [0.65, 1.79] 1.64 [1.03, 2.62] <b>1.35 [1.08, 1.69]</b>	• • • • • • • • • • • • • • • • • • •

Figure 9.6: SNRIs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by drug type

	SNR		Place			Risk Ratio	Risk Ratio
Study or Subgroup				Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
1.25.1 Less than or	equal to 1	150 pa	tients				
Allen 2014	30	63	8	22	2.5%	1.31 [0.71, 2.41]	
Allen 2014a	47	86	8	22	2.7%	1.50 [0.84, 2.70]	
Allen 2014b	51	99	8	22	2.7%	1.42 [0.79, 2.54]	+
Allen 2014c	31	68	9	23	2.8%	1.17 [0.66, 2.06]	
Rowbotham 2005	31	82	14	40	3.9%	1.08 [0.65, 1.79]	+-
Rowbotham 2005a	46	82	14	41	3.9%	1.64 [1.03, 2.62]	
Subtotal (95% CI)		480		170	18.5%	1.35 [1.08, 1.69]	•
Total events	236		61				
Heterogeneity: Chi <sup>2</sup> =	= 1.85, df	= 5 (P	= 0.87);	$I^2 = 0\%$			
Test for overall effect	z = 2.66	6 (P = 0)	.008)				
1.25.2 Greater than	150 patie	ents					
Gao 2010	74	106	67	109	13.8%	1.14 [0.94, 1.38]	+
Gao 2014	127	202	94	202	19.6%	1.35 [1.13, 1.62]	+
Goldstein 2005	46	115	10	38	3.1%	1.52 [0.85, 2.71]	
Goldstein 2005a	55	114	10	38	3.1%	1.83 [1.04, 3.23]	
Goldstein 2005b	57	113	9	39	2.8%	2.19 [1.20, 3.99]	
Raskin 2005	79	116	25	58	7.0%	1.58 [1.15, 2.18]	
Raskin 2005a	74	116	25	58	7.0%	1.48 [1.07, 2.05]	
Wernicke 2006	72	114	22	54	6.2%	1.55 [1.09, 2.20]	
Wernicke 2006a	77	112	23	54	6.5%	1.61 [1.16, 2.25]	
Yasuda 2011	47	85	29	84	6.1%	1.60 [1.13, 2.28]	
Yasuda 2011a	51	86	30	83	6.4%	1.64 [1.17, 2.29]	
Subtotal (95% CI)		1279		817	81.5%	1.48 [1.34, 1.62]	♦
Total events	759		344				
Heterogeneity: Chi <sup>2</sup> =	= 11.23, d	lf = 10	(P = 0.34)	1); I <sup>2</sup> =	11%		
Test for overall effect	z = 8.09	9 (P < 0	.00001)				
Total (95% CI)		1759		987	100.0%	1.45 [1.33, 1.59]	•
Total events	995		405				
Heterogeneity: Chi <sup>2</sup> =		f = 16		5); $I^2 =$	0%		
Test for overall effect	,			.,			
Test for subgroup dif				- 1 (P	- 0.48)	$1^2 - 0\%$	Favours Placebo Favours SNRIs

Figure 9.7: SNRIs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size

### TCAs

Figure 10.1: TCAs versus control; Outcome: Proportion of patients with a meaningful response to treatment (fixed effects)

	TCA	s	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Achar 2010	11	15	8	15	36.4%	1.38 [0.78, 2.41]	
Shabbir 2011	55	70	14	70	63.6%	3.93 [2.42, 6.38]	
Total (95% CI)		85		85	100.0%	3.00 [2.05, 4.38]	•
Total events	66		22				
Heterogeneity: Chi <sup>2</sup> =	8.56, df	= 1 (P)	= 0.003)	); $I^2 = 8$	8%		0.01 0.1 1 10 100
Test for overall effect:	Z = 5.68	8 (P < 0	).00001)				Favours placebo Favours TCAs

Figure 10.2: TCAs versus control; Outcome: Proportion of patients with a meaningful response to treatment (random effects)

	ТСА	S	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Achar 2010	11	15	8	15	49.1%	1.38 [0.78, 2.41]	
Shabbir 2011	55	70	14	70	50.9%	3.93 [2.42, 6.38]	
Total (95% CI)		85		85	100.0%	2.35 [0.79, 6.95]	
Total events	66		22				
Heterogeneity: Tau <sup>2</sup> = Test for overall effect	,		,	1 (P =	0.003); I <sup>2</sup>	2 = 88%	0.01 0.1 1 10 100 Favours placebo Favours TCAs

Figure 10.3: TCAs versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater (fixed effects)

1.4.1 Outcome data reported at less than or equal to 4 weeksSubtotal (95% CI)0Not estimableTotal events0Not estimableTotal events0Not estimableTest for overall effect: Not applicable1.4.2 Outcome data reported at greater than 4 weeks to less than 12 weeksAchar 2010111581536.4%1.38 [0.78, 2.41]Achar 2010111581536.4%1.38 [0.78, 2.41]Shabbir 20115570147063.6%3.93 [2.42, 6.38]Subtotal (95% CI)8585100.0%3.00 [2.05, 4.38]Total events6622Heterogeneity: Chi <sup>2</sup> = 8.56, df = 1 (P = 0.003); l <sup>2</sup> = 88%Test for overall effect: Z = 5.68 (P < 0.00001)1.4.3 Outcome data reported at greater than or equal to 12 weeksSubtotal (95% CI)0ONot estimableTotal events0ONot estimableTotal events0ONot estimableTotal events0OOOTotal events <th></th> <th>d, 95% Cl</th> <th>M–H, Fixed</th> <th></th> <th colspan="2">Weight M–H, Fixed, 95% Cl</th> <th>Total</th> <th>Events</th> <th>Total</th> <th>Events</th> <th>Study or Subgroup</th>		d, 95% Cl	M–H, Fixed		Weight M–H, Fixed, 95% Cl		Total	Events	Total	Events	Study or Subgroup
Total events 0 0 Heterogeneity: Not applicable Test for overall effect: Not applicable <b>1.4.2 Outcome data reported at greater than 4 weeks to less than 12 weeks</b> Achar 2010 11 15 8 15 36.4% 1.38 [0.78, 2.41] Shabbir 2011 55 70 14 70 63.6% 3.93 [2.42, 6.38] <b>Subtotal (95% CI)</b> 85 85 100.0% 3.00 [2.05, 4.38] Total events 66 22 Heterogeneity: Chi <sup>2</sup> = 8.56, df = 1 (P = 0.003); l <sup>2</sup> = 88% Test for overall effect: Z = 5.68 (P < 0.00001) <b>1.4.3 Outcome data reported at greater than or equal to 12 weeks</b> <b>Subtotal (95% CI)</b> 0 0 Not estimable Total events 0 0 Heterogeneity: Not applicable Test for overall effect: Not applicable					S	to 4 weel	equal	than or	at less	reported	1.4.1 Outcome data
Heterogeneity: Not applicable Test for overall effect: Not applicable <b>1.4.2 Outcome data reported at greater than 4 weeks to less than 12 weeks</b> Achar 2010 11 15 8 15 36.4% 1.38 [0.78, 2.41] Shabbir 2011 55 70 14 70 63.6% 3.93 [2.42, 6.38] <b>Subtotal (95% CI)</b> 85 85 100.0% 3.00 [2.05, 4.38] Total events 66 22 Heterogeneity: Chi <sup>2</sup> = 8.56, df = 1 (P = 0.003); l <sup>2</sup> = 88% Test for overall effect: Z = 5.68 (P < 0.00001) <b>1.4.3 Outcome data reported at greater than or equal to 12 weeks</b> <b>Subtotal (95% CI)</b> 0 0 Not estimable Total events 0 0 Heterogeneity: Not applicable Test for overall effect: Not applicable Test for overall effect: Not applicable Test for overall effect: Not applicable					Not estimable		0		0		Subtotal (95% CI)
Test for overall effect: Not applicable <b>1.4.2 Outcome data reported at greater than 4 weeks to less than 12 weeks</b> Achar 2010 11 15 8 15 36.4% 1.38 [0.78, 2.41] Shabbir 2011 55 70 14 70 63.6% 3.93 [2.42, 6.38] <b>Subtotal (95% CI)</b> 85 85 100.0% 3.00 [2.05, 4.38] Total events 66 22 Heterogeneity: Chi <sup>2</sup> = 8.56, df = 1 (P = 0.003); l <sup>2</sup> = 88% Test for overall effect: Z = 5.68 (P < 0.00001) <b>1.4.3 Outcome data reported at greater than or equal to 12 weeks</b> <b>Subtotal (95% CI)</b> 0 0 Not estimable Total events 0 0 Heterogeneity: Not applicable Test for overall effect: Not applicable Test for overall effect: Not applicable								0		0	Total events
<b>1.4.2 Outcome data reported at greater than 4 weeks to less than 12 weeks</b> Achar 2010       11       15       8       15 $36.4\%$ $1.38 [0.78, 2.41]$ Shabbir 2011       55       70       14       70 $63.6\%$ $3.93 [2.42, 6.38]$ Subtotal (95% CI)       85       85       100.0% $3.00 [2.05, 4.38]$ Total events       66       22         Heterogeneity: Chi <sup>2</sup> = 8.56, df = 1 (P = 0.003); l <sup>2</sup> = 88%         Test for overall effect: Z = 5.68 (P < 0.00001)										plicable	Heterogeneity: Not ap
Achar 2010 11 15 8 15 36.4% 1.38 [0.78, 2.41] Shabbir 2011 55 70 14 70 63.6% $3.93$ [2.42, 6.38] Subtotal (95% CI) 85 85 100.0% $3.00$ [2.05, 4.38] Total events 66 22 Heterogeneity: Chi <sup>2</sup> = 8.56, df = 1 (P = 0.003); l <sup>2</sup> = 88% Test for overall effect: Z = 5.68 (P < 0.00001) 1.4.3 Outcome data reported at greater than or equal to 12 weeks Subtotal (95% CI) 0 0 Not estimable Total events 0 0 Heterogeneity: Not applicable Test for overall effect: Not applicable Test for overall effect: Not applicable									icable	Not appl	Test for overall effect
Shabbir 2011 55 70 14 70 63.6% $3.93$ [2.42, 6.38] Subtotal (95% CI) 85 85 100.0% $3.00$ [2.05, 4.38] Total events 66 22 Heterogeneity: Chi <sup>2</sup> = 8.56, df = 1 (P = 0.003); l <sup>2</sup> = 88% Test for overall effect: Z = 5.68 (P < 0.00001) 1.4.3 Outcome data reported at greater than or equal to 12 weeks Subtotal (95% CI) 0 0 Not estimable Total events 0 0 Heterogeneity: Not applicable Test for overall effect: Not applicable Test for overall effect: Not applicable					than 12 weeks	ks to les	4 wee	ater than	at grea	reported	1.4.2 Outcome data
Subtotal (95% CI)       85       85       100.0%       3.00 [2.05, 4.38]         Total events       66       22         Heterogeneity: Chi <sup>2</sup> = 8.56, df = 1 (P = 0.003); l <sup>2</sup> = 88%         Test for overall effect: Z = 5.68 (P < 0.00001)		-	+		1.38 [0.78, 2.41]	36.4%	15	8	15	11	Achar 2010
Total events $66$ $22$ Heterogeneity: Chi <sup>2</sup> = 8.56, df = 1 (P = 0.003); l <sup>2</sup> = 88% Test for overall effect: Z = 5.68 (P < 0.00001) <b>1.4.3 Outcome data reported at greater than or equal to 12 weeks</b> <b>Subtotal (95% CI) 0 0 Not estimable</b> Total events 0 0 Heterogeneity: Not applicable Test for overall effect: Not applicable Test for overall effect: Not applicable					3.93 [2.42, 6.38]	63.6%	70	14	70	55	Shabbir 2011
Heterogeneity: $Chi^2 = 8.56$ , $df = 1$ (P = 0.003); $l^2 = 88\%$ Test for overall effect: Z = 5.68 (P < 0.00001) <b>1.4.3 Outcome data reported at greater than or equal to 12 weeks</b> <b>Subtotal (95% CI)</b> 0 0 Not estimable Total events 0 0 Heterogeneity: Not applicable Test for overall effect: Not applicable 1000000000000000000000000000000000000		•			3.00 [2.05, 4.38]	100.0%	85		85		Subtotal (95% CI)
Test for overall effect: Z = 5.68 (P < 0.00001) 1.4.3 Outcome data reported at greater than or equal to 12 weeks Subtotal (95% CI) 0 0 Not estimable Total events 0 0 Heterogeneity: Not applicable Test for overall effect: Not applicable 0.01 0.1 1 10								22		66	Total events
1.4.3 Outcome data reported at greater than or equal to 12 weeks         Subtotal (95% CI)       0       0       Not estimable         Total events       0       0       0         Heterogeneity: Not applicable       Test for overall effect: Not applicable       0.01       0.1						8%	$ I^2 = 8$	= 0.003)	= 1 (P	8.56, df	Heterogeneity: Chi <sup>2</sup> =
Subtotal (95% CI)       0       0       Not estimable         Total events       0       0         Heterogeneity: Not applicable       0       0         Test for overall effect: Not applicable       0.01       0.1         0.01       0.1       1								.00001)	8 (P < 0	Z = 5.68	Test for overall effect
Subtotal (95% CI)       0       0       Not estimable         Total events       0       0         Heterogeneity: Not applicable       0       0         Test for overall effect: Not applicable       0.01       0.1         0.01       0.1       1					weeks	al to 12	or equ	ater than	at grea	reported	1.4.3 Outcome data
Heterogeneity: Not applicable Test for overall effect: Not applicable 0.01 0.1 1 10									-		
Test for overall effect: Not applicable								0		0	Total events
0.01 0.1 1 10										plicable	Heterogeneity: Not ap
									licable	Not appl	Test for overall effect
				<b>L</b>							
	10			0.01							

Figure 10.4: TCAs versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater (random effects)

	TCAs		Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events 7	Total	Events	Total	Weight I	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.4.1 Outcome data	reported a	t less	than or	equal	to 4 week	s	
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not a	pplicable						
Test for overall effec	t: Not applie	cable					
1.4.2 Outcome data	reported a	t grea	ter thar	14 wee	eks to less	than 12 weeks	
Achar 2010	11	15	8	15	49.1%	1.38 [0.78, 2.41]	- <b>+=</b>
Shabbir 2011	55	70	14	70	50.9%	3.93 [2.42, 6.38]	
Subtotal (95% CI)		85		85	100.0%	2.35 [0.79, 6.95]	
Total events	66		22				
Heterogeneity: Tau <sup>2</sup>	- 0 5 4: Chi		C df	1 /P	0.0023-12.	- 9.9%	
meanogenery. Tau	= 0.54; Chi	= 0.5	o, ar =	1 (P =	0.005), 1 -	- 00%	
Test for overall effec				1 (r =	0.003), 1	- 33%	
	t: Z = 1.54	(P = 0.)	12)	~			
Test for overall effec	t: Z = 1.54	(P = 0.)	12)	~			
Test for overall effect 1.4.3 Outcome data	t: Z = 1.54	(P = 0. t grea	12)	n or eq		weeks	
Test for overall effect 1.4.3 Outcome data Subtotal (95% CI)	t: Z = 1.54 reported a	(P = 0. t grea	12) ter thar	n or eq		weeks	
Test for overall effect 1.4.3 Outcome data Subtotal (95% CI) Total events	reported a opplicable	(P = 0. t grea 0	12) ter thar	n or eq		weeks	
Test for overall effect 1.4.3 Outcome data Subtotal (95% Cl) Total events Heterogeneity: Not a	reported a opplicable	(P = 0. t grea 0	12) ter thar	n or eq O		weeks	
Test for overall effect 1.4.3 Outcome data Subtotal (95% Cl) Total events Heterogeneity: Not a Test for overall effect	reported a opplicable	(P = 0. t grea 0 cable	12) ter thar	n or eq O	ual to 12 v	weeks Not estimable	-
Test for overall effect 1.4.3 Outcome data Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect Total (95% CI) Total events	tt: Z = 1.54 reported a opplicable tt: Not applic 66	(P = 0. t great 0 cable 85	12) ter thar 0 22	or eq 0 85	ual to 12 v 100.0%	veeks Not estimable 2.35 [0.79, 6.95]	
Test for overall effect 1.4.3 Outcome data Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect Total (95% CI)	tt: Z = 1.54 ( a reported a opplicable tt: Not applie 66 = 0.54; Chi <sup>2</sup>	(P = 0. t great 0 cable 85 2 = 8.5	12) ter thar 0 22 66, df =	or eq 0 85	ual to 12 v 100.0%	veeks Not estimable 2.35 [0.79, 6.95]	0.01 0.1 1 10 100 Favours placebo Favours TCAs

Figure 10.5: TCAs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by neuropathic pain type (fixed effects)

	TCA	5	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.2.1 Diabetic Neuro	pathy						
Shabbir 2011	55	70	14	70	63.6%		
Subtotal (95% CI)		70		70	63.6%	3.93 [2.42, 6.38]	•
Total events	55		14				
Heterogeneity: Not ap	plicable						
Test for overall effect:	: Z = 5.54	(P < 0	).00001)				
1.2.2 Postherpetic No	euralgia						
Achar 2010	11	15	8	15	36.4%	1.38 [0.78, 2.41]	-+ <b>e</b>
Subtotal (95% CI)		15		15	36.4%	1.38 [0.78, 2.41]	◆
Total events	11		8				
Heterogeneity: Not ap	plicable						
Test for overall effect	Z = 1.11	(P = 0	).27)				
1.2.3 Trigeminal Neu	ıralgia						
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect	•	icable					
Total (95% CI)		85		85	100.0%	3.00 [2.05, 4.38]	•
Total events	66		22				
Heterogeneity: Chi <sup>2</sup> =	8.56, df	= 1 (P	= 0.003)	; $I^2 = 8$	8%		
Test for overall effect:	,						0.01 0.1 1 10 100 Favours placebo Favours TCAs
Test for subgroup diff	ferences:	Chi <sup>2</sup> =	7.67, df	= 1 (P)	= 0.006)	$I^2 = 87.0\%$	Favours placebo Favours TCAs
5			,		,		

Figure 10.6: TCAs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by neuropathic pain type (random effects)

	TCA	s	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M–H, Random, 95% Cl
1.2.1 Diabetic Neuro	pathy						
Shabbir 2011 Subtotal (95% CI)	55	70 70	14	70 70	50.9% 50.9%	and a fait of a constant	
Total events	55		14				•
Heterogeneity: Not ap	plicable						
Test for overall effect	: Z = 5.54	4 (P < 0	0.00001)				
1.2.2 Postherpetic N	euralgia						
Achar 2010 Subtotal (95% CI)	11	15 15	8	15 15	49.1% <b>49.1%</b>		<b></b>
Total events Heterogeneity: Not ap	11 Indicable		8				
Test for overall effect		1 (P = 0	).27)				
1.2.3 Trigeminal Neu	uralgia						
Subtotal (95% CI)	aagaa	0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable		-				
Test for overall effect		licable					
Total (95% CI)		85		85	100.0%	2.35 [0.79, 6.95]	
Total events	66		22				-
Heterogeneity: Tau <sup>2</sup> =		$hi^2 = 8$ .	56. df =	1 (P =	0.003); I <sup>2</sup>	= 88%	
Test for overall effect							0.01 0.1 1 10 10
Test for subgroup dif				1 /0	0.000	12 07 04	Favours placebo Favours TCAs

Figure 10.7: TCAs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size (fixed effects)

	TCA		Place			Risk Ratio	Risk Ratio
Study or Subgroup				Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.3.1 Less than or ec	qual to 15	50 pati	ents				
Achar 2010	11	15	8	15	36.4%	1.38 [0.78, 2.41]	
Shabbir 2011	55	70	14	70	63.6%	3.93 [2.42, 6.38]	
Subtotal (95% CI)		85		85	100.0%	3.00 [2.05, 4.38]	•
Total events	66		22				
Heterogeneity: Chi <sup>2</sup> =	8.56, df	= 1 (P	= 0.003)	; $I^2 = 8$	8%		
Test for overall effect	: Z = 5.68	8 (P < C	0.00001)				
1.3.2 Greater than 1	50 patien						
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect	: Not appl	icable					
Total (95% CI)		85		85	100.0%	3.00 [2.05, 4.38]	•
Total events	66		22				
Heterogeneity: Chi <sup>2</sup> =	8.56, df	= 1 (P	= 0.003)	$I^2 = 8$	8%		
Test for overall effect	,						0.01 0.1 1 10 100
Test for subgroup dif							Favours placebo Favours TCAs

Figure 10.8: TCAs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size (random effects)

	TCA	s	Place	bo		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% Cl	
1.3.1 Less than or ec	ual to 15	50 pati	ents						
Achar 2010	11	15	8	15	49.1%	1.38 [0.78, 2.41]		-+=	
Shabbir 2011 Subtotal (95% CI)	55	70 85	14	70 85	50.9% 100.0%	3.93 [2.42, 6.38] 2.35 [0.79, 6.95]			
Total events	66		22						
Heterogeneity: Tau <sup>2</sup> =	= 0.54; Ch	i <sup>2</sup> = 8.	56, df =	1 (P =	0.003); I <sup>2</sup>	= 88%			
Test for overall effect	: Z = 1.54	(P = 0	.12)						
1.3.2 Greater than 1	50 patien	ts							
Subtotal (95% CI)	-	0		0		Not estimable			
Total events	0		0						
Heterogeneity: Not ap	plicable								
Test for overall effect	Not appl	icable							
Total (95% CI)		85		85	100.0%	2.35 [0.79, 6.95]		-	
Total events	66		22					_	
Heterogeneity: Tau <sup>2</sup> =	0.54; Ch	i <sup>2</sup> = 8.	56, df =	1 (P =	0.003); I <sup>2</sup>	= 88%	0.01	0.1 1 10	100
Test for overall effect	: Z = 1.54	(P = 0)	.12)				0.01	0.1 1 10 Favours placebo Favours TCAs	100
Test for subgroup diff	ferences:	Not ap	nlicable					ravours placebo ravours TCAS	

## Adverse Events

## Table 11: Individual Adverse Events (reported by single RCTs)

Intervention Type	Type of Adverse Event	Randomized Controlled Trials	Intervention Control	# of RCTs	# of Participants	Intervention Event Rate	Control Event Rate	Risk Ratio (95% Confidence Interval)	NNH
Acupuncture	Withdrawals due to Adverse Events	Garrow 2014	Standardized Acupuncture; 10 weekly sessions Sham Acupuncture; 10 weekly sessions	1	59	7.1% (2/28)	3.2% (1/31)	RR 2.21 (95% Cl 0.21, 23.11)	NSS
Anticonvulsants- Gabapentin	≥1 treatment- emergent adverse event	Sang 2013	Gabapentin 1800 mg daily Placebo	1	452	31.2% (69/221)	17.3% (40/231)	RR 1.80 (95% Cl 1.28, 2.54)	8
Anticonvulsants- Gabapentin	Adverse Events	Rice 2001	Gabapentin 1800 mg daily Placebo	1	334	70.4% (81/115)	49.1% (27/55)	RR 1.43 (95% Cl 1.07, 1.93)	5
Anticonvulsants- Gabapentin	Adverse Events	Rice 2001	Gabapentin 2400 mg daily Placebo	1	334	75% (81/108)	50% (28/56)	RR 1.50 (95% Cl 1.13, 1.99)	4
Anticonvulsants- Gabapentin	Adverse Events	Sang 2013	Gabapentin 1800 mg daily Placebo	1	452	53.4% (118/221)	39.8% (92/231)	RR 1.34 (95% Cl 1.10, 1.64)	8
Anticonvulsants- Gabapentin	Ataxia	Rowbotham 1998	Gabapentin 3600 mg daily Placebo	1	229	7.1% (8/113)	0% (0/116)	RR 17.45 (95% Cl 1.02, 298.78)	15
Anticonvulsants- Gabapentin	Nervous System Disorders	Wallace 2010	Gabapentin 1800 mg in divided doses	1	405	25.4% (34/134)	11.9% (8/67)	RR 2.13 (95% Cl 1.04, 4.33)	8

			Placebo						
Anticonvulsants- Gabapentin	Treatment-related adverse events	Rowbotham 1998	Gabapentin 3600 mg daily Placebo	1	229	54.9% (62/113)	27.6% (32/116)	RR 1.99 (95% Cl 1.42, 2.79)	4
Anticonvulsants- Gabapentin	Adverse Events	Backonja 2011	Gabapentin 624 mg daily Placebo	1	101	53.2% (25/47)	46.35 (25/54)	RR 1.15 (95% Cl 0.78, 1.70)	NSS
Anticonvulsants- Gabapentin	Adverse Events	Rauck 2012	Gabapentin 1200 mg daily Placebo	1	420	72.6% (45/62)	63.3% (19/30)	RR 1.15 (95% Cl 0.84, 1.57)	NSS
Anticonvulsants- Gabapentin	Adverse Events	Rauck 2012	Gabapentin 2400 mg daily Placebo	1	420	67.9% (38/56)	66.7% (20/30)	RR 1.02 (95% Cl 0.75, 1.39)	NSS
Anticonvulsants- Gabapentin	Adverse Events	Rauck 2012	Gabapentin 3600 mg daily Placebo	1	420	74.1% (86/116)	66.7% (20/30)	RR 1.11 (95% Cl 0.84, 1.46)	NSS
Anticonvulsants- Gabapentin	Adverse Events	Sandercock 2012	Gabapentin 3000 mg once daily Placebo	1	147	57.4% (27/47)	40% (10/25)	RR 1.44 (95% Cl 0.84, 2.46)	NSS
Anticonvulsants- Gabapentin	Adverse Events	Sandercock 2012	Gabapentin 3000 mg in divided doses Placebo	1	147	46.9% (23/49)	38.5% (10/26)	RR 1.22 (95% Cl 0.69, 2.16)	NSS
Anticonvulsants- Gabapentin	Adverse Events	Wallace 2010	Gabapentin 1800 mg daily dose Placebo	1	405	56.5% (78/138)	48.5% (32/66)	RR 1.17 (95% Cl 0.87, 1.56)	NSS
Anticonvulsants- Gabapentin	Adverse Events	Wallace 2010	Gabapentin 1800 mg in divided doses Placebo	1	405	57.5% (77/134)	47.8% (32/67)	RR 1.20 (95% Cl 0.90, 1.61)	NSS
Anticonvulsants- Gabapentin	Adverse Events	Zhang 2013	Gabapentin 1200 mg daily Placebo	1	371	70.1% (75/107)	67.7% (21/31)	RR 1.03 (95% Cl 0.79, 1.36)	NSS

Anticonvulsants- Gabapentin	Adverse Events	Zhang 2013	Gabapentin 2400 mg daily Placebo	1	371	78.0% (64/82)	65.6% (21/32)	RR 1.19 (95% Cl 0.90, 1.57)	NSS
Anticonvulsants- Gabapentin	Adverse Events	Zhang 2013	Gabapentin 3600 mg daily Placebo	1	371	81.6% (71/87)	65.6% (21/32)	RR 1.24 (95% Cl 0.95, 1.63)	NSS
Anticonvulsants- Gabapentin	Asthenia	Rice 2001	Gabapentin 1800 mg daily Placebo	1	334	6.1% (7/115)	3.6% (2/55)	RR 1.67 (95% Cl 0.36, 7.79)	NSS
Anticonvulsants- Gabapentin	Asthenia	Rice 2001	Gabapentin 2400 mg daily Placebo	1	334	5.6% (6/108)	3.6% (2/56)	RR 1.56 (95% Cl 0.32, 7.46)	NSS
Anticonvulsants- Gabapentin	Bronchitis	Rauck 2012	Gabapentin 1200 mg daily Placebo	1	420	4.8% (3/62)	0% (0/30)	RR 3.44 (95% Cl 0.18, 64.63)	NSS
Anticonvulsants- Gabapentin	Bronchitis	Rauck 2012	Gabapentin 2400 mg daily Placebo	1	420	1.8% (1/56)	0% (0/30)	RR 1.63 (95% Cl 0.07, 38.87)	NSS
Anticonvulsants- Gabapentin	Bronchitis	Rauck 2012	Gabapentin 3600 mg daily Placebo	1	420	0% (0/116)	0% (0/30)	-	-
Anticonvulsants- Gabapentin	Confusion	Backonja 1998	Gabapentin 3600 mg daily Placebo	1	165	8.3% (7/84)	1.2% (1/81)	RR 6.75 (95% Cl 0.85, 53.65)	NSS
Anticonvulsants- Gabapentin	Death	Rice 2001	Gabapentin 1800 mg daily Placebo	1	334	0% (0/115)	0% (0/55)	-	-
Anticonvulsants- Gabapentin	Death	Rice 2001	Gabapentin 2400 mg daily Placebo	1	334	0.93% (1/108)	0% (0/56)	RR 1.57 (95% Cl 0.06, 37.90)	NSS
Anticonvulsants- Gabapentin	Depression	Backonja 2011	Gabapentin 624 mg daily Placebo	1	101	0% (0/47)	5.6% (3/54)	RR 0.16 (95% Cl 0.01, 3.09)	NSS

Anticonvulsants- Gabapentin	Disturbance in Attention	Rauck 2012	Gabapentin 1200 mg daily Placebo	1	420	3.2% (2/62)	0% (0/30)	RR 2.46 (95% Cl 0.12, 49.71)	NSS
Anticonvulsants- Gabapentin	Disturbance in Attention	Rauck 2012	Gabapentin 2400 mg daily Placebo	1	420	0% (0/56)	0% (0/30)	-	-
Anticonvulsants- Gabapentin	Disturbance in Attention	Rauck 2012	Gabapentin 3600 mg daily Placebo	1	420	1.7% (2/116)	3.3% (1/30)	RR 0.52 (95% Cl 0.05, 5.51)	NSS
Anticonvulsants- Gabapentin	Excoriation	Rauck 2012	Gabapentin 1200 mg daily Placebo	1	420	1.6% (1/62)	0% (0/30)	RR 1.48 (95% Cl 0.06, 35.20)	NSS
Anticonvulsants- Gabapentin	Excoriation	Rauck 2012	Gabapentin 2400 mg daily Placebo	1	420	1.8% (1/56)	0% (0/30)	RR 1.63 (95% Cl 0.07, 38.87)	NSS
Anticonvulsants- Gabapentin	Excoriation	Rauck 2012	Gabapentin 3600 mg daily Placebo	1	420	0.86% (1/116)	0% (0/30)	RR 0.79 (95% Cl 0.03, 19.04)	NSS
Anticonvulsants- Gabapentin	Falls	Rauck 2012	Gabapentin 1200 mg daily Placebo	1	420	4.8% (3/62)	0% (0/30)	RR 3.44 (95% Cl 0.18, 64.63)	NSS
Anticonvulsants- Gabapentin	Falls	Rauck 2012	Gabapentin 2400 mg daily Placebo	1	420	1.8% (1/56)	0% (0/30)	RR 1.63 (95% Cl 0.07, 38.87)	NSS
Anticonvulsants- Gabapentin	Falls	Rauck 2012	Gabapentin 3600 mg daily Placebo	1	420	0.86% (1/116)	0% (0/30)	RR 0.79 (95% Cl 0.03, 19.04)	NSS
Anticonvulsants- Gabapentin	Flatulence	Zhang 2013	Gabapentin 1200 mg daily Placebo	1	371	0.93% (1/107)	0% (0/31)	RR 0.89 (95% Cl	NSS

								0.04 <i>,</i> 21.30)	
Anticonvulsants- Gabapentin	Flatulence	Zhang 2013	Gabapentin 2400 mg daily Placebo	1	371	1.2% (1/82)	0% (0/32)	RR 1.19 (95% Cl 0.05, 28.54)	NSS
Anticonvulsants- Gabapentin	Flatulence	Zhang 2013	Gabapentin 3600 mg daily Placebo	1	371	4.6% (4/87)	0% (0/32)	RR 3.38 (95% Cl 0.19, 60.99)	NSS
Anticonvulsants- Gabapentin	Gastrointestinal Disorders	Wallace 2010	Gabapentin 1800 mg daily dose Placebo	1	405	13.8% (19/138)	16.7% (11/66)	RR 0.83 (95% Cl 0.42, 1.63)	NSS
Anticonvulsants- Gabapentin	Gastrointestinal Disorders	Wallace 2010	Gabapentin 1800 mg in divided doses Placebo	1	405	15.7% (21/134)	16.4% (11/67)	RR 0.95 (95% Cl 0.49, 1.86)	NSS
Anticonvulsants- Gabapentin	Hypertension	Zhang 2013	Gabapentin 1200 mg daily Placebo	1	371	1.9% (2/107)	0% (0/31)	RR 1.48 (95% Cl 0.07, 30.08)	NSS
Anticonvulsants- Gabapentin	Hypertension	Zhang 2013	Gabapentin 2400 mg daily Placebo	1	371	4.9% (4/82)	0% (0/32)	RR 3.58 (95% Cl 0.20, 64.63)	NSS
Anticonvulsants- Gabapentin	Hypertension	Zhang 2013	Gabapentin 3600 mg daily Placebo	1	371	2.3% (2/87)	3.1% (1/32)	RR 0.74 (95% Cl 0.07, 7.84)	NSS
Anticonvulsants- Gabapentin	Hypoesthesia	Rauck 2012	Gabapentin 1200 mg daily Placebo	1	420	1.6% (1/62)	0% (0/30)	RR 1.48 (95% Cl 0.06, 35.20)	NSS
Anticonvulsants- Gabapentin	Hypoesthesia	Rauck 2012	Gabapentin 2400 mg daily Placebo	1	420	1.8% (1/56)	0% (0/30)	RR 1.63 (95% Cl 0.07, 38.87)	NSS

Anticonvulsants- Gabapentin	Hypoesthesia	Rauck 2012	Gabapentin 3600 mg daily Placebo	1	420	0% (0/116)	0% (0/30)	-	-
Anticonvulsants- Gabapentin	Increased Appetite	Rauck 2012	Gabapentin 1200 mg daily Placebo	1	420	0% (0/62)	3.3% (1/30)	RR 0.16 (95% Cl 0.01, 3.91)	NSS
Anticonvulsants- Gabapentin	Increased Appetite	Rauck 2012	Gabapentin 2400 mg daily Placebo	1	420	5.4% (3/56)	3.3% (1/30)	RR 1.61 (95% Cl 0.17, 14.79)	NSS
Anticonvulsants- Gabapentin	Increased Appetite	Rauck 2012	Gabapentin 3600 mg daily Placebo	1	420	0.86% (1/116)	3.3% (1/30)	RR 0.26 (95% Cl 0.02, 4.02)	NSS
Anticonvulsants- Gabapentin	Infection	Rowbotham 1998	Gabapentin 3600 mg daily Placebo	1	229	8.0% (9/113)	2.6% (3/116)	RR 3.08 (95% Cl 0.86, 11.08)	NSS
Anticonvulsants- Gabapentin	Joint Sprain	Zhang 2013	Gabapentin 1200 mg daily Placebo	1	371	1.9% (2/107)	0% (0/31)	RR 1.48 (95% Cl 0.07, 30.08)	NSS
Anticonvulsants- Gabapentin	Joint Sprain	Zhang 2013	Gabapentin 2400 mg daily Placebo	1	371	0% (0/82)	0% (0/32)	-	-
Anticonvulsants- Gabapentin	Joint Sprain	Zhang 2013	Gabapentin 3600 mg daily Placebo	1	371	4.6% (4/87)	0% (0/32)	RR 3.38 (95% Cl 0.19, 60.99)	NSS
Anticonvulsants- Gabapentin	Muscle Spasms	Rauck 2012	Gabapentin 1200 mg daily Placebo	1	420	9.7% (6/62)	3.3% (1/30)	RR 2.90 (95% Cl 0.37, 23.05)	NSS
Anticonvulsants- Gabapentin	Muscle Spasms	Rauck 2012	Gabapentin 2400 mg daily Placebo	1	420	0% (0/56)	3.3% (1/30)	RR 0.18 (95% Cl 0.01, 4.32)	NSS
(Anticonvulsants- Gabapentin	Muscle Spasms	Rauck 2012	Gabapentin 3600 mg daily	1	420	9.5% (11/116)	3.3% (1/30)	RR 2.84 (95% Cl	NSS

			Placebo					0.38 <i>,</i> 21.18)	
Anticonvulsants- Gabapentin	Nasal Congestion	Zhang 2013	Gabapentin 1200 mg daily Placebo	1	371	1.9% (2/107)	0% (0/31)	RR 1.48 (95% Cl 0.07, 30.08)	NSS
Anticonvulsants- Gabapentin	Nasal Congestion	Zhang 2013	Gabapentin 2400 mg daily Placebo	1	371	0% (0/82)	0% (0/32)	-	-
Anticonvulsants- Gabapentin	Nasal Congestion	Zhang 2013	Gabapentin 3600 mg daily Placebo	1	371	5.8% (5/87)	3.1% (1/32)	RR 1.84 (95% Cl 0.22, 15.15)	NSS
Anticonvulsants- Gabapentin	Nervous System Disorders	Wallace 2010	Gabapentin 1800 mg daily dose Placebo	1	405	19.6% (27/138)	12.1% (8/66)	RR 1.61 (95% Cl 0.78, 3.36)	NSS
Anticonvulsants- Gabapentin	Pain	Rowbotham 1998	Gabapentin 3600 mg daily Placebo	1	229	4.4% (5/113)	10.3% (12/116)	RR 0.43 (95% Cl 0.16, 1.18)	NSS
Anticonvulsants- Gabapentin	Pain in Extremity	Rauck 2012	Gabapentin 1200 mg daily Placebo	1	420	1.6% (1/62)	0% (0/30)	RR 1.48 (95% Cl 0.06, 35.20)	NSS
Anticonvulsants- Gabapentin	Pain in Extremity	Rauck 2012	Gabapentin 2400 mg daily Placebo	1	420	7.1% (4/56)	0% (0/30)	RR 4.89 (95% Cl 0.27, 87.97)	NSS
Anticonvulsants- Gabapentin	Pain in Extremity	Rauck 2012	Gabapentin 3600 mg daily Placebo	1	420	5.2% (6/116)	3.3% (1/30)	RR 1.55 (95% Cl 0.19, 12.40)	NSS
Anticonvulsants- Gabapentin	Paresthesia	Rauck 2012	Gabapentin 1200 mg daily Placebo	1	420	3.2% (2/62)	0% (0/30)	RR 2.46 (95% Cl 0.12, 49.71)	NSS

Anticonvulsants- Gabapentin	Paresthesia	Rauck 2012	Gabapentin 2400 mg daily Placebo	1	420	1.8% (1/56)	0% (0/30)	RR 1.63 (95% Cl 0.07, 38.87)	NSS
Anticonvulsants- Gabapentin	Paresthesia	Rauck 2012	Gabapentin 3600 mg daily Placebo	1	420	0% (0/116)	0% (0/30)	-	-
Anticonvulsants- Gabapentin	Postherpetic Neuralgia	Backonja 2011	Gabapentin 624 mg daily Placebo	1	101	2.1% (1/47)	5.6% (3/54)	RR 0.38 (95% Cl 0.04, 3.56)	NSS
Anticonvulsants- Gabapentin	Tremor	Zhang 2013	Gabapentin 1200 mg daily Placebo	1	371	0% (0/107)	0% (0/31)	-	-
Anticonvulsants- Gabapentin	Tremor	Zhang 2013	Gabapentin 2400 mg daily Placebo	1	371	0% (0/82)	0% (0/32)	-	-
Anticonvulsants- Gabapentin	Tremor	Zhang 2013	Gabapentin 3600 mg daily Placebo	1	371	4.6% (4/87)	0% (0/32)	RR 3.38 (95% Cl 0.19, 60.99)	NSS
Anticonvulsants- Gabapentin	Vomiting	Rauck 2012	Gabapentin 1200 mg daily Placebo	1	420	4.8% (3/62)	0% (0/30)	RR 3.44 (95% Cl 0.18, 64.63)	NSS
Anticonvulsants- Gabapentin	Vomiting	Rauck 2012	Gabapentin 2400 mg daily Placebo	1	420	1.8% (1/56)	3.3% (1/30)	RR 0.54 (95% Cl 0.03, 8.26)	NSS
Anticonvulsants- Gabapentin	Vomiting	Rauck 2012	Gabapentin 3600 mg daily Placebo	1	420	1.7% (2/116)	3.3% (1/30)	RR 0.52 (95% Cl 0.05, 5.51)	NSS
Anticonvulsants- Oxcarbazepine	Adverse Events	CTRI476G2301	Oxcarbazepine 1200 mg daily Placebo	1	141	87.3% (62/71)	58.6% (41/70)	RR 1.49 (95% Cl 1.20, 1.85)	4
Anticonvulsants- Oxcarbazepine	Aggravated Hypertension	CTRI476G2301	Oxcarbazepine 1200 mg daily Placebo	1	141	8.5% (6/71)	2.9% (2/70)	RR 2.96 (95% Cl 0.62, 14.16)	NSS

Anticonvulsants- Oxcarbazepine	Blurred Vision	Dogra 2005	Oxcarbazepine 1800 mg daily Placebo	1	146	1.8% (1/55)	1.4% (1/70)	RR 1.27 (95% Cl 0.08, 19.89)	NSS
Anticonvulsants- Oxcarbazepine	Cough	CTRI476G2301	Oxcarbazepine 1200 mg daily Placebo	1	141	5.6% (4/71)	2.9% (2/70)	RR 1.97 (95% Cl 0.37, 10.42)	NSS
Anticonvulsants- Oxcarbazepine	Death	CTRI476G2301	Oxcarbazepine 1200 mg daily Placebo	1	141	0% (0/71)	0% (0/70)	-	-
Anticonvulsants- Oxcarbazepine	Dyspepsia	CTRI476G2301	Oxcarbazepine 1200 mg daily Placebo	1	141	5.6% (4/71)	0% (0/70)	RR 8.88 (95% Cl 0.49, 161.84)	NSS
Anticonvulsants- Oxcarbazepine	Hyponatremia	CTRI476G2301	Oxcarbazepine 1200 mg daily Placebo	1	141	9.9% (7/71)	0% (0/70)	RR 14.79 (95% Cl 0.86, 254.17)	NSS
Anticonvulsants- Oxcarbazepine	Peripheral Edema	CTRI476G2301	Oxcarbazepine 1200 mg daily Placebo	1	141	5.6% (4/71)	0% (0/70)	RR 8.88 (95% Cl 0.49, 161.84)	NSS
Anticonvulsants- Oxcarbazepine	Upper Abdominal Pain	CTRI476G2301	Oxcarbazepine 1200 mg daily Placebo	1	141	5.6% (4/71)	0% (0/70)	RR 8.88 (95% Cl 0.49, 161.84)	NSS
Anticonvulsants- Oxcarbazepine	Vertigo	CTRI476G2301	Oxcarbazepine 1200 mg daily Placebo	1	141	8.5% (6/71)	0% (0/70)	RR 12.82 (95% Cl 0.74, 223.34)	NSS
Anticonvulsants- Oxcarbazepine	Vomiting	Dogra 2005	Oxcarbazepine 1800 mg daily Placebo	1	146	3.6% (2/55)	1.4% (1/70)	RR 2.55 (95% Cl 0.24, 27.35)	NSS

Anticonvulsants- Pregabalin	≥1 Adverse Event	Stacey 2008	Pregabalin Flexible Dose (mean 396 mg) Placebo	1	269	72.5% (66/91)	42.2% (19/45)	RR 1.72 (95% Cl 1.19, 2.47)	4
Anticonvulsants- Pregabalin	Adverse Events	Dworkin 2003	Pregabalin 300-600 mg daily Placebo	1	173	86.5% (77/89)	63.1% (53/84)	RR 1.37 (95% Cl 1.14, 1.65)	5
Anticonvulsants- Pregabalin	Adverse Events	Liu 2017	Pregabalin 300 mg daily Placebo	1	220	64.0% (71/111)	44.0% (48/109)	RR 1.45 (95% Cl 1.13, 1.87)	5
Anticonvulsants- Pregabalin	Adverse Events	Moon 2010	Pregabalin 600 mg daily Placebo	1	240	50% (81/162)	35.9% (28/78)	RR 1.39 (95% Cl 1.00, 1.95)	8
Anticonvulsants- Pregabalin	Adverse Events	NCT00394901 2006	Pregabalin 300 mg daily Placebo	1	372	68.5% (61/89)	36.4% (12/33)	RR 1.88 (95% Cl 1.17, 3.02)	4
Anticonvulsants- Pregabalin	Adverse Events	NCT00394901 2006	Pregabalin 600 mg daily Placebo	1	372	79.4% (77/97)	36.4% (12/33)	RR 2.18 (95% Cl 1.37, 3.47)	3
Anticonvulsants- Pregabalin	≥1 Adverse Event	Arezzo 2008	Pregabalin 600 mg daily Placebo	1	167	84.1% (69/82)	77.6% (66/85)	RR 1.08 (95% Cl 0.93, 1.26)	NSS
Anticonvulsants- Pregabalin	≥1 Adverse Event	Stacey 2008	Pregabalin Fixed Dose (mean 295 mg) Placebo	1	269	62.5% (55/88)	44.4% (20/45)	RR 1.41 (95% Cl 0.98, 2.02)	NSS
Anticonvulsants- Pregabalin	>1 treatment- emergent adverse events	Huffman 2015	Pregabalin 150-300 mg daily Placebo	1	384	47.5% (94/198)	41.9% (78/186)	RR 1.13 (95% Cl 0.91, 1.42)	NSS
Anticonvulsants- Pregabalin	Abdominal Distention	Ziegler 2015	Pregabalin 150 mg twice daily Placebo	1	132	0% (0/70)	0% (0/62)	-	-
Anticonvulsants- Pregabalin	Adverse Events	Guan 2011	Pregabalin 150-600 mg daily	1	308	50% (103/206)	40.2% (41/102)	RR 1.24 (95% Cl 0.95, 1.63)	NSS

Anticonvulsants- Pregabalin	Adverse Events	Mu 2018	Pregabalin 300 mg daily Placebo	1	620	36.0% (113/314)	31.8% (98/308)	RR 1.13 (95% Cl 0.91, 1.41)	NSS
Anticonvulsants- Pregabalin	Adverse Events	NCT00394901 2006	Pregabalin 150 mg daily Placebo	1	372	50.6% (44/87)	34.4% (11/32)	RR 1.47 (95% Cl 0.87, 2.48)	NSS
Anticonvulsants- Pregabalin	Adverse Events	Rauck 2012	Pregabalin 300 mg daily Placebo	1	420	71.2% (47/66)	66.7% (20/30)	RR 1.07 (95% Cl 0.79, 1.44)	NSS
Anticonvulsants- Pregabalin	Anemia	McDonnell 2018	Pregabalin 300 mg daily Placebo	1	91	4.3% (2/46)	0% (0/45)	RR 4.89 (0.24 to 99.19)	NSS
Anticonvulsants- Pregabalin	Angina Pectoris	NCT00394901 2006	Pregabalin 150 mg daily Placebo	1	372	0% (0/87)	0% (0/32)	-	-
Anticonvulsants- Pregabalin	Angina Pectoris	NCT00394901 2006	Pregabalin 300 mg daily Placebo	1	372	0% (0/89)	0% (0/33)	-	-
Anticonvulsants- Pregabalin	Angina Pectoris	NCT00394901 2006	Pregabalin 600 mg daily Placebo	1	372	0% (0/97)	3.0% (1/33)	RR 0.12 (95% Cl 0.00, 2.77)	NSS
Anticonvulsants- Pregabalin	Arrhythmias	Vinik 2014	Pregabalin 300 mg daily Placebo	1	158	2% (1/50)	0% (0/108)	RR 6.41 (95% Cl 0.27, 154.70)	NSS
Anticonvulsants- Pregabalin	Arthralgia	Rauck 2012	Pregabalin 300 mg daily Placebo	1	96	4.5% (3/66)	6.7% (2/30)	RR 0.68 (95% Cl 0.12, 3.87)	NSS
Anticonvulsants- Pregabalin	Asthma	NCT00394901 2006	Pregabalin 150 mg daily Placebo	1	372	0% (0/87)	0% (0/32)	-	-
Anticonvulsants- Pregabalin	Asthma	NCT00394901 2006	Pregabalin 300 mg daily Placebo	1	372	1.1% (1/89)	0% (0/33)	RR 1.13 (95% Cl 0.05, 27.15)	NSS
Anticonvulsants- Pregabalin	Asthma	NCT00394901 2006	Pregabalin 600 mg daily	1	372	0% (0/97)	0% (0/33)	-	-

			Placebo						
Anticonvulsants- Pregabalin	Blood creatine phosphokinase increased	Satoh 2011	Pregabalin 300 mg daily Placebo	1	314	1.5% (2/134)	0% (0/67)	RR 2.52 (95% Cl 0.12, 51.73)	NSS
Anticonvulsants- Pregabalin	Blood creatine phosphokinase increased	Satoh 2011	Pregabalin 600 mg daily Placebo	1	314	4.4% (2/45)	0% (0/68)	RR 7.50 (95% Cl 0.37, 152.68)	NSS
Anticonvulsants- Pregabalin	Body Aches	Stacey 2008	Pregabalin Flexible Dose (mean 396 mg) Placebo	1	269	2.2% (2/91)	0% (0/45)	RR 2.50 (95% Cl 0.12, 51.01)	NSS
Anticonvulsants- Pregabalin	Body Aches	Stacey 2008	Pregabalin Fixed Dose (mean 295 mg) Placebo	1	269	0% (0/88)	0% (0/45)	-	-
Anticonvulsants- Pregabalin	Bronchitis	Rauck 2012	Pregabalin 300 mg daily Placebo	1	420	1.5% (1/66)	3.3% (1/30)	RR 0.45 (95% Cl 0.03, 7.03)	NSS
Anticonvulsants- Pregabalin	Cardiac Conduction Abnormalities	Vinik 2014	Pregabalin 300 mg daily Placebo	1	158	0% (0/50)	0.93% (1/108)	RR 0.71 (95% Cl 0.03, 17.19)	NSS
Anticonvulsants- Pregabalin	Cerebral infarction	NCT00394901 2006	Pregabalin 150 mg daily Placebo	1	372	0% (0/87)	0% (0/32)	-	-
Anticonvulsants- Pregabalin	Cerebral infarction	NCT00394901 2006	Pregabalin 300 mg daily Placebo	1	372	0% (0/89)	0% (0/33)	-	-
Anticonvulsants- Pregabalin	Cerebral infarction	NCT00394901 2006	Pregabalin 600 mg daily Placebo	1	372	0% (0/97)	3.0% (1/33)	RR 0.12 (95% Cl 0.00, 2.77)	NSS
Anticonvulsants- Pregabalin	Completed suicide	NCT00394901 2006	Pregabalin 150 mg daily Placebo	1	372	0% (0/87)	0% (0/32)	-	-

Anticonvulsants- Pregabalin	Completed suicide	NCT00394901 2006	Pregabalin 300 mg daily Placebo	1	372	0% (0/89)	0% (0/33)	-	-
Anticonvulsants- Pregabalin	Completed suicide	NCT00394901 2006	Pregabalin 600 mg daily Placebo	1	372	0% (0/97)	3.0% (1/33)	RR 0.12 (95% Cl 0.00, 2.77)	NSS
Anticonvulsants- Pregabalin	Congestive Heart Failure	NCT02215252 2014	Pregabalin 300 mg daily Placebo	1	91	2.2% (1/46)	0% (0/45)	RR 2.94 (95% Cl 0.12, 70.24)	NSS
Anticonvulsants- Pregabalin	COPD	NCT02215252 2014	Pregabalin 300 mg daily Placebo	1	91	0% (0/46)	0% (0/45)	-	-
Anticonvulsants- Pregabalin	Cough	McDonnell 2018	Pregabalin 300 mg daily Placebo	1	91	4.3% (2/46)	0% (0/45)	RR 4.89 (0.24 to 99.19)	NSS
Anticonvulsants- Pregabalin	Death	Moon 2010	Pregabalin 600 mg daily Placebo	1	240	0.62% (1/162)	0% (0/78)	RR 1.45 (95% Cl 0.06, 35.29)	NSS
Anticonvulsants- Pregabalin	Depressed Level of Consciousness	Stacey 2008	Pregabalin Flexible Dose (mean 396 mg) Placebo	1	269	2.2% (2/91)	0% (0/45)	RR 2.50 (95% Cl 0.12, 51.01)	NSS
Anticonvulsants- Pregabalin	Depressed Level of Consciousness	Stacey 2008	Pregabalin Fixed Dose (mean 295 mg) Placebo	1	269	1.1% (1/88)	2.2% (1/45)	RR 0.51 (95% Cl 0.03, 7.99)	NSS
Anticonvulsants- Pregabalin	Disorientation	Stacey 2008	Pregabalin Flexible Dose (mean 396 mg) Placebo	1	269	2.2% (2/91)	0% (0/45)	RR 2.50 (95% Cl 0.12, 51.01)	NSS
Anticonvulsants- Pregabalin	Disorientation	Stacey 2008	Pregabalin Fixed Dose (mean 295 mg) Placebo	1	269	2.3% (2/88)	0% (0/45)	RR 2.58 (95% Cl 0.13, 52.72)	NSS

Anticonvulsants- Pregabalin	ECG Result Changes	Guan 2011	Pregabalin 150-600 mg daily	1	308	1.9% (4/206)	2.9% (3/102)	RR 0.66 (95% Cl 0.15, 2.89)	NSS
Anticonvulsants- Pregabalin	Eczema	NCT00394901 2006	Pregabalin 150 mg daily Placebo	1	372	3.4% (3/87)	0% (0/32)	RR 2.63 (95% Cl 0.14, 49.46)	NSS
Anticonvulsants- Pregabalin	Eczema	NCT00394901 2006	Pregabalin 300 mg daily Placebo	1	372	0% (0/89)	3.0% (1/33)	RR 0.13 (95% Cl 0.01, 3.02)	NSS
Anticonvulsants- Pregabalin	Eczema	NCT00394901 2006	Pregabalin 600 mg daily Placebo	1	372	6.2% (6/97)	3.0% (1/33)	RR 2.04 (95% Cl 0.26, 16.34)	NSS
Anticonvulsants- Pregabalin	Enlarged Abdomen	Arezzo 2008	Pregabalin 600 mg daily Placebo	1	167	3.7% (3/82)	4.7% (4/85)	RR 0.78 (95% Cl 0.18, 3.37)	NSS
Anticonvulsants- Pregabalin	Excoriation	Rauck 2012	Pregabalin 300 mg daily Placebo	1	420	4.5% (3/66)	0% (0/30)	RR 3.24 (95% CL 0.17, 60.81)	NSS
Anticonvulsants- Pregabalin	Feeling Abnormal	Stacey 2008	Pregabalin Flexible Dose (mean 396 mg) Placebo	1	269	5.5% (5/91)	0% (0/45)	RR 5.50 (95% Cl 0.31, 97.33)	NSS
Anticonvulsants- Pregabalin	Feeling Abnormal	Stacey 2008	Pregabalin Fixed Dose (mean 295 mg) Placebo	1	269	1.1% (1/88)	0% (0/45)	RR 1.55 (95% Cl 0.06, 37.32)	NSS
Anticonvulsants- Pregabalin	Flu Syndrome	Rosenstock 2004	Pregabalin 300 mg daily Placebo	1	146	3.9% (3/76)	4.3% (3/70)	RR 0.92 (95% Cl 0.19, 4.41)	NSS
Anticonvulsants- Pregabalin	Gait disturbance	McDonnell 2018	Pregabalin 300 mg daily Placebo	1	91	4.3% (2/46)	0% (0/45)	RR 4.89 (0.24 to 99.19)	NSS
Anticonvulsants- Pregabalin	Hot Flush	Satoh 2011	Pregabalin 300 mg daily	1	314	0.75% (1/134)	0% (0/67)	RR 1.51 (95% Cl	NSS

			Placebo					0.06, 36.61)	
Anticonvulsants- Pregabalin	Hot Flush	Satoh 2011	Pregabalin 600 mg daily Placebo	1	314	4.4% (2/45)	1.5% (1/68)	RR 3.02 (95% Cl 0.28, 32.35)	NSS
Anticonvulsants- Pregabalin	Hyperglycemia	Smith 2014	Pregabalin 300 mg daily Placebo	1	191	7.1% (7/98)	2.2% (2/93)	RR 3.32 (95% Cl 0.71, 15.58)	NSS
Anticonvulsants- Pregabalin	Hypoesthesia	Rauck 2012	Pregabalin 300 mg daily Placebo	1	420	4.5% (3/66)	3.3% (1/30)	1.36 (95% Cl 0.15, 12.58)	NSS
Anticonvulsants- Pregabalin	Hypotension	NCT00394901 2006	Pregabalin 150 mg daily Placebo	1	372	0% (0/87)	0% (0/32)	-	-
Anticonvulsants- Pregabalin	Hypotension	NCT00394901 2006	Pregabalin 300 mg daily Placebo	1	372	1.1% (1/89)	0% (0/33)	RR 1.13 (95% Cl 0.05, 27.15)	NSS
Anticonvulsants- Pregabalin	Hypotension	NCT00394901 2006	Pregabalin 600 mg daily Placebo	1	372	0% (0/97)	0% (0/33)	-	-
Anticonvulsants- Pregabalin	Insomnia	Ziegler 2015	Pregabalin 150 mg twice daily Placebo	1	132	2.9% (2/70)	1.6% (1/62)	RR 1.77 (95% Cl 0.16, 19.06)	NSS
Anticonvulsants- Pregabalin	Joint Swelling	Stacey 2008	Pregabalin Flexible Dose (mean 396 mg) Placebo	1	269	0% (0/91)	0% (0/45)	-	-
Anticonvulsants- Pregabalin	Joint Swelling	Stacey 2008	Pregabalin Fixed Dose (mean 295 mg) Placebo	1	269	2.3% (2/88)	2.2% (1/45)	RR 1.02 (95% Cl 0.10, 10.98)	NSS

Anticonvulsants- Pregabalin	Lab Result Changes	Guan 2011	Pregabalin 150-600 mg daily	1	308	6.3% (13/206)	6.9% (7/102)	RR 0.92 (95% Cl 0.38, 2.23)	NSS
Anticonvulsants- Pregabalin	Large Intestinal Stricture	NCT00394901 2006	Pregabalin 150 mg daily Placebo	1	372	0% (0/87)	0% (0/32)	-	-
Anticonvulsants- Pregabalin	Large Intestinal Stricture	NCT00394901 2006	Pregabalin 300 mg daily Placebo	1	372	0% (0/89)	0% (0/33)	-	-
Anticonvulsants- Pregabalin	Large Intestinal Stricture	NCT00394901 2006	Pregabalin 600 mg daily Placebo	1	372	1.0% (1/97)	0% (0/33)	RR 1.04 (95% Cl 0.04, 24.95)	NSS
Anticonvulsants- Pregabalin	Loss of consciousness	NCT00394901 2006	Pregabalin 150 mg daily Placebo	1	372	0% (0/87)	0% (0/32)	-	-
Anticonvulsants- Pregabalin	Loss of consciousness	NCT00394901 2006	Pregabalin 300 mg daily Placebo	1	372	0% (0/89)	0% (0/33)	-	-
Anticonvulsants- Pregabalin	Loss of consciousness	NCT00394901 2006	Pregabalin 600 mg daily Placebo	1	372	0% (0/97)	3.0% (1/33)	RR 0.12 (95% Cl 0.00, 2.77)	NSS
Anticonvulsants- Pregabalin	Memory Impairment	Stacey 2008	Pregabalin Flexible Dose (mean 396 mg) Placebo	1	269	3.3% (3/91)	0% (0/45)	RR 3.50 (95% Cl 0.18, 66.34)	NSS
Anticonvulsants- Pregabalin	Memory Impairment	Stacey 2008	Pregabalin Fixed Dose (mean 295 mg) Placebo	1	269	0% (0/88)	0% (0/45)	-	-
Anticonvulsants- Pregabalin	Muscle spasms	McDonnell 2018	Pregabalin 300 mg daily Placebo	1	91	2.2% (1/46)	4.4% (2/45)	RR 0.49 (0.05 to 5.21)	NSS
Anticonvulsants- Pregabalin	Muscular Weakness	Satoh 2011	Pregabalin 300 mg daily Placebo	1	314	0% (0/134)	0% (0/67)	-	-

Anticonvulsants- Pregabalin	Muscular Weakness	Satoh 2011	Pregabalin 600 mg daily Placebo	1	314	4.4% (2/45)	0% (0/68)	RR 7.50 (95% Cl 0.37, 152.68)	NSS
Anticonvulsants- Pregabalin	Myalgia	McDonnell 2018	Pregabalin 300 mg daily Placebo	1	91	4.3% (2/46)	0% (0/45)	RR 4.89 (0.24 to 99.19)	NSS
Anticonvulsants- Pregabalin	Myocardial Infarction	NCT00394901 2006	Pregabalin 150 mg daily Placebo	1	372	1.1% (1/87)	0% (0/32)	RR 1.13 (95% Cl 0.05, 26.93)	NSS
Anticonvulsants- Pregabalin	Myocardial Infarction	NCT00394901 2006	Pregabalin 300 mg daily Placebo	1	372	0% (0/89)	0% (0/33)	-	-
Anticonvulsants- Pregabalin	Myocardial Infarction	NCT00394901 2006	Pregabalin 600 mg daily Placebo	1	372	0% (0/97)	0% (0/33)	-	-
Anticonvulsants- Pregabalin	Neuropathy	Lesser 2004	Pregabalin 75 mg daily Placebo	1	337	9.1% (7/77)	6.3% (2/32)	RR 1.45 (95% Cl 0.32, 6.63)	NSS
Anticonvulsants- Pregabalin	Neuropathy	Lesser 2004	Pregabalin 300 mg daily Placebo	1	337	8.6% (7/81)	9.4% (3/32)	RR 0.92 (95% Cl 0.25, 3.35)	NSS
Anticonvulsants- Pregabalin	Neuropathy	Lesser 2004	Pregabalin 600 mg daily Placebo	1	337	8.5% (7/82)	9.1% (3/33)	RR 0.94 (95% Cl 0.26, 3.41)	NSS
Anticonvulsants- Pregabalin	Pain in Extremity	Rauck 2012	Pregabalin 300 mg daily Placebo	1	420	3.0% (2/66)	3.3% (1/30)	RR 0.91 (95% Cl 0.09, 9.64)	NSS
Anticonvulsants- Pregabalin	Paresthesia	Rauck 2012	Pregabalin 300 mg daily Placebo	1	420	4.5% (3/66)	0% (0/30)	RR 3.24 (95% CL 0.17, 60.81)	NSS
Anticonvulsants- Pregabalin	Pneumonia	NCT02215252 2014	Pregabalin 300 mg daily Placebo	1	91	0% (0/46)	0% (0/45)	-	-

Anticonvulsants- Pregabalin	Prostate cancer	NCT00394901 2006	Pregabalin 150 mg daily Placebo	1	372	0% (0/87)	0% (0/32)	-	-
Anticonvulsants- Pregabalin	Prostate cancer	NCT00394901 2006	Pregabalin 300 mg daily Placebo	1	372	0% (0/89)	0% (0/33)	-	-
Anticonvulsants- Pregabalin	Prostate cancer	NCT00394901 2006	Pregabalin 600 mg daily Placebo	1	372	0% (0/97)	3.0% (1/33)	RR 0.12 (95% Cl 0.00, 2.77)	NSS
Anticonvulsants- Pregabalin	Pruritus	Liu 2017	Pregabalin 300 mg daily Placebo	1	220	0.90% (1/111)	4.6% (5/109)	RR 0.20 (95% Cl 0.02, 1.65)	NSS
Anticonvulsants- Pregabalin	Rash	Ziegler 2015	Pregabalin 150 mg twice daily Placebo	1	132	0% (0/70)	1.6% (1/62)	RR 0.30 (95% Cl 0.01, 7.13)	NSS
Anticonvulsants- Pregabalin	Severe Adverse Events	Tolle 2008	Pregabalin 150 mg daily Placebo	1	395	6.1% (6/99)	3.1% (1/32)	RR 1.94 (95% Cl 0.24, 15.51)	NSS
Anticonvulsants- Pregabalin	Severe Adverse Events	Tolle 2008	Pregabalin 300 mg daily Placebo	1	395	8.1% (8/99)	0% (0/32)	RR 5.61 (95% Cl 0.33, 94.58)	NSS
Anticonvulsants- Pregabalin	Severe Adverse Events	Tolle 2008	Pregabalin 600 mg daily Placebo	1	395	10.9% (11/101)	0% (0/32)	RR 7.44 (95% Cl 0.45, 122.87)	NSS
Anticonvulsants- Pregabalin	Small intestinal obstruction	NCT00394901 2006	Pregabalin 150 mg daily Placebo	1	372	1.1% (1/87)	0% (0/32)	RR 1.13 (95% Cl 0.05, 26.93)	NSS
Anticonvulsants- Pregabalin	Small intestinal obstruction	NCT00394901 2006	Pregabalin 300 mg daily Placebo	1	372	0% (0/89)	0% (0/33)	-	-
Anticonvulsants- Pregabalin	Small intestinal obstruction	NCT00394901 2006	Pregabalin 600 mg daily	1	372	0% (0/97)	0% (0/33)	-	-

			Placebo						
Anticonvulsants- Pregabalin	Speech Disorder	Dworkin 2003	Pregabalin 300-600 mg daily Placebo	1	173	5.6% (5/89)	0% (0/84)	RR 10.39 (95% Cl 0.58, 185.05)	NSS
Anticonvulsants- Pregabalin	Subdural haematoma	NCT00394901 2006	Pregabalin 150 mg daily Placebo	1	372	0% (0/87)	0% (0/32)	-	-
Anticonvulsants- Pregabalin	Subdural haematoma	NCT00394901 2006	Pregabalin 300 mg daily Placebo	1	372	1.1% (1/89)	0% (0/33)	RR 1.13 (95% Cl 0.05, 27.15)	NSS
Anticonvulsants- Pregabalin	Subdural haematoma	NCT00394901 2006	Pregabalin 600 mg daily Placebo	1	372	0% (0/97)	3.0% (1/33)	RR 0.12 (95% Cl 0.00, 2.77)	NSS
Anticonvulsants- Pregabalin	Thirst	NCT00394901 2006	Pregabalin 150 mg daily Placebo	1	372	3.4% (3/87)	3.1% (1/32)	RR 1.10 (95% Cl 0.12, 10.23)	NSS
Anticonvulsants- Pregabalin	Thirst	NCT00394901 2006	Pregabalin 300 mg daily Placebo	1	372	7.9% (7/89)	3.0% (1/33)	RR 2.60 (95% Cl 0.33, 20.30)	NSS
Anticonvulsants- Pregabalin	Thirst	NCT00394901 2006	Pregabalin 600 mg daily Placebo	1	372	7.2% (7/97)	3.0% (1/33)	RR 2.38 (95% Cl 0.30, 18.64)	NSS
Anticonvulsants- Pregabalin	Treatment- emergent adverse events	NCT02215252 2014	Pregabalin 300 mg daily Placebo	1	91	52.2% (24/46)	37.8% (17/45)	RR 1.38 (95% Cl 0.87, 2.20)	NSS
Anticonvulsants- Pregabalin	Treatment- emergent adverse events	Smith 2014	Pregabalin 300 mg daily Placebo	1	191	62.2% (61/98)	64.5% (60/93)	RR 0.96 (95% Cl 0.78, 1.20)	NSS
Anticonvulsants- Pregabalin	Treatment- emergent Adverse Events	Ziegler 2015	Pregabalin 150 mg twice daily Placebo	1	132	54.3% (38/70)	54.8% (34/62)	RR 0.99 (95% Cl 0.72, 1.35)	NSS

Anticonvulsants- Pregabalin	Tremor	Stacey 2008	Pregabalin Flexible Dose (mean 396 mg) Placebo	1	269	3.3% (3/91)	0% (0/45)	RR 3.50 (95% Cl 0.18, 66.34)	NSS
Anticonvulsants- Pregabalin	Tremor	Stacey 2008	Pregabalin Fixed Dose (mean 295 mg) Placebo	1	269	1.1% (1/88)	0% (0/45)	RR 1.55 (95% Cl 0.06, 37.32)	NSS
Anticonvulsants- Pregabalin	Viral Gastroenteritis	Ziegler 2015	Pregabalin 150 mg twice daily Placebo	1	132	0% (0/70)	0% (0/62)	-	-
Anticonvulsants- Pregabalin	Visual Disturbance	Stacey 2008	Pregabalin Flexible Dose (mean 396 mg) Placebo	1	269	4.4% (4/91)	0% (0/45)	RR 4.50 (95% Cl 0.25, 81.81)	NSS
Anticonvulsants- Pregabalin	Visual Disturbance	Stacey 2008	Pregabalin Fixed Dose (mean 295 mg) Placebo	1	269	0% (0/88)	0% (0/45)	-	-
Anticonvulsants- Pregabalin	Vulvovaginal Pruritus	NCT02215252 2014	Pregabalin 300 mg daily Placebo	1	91	5.3% (1/19)	0% (0/14)	RR 2.25 (95% Cl 0.10, 51.46)	NSS
Anticonvulsants- Pregabalin	Weight Change	Tolle 2008	Pregabalin 150 mg daily Placebo	1	395	6.1% (6/99)	0% (0/32)	RR 4.29 (95% Cl 0.25, 74.12)	NSS
Anticonvulsants- Pregabalin	Weight Change	Tolle 2008	Pregabalin 300 mg daily Placebo	1	395	6.1% (6/99)	0% (0/32)	RR 4.29 (95% Cl 0.25, 74.12)	NSS
Anticonvulsants- Pregabalin	Weight Change	Tolle 2008	Pregabalin 600 mg daily Placebo	1	395	6.9% (7/101)	0% (0/32)	RR 4.85 (95% Cl 0.28, 82.71)	NSS
Anticonvulsants- Topiramate	Diarrhea	Raskin 2004	Topiramate 400 mg	1	323	11.2% (24/214)	3.7% (4/109)	RR 3.06 (95% Cl	14

			Placebo					1.09, 8.59)	
Anticonvulsants- Topiramate	Loss of Appetite	Raskin 2004	Topiramate 400 mg Placebo	1	323	10.7% (23/214)	0.92% (1/109)	RR 11.72 (95% Cl 1.60, 85.60)	11
Anticonvulsants- Topiramate	Paresthesia	Raskin 2004	Topiramate 400 mg Placebo	1	323	8.4% (18/214)	1.8% (2/109)	RR 4.58 (95% Cl 1.08, 19.40)	16
Anticonvulsants- Topiramate	Weight loss 0-5%	Raskin 2004	Topiramate 400 mg Placebo	1	323	52.6% (111/211)	38.8% (31/80)	RR 1.36 (95% Cl 1.00, 1.84)	8
Anticonvulsants- Topiramate	Weight loss 5-10%	Raskin 2004	Topiramate 400 mg Placebo	1	323	21.8% (46/211)	5% (4/80)	RR 4.36 (95% Cl 1.62, 11.72)	6
Anticonvulsants- Topiramate	Arthralgia	Raskin 2004	Topiramate 400 mg Placebo	1	323	3.7% (8/214)	5.5% (6/109)	RR 0.68 (95% Cl 0.24, 1.91)	NSS
Anticonvulsants- Topiramate	Difficulty concentrating	Raskin 2004	Topiramate 400 mg Placebo	1	323	5.1% (11/214)	0.92% (1/109)	RR 5.60 (95% Cl 0.73, 42.84)	NSS
Anticonvulsants- Topiramate	Dizziness	Raskin 2004	Topiramate 400 mg Placebo	1	323	7.0% (15/214)	5.5% (6/109)	RR 1.27 (95% Cl 0.51, 3.19)	NSS
Anticonvulsants- Topiramate	Fatigue	Raskin 2004	Topiramate 400 mg Placebo	1	323	7.0% (15/214)	1.8% (2/109)	RR 3.82 (95% Cl 0.89, 16.40)	NSS
Anticonvulsants- Topiramate	Headache	Raskin 2004	Topiramate 400 mg Placebo	1	323	5.6% (12/214)	9.2% (10/109)	RR 0.61 (95% Cl 0.27, 1.37)	NSS
Anticonvulsants- Topiramate	Injury	Raskin 2004	Topiramate 400 mg Placebo	1	323	3.7% (8/214)	7.3% (8/109)	RR 0.51 (95% Cl 0.20, 1.32)	NSS

Anticonvulsants- Topiramate	Markedly severe adverse events	Raskin 2004	Topiramate 400 mg Placebo	1	323	15.0% (32/214)	11.0% (12/109)	RR 1.36 (95% Cl 0.73, 2.53)	NSS
Anticonvulsants- Topiramate	Nausea	Raskin 2004	Topiramate 400 mg Placebo	1	323	9.3% (20/214)	5.5% (6/109)	RR 1.70 (95% Cl 0.70, 4.10)	NSS
Anticonvulsants- Topiramate	Pain	Raskin 2004	Topiramate 400 mg Placebo	1	323	1.9% (4/214)	6.4% (7/109)	RR 0.29 (95% Cl 0.09, 0.97)	NSS
Anticonvulsants- Topiramate	Serious adverse events	Raskin 2004	Topiramate 400 mg Placebo	1	323	4.7% (10/214)	5.5% (6/109)	RR 0.85 (95% Cl 0.32, 2.27)	NSS
Anticonvulsants- Topiramate	Sinusitis	Raskin 2004	Topiramate 400 mg Placebo	1	323	6.1% (13/214)	5.5% (6/109)	RR 1.10 (95% Cl 0.43, 2.82)	NSS
Anticonvulsants- Topiramate	Somnolence	Raskin 2004	Topiramate 400 mg Placebo	1	323	9.8% (21/214)	3.7% (4/109)	RR 2.67 (95% Cl 0.94, 7.60)	NSS
Anticonvulsants- Topiramate	Taste Change	Raskin 2004	Topiramate 400 mg Placebo	1	323	6.5% (14/214)	0% (0/109)	RR 14.84 (95% Cl 0.89, 246.41)	NSS
Anticonvulsants- Topiramate	Upper Respiratory Tract Infection	Raskin 2004	Topiramate 400 mg Placebo	1	323	8.9% (19/214)	5.5% (6/109)	RR 1.61 (95% Cl 0.66, 3.92)	NSS
Anticonvulsants- Topiramate	Weight Increased	Raskin 2004	Topiramate 400 mg Placebo	1	323	16.6% (35/211)	55% (44/80)	RR 0.30 (95% Cl 0.21, 0.43)	NSS
Anticonvulsants- Topiramate	Weight loss 10-20%	Raskin 2004	Topiramate 400 mg Placebo	1	323	1.9% (4/211)	0% (0/80)	RR 3.44 (95% Cl 0.19, 63.16)	NSS
Opioids	Any adverse event	Simpson 2016	Buprenorphine Patch 5-40 mg/hour Placebo Patch	1	186	93.5% (87/93)	81.7% (76/93)	RR 1.14 (95% Cl 1.03, 1.28)	9

Opioids	Infections and Infestations	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	29.6% (50/169)	17.8% (30/169)	RR 1.67 (95% Cl 1.12, 2.48)	9
Opioids	Metabolism and Nutrition Disorders	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	8.9% (15/169)	2.4% (4/169)	RR 3.75 (95% Cl 1.27, 11.07)	16
Opioids	Psychiatric Disorders	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	17.2% (29/169)	9.5% (16/169)	RR 1.81 (95% Cl 1.02, 3.21)	13
Opioids	Skin and Subcutaneous Disorders	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	20.1% (34/169)	11.2% (19/169)	RR 1.79 (95% Cl 1.06, 3.01)	12
Opioids	Abdominal Discomfort	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	6.7% (4/60)	3.2% (1/31)	RR 2.07 (95% Cl 0.24, 17.71)	NSS
Opioids	Abdominal Distension	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Abnormal Hepatic Function	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	3.2% (1/31)	RR 0.52 (95% Cl 0.03, 7.98)	NSS
Opioids	Abnormal Liver Function Test	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	3.3% (2/60)	3.2% (1/31)	RR 1.03 (95% Cl 0.10, 10.96)	NSS
Opioids	Anaemia	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Angina Pectoris (SAE)	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS

Opioids	Anxiety	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Autonomic Nervous System Imbalance	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Back Pain	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Blood and Lymphatic System Disorders	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	0.59% (1/169)	1.8% (3/169)	RR 0.33 (95% Cl 0.04, 3.17)	NSS
Opioids	Blood Urine Present	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	5% (3/60)	0% (0/31)	RR 3.67 (95% Cl 0.20, 68.92)	NSS
Opioids	Cardiac Disorders	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	3.6% (6/169)	2.4% (4/169)	RR 1.50 (95% Cl 0.43, 5.22)	NSS
Opioids	Chalazion	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Chest Pain	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Cystitis	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Decreased Appetite	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily	1	91	15% (9/60)	3.2% (1/31)	RR 4.65 (95% Cl	NSS

			Placebo					0.62 <i>,</i> 35.05)	
Opioids	Decreased Lymphocyte Percentage	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Dehydration	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Delirium (SAE)	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Depression	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Dermatitis	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Diabetic Retinopathy	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Diabetic Ulcer (SAE)	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Drug Withdrawal Syndrome	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	8.3% (5/60)	0% (0/31)	RR 5.77 (95% Cl 0.33, 101.10)	NSS
Opioids	Drug Withdrawal Syndrome (SAE)	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl	NSS

			Placebo					0.07 <i>,</i> 37.54)	
Opioids	Dyspnoea	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Dysuria	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Ear and Labyrinth Disorders	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	7.7% (13/169)	4.1% (7/169)	RR 1.86 (95% Cl 0.76, 4.54)	NSS
Opioids	ECG ST Segment Depression	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Eczema	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	3.3% (2/60)	0% (0/31)	RR 2.62 (95% Cl 0.13, 53.01)	NSS
Opioids	Erythema	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	3.3% (2/60)	0% (0/31)	RR 2.62 (95% Cl 0.13, 53.01)	NSS
Opioids	Eye Disorders	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	4.7% (8/169)	1.2% (2/169)	RR 4.00 (95% Cl 0.86, 18.56)	NSS
Opioids	Facet Joint Syndrome	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Fall	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS

Opioids	Feeling Abnormal	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Feeling Hot	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Gastritis	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Gastroenteritis	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	5% (3/60)	3.2% (1/31)	RR 1.55 (95% Cl 0.17, 14.29)	NSS
Opioids	Hallucination	Zin 2010	Oxycodone 2 mg/ml twice daily Placebo	1	62	6.9% (2/29)	0% (0/33)	RR 5.67 (95% Cl 0.28, 113.42)	NSS
Opioids	Hepatobiliary Disorders	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	0% (0/169)	0.59% (1/169)	RR 0.33 (95% Cl 0.01, 8.13)	NSS
Opioids	Herpes Simplex	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Hot Flush	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Hyperglyaemia	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS

Opioids	Hyperhidrosis	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Hyperlipidaemia	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Hypertension	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	3.3% (2/60)	0% (0/31)	RR 2.62 (95% Cl 0.13, 53.01)	NSS
Opioids	Hypoglycaemia	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	3.3% (2/60)	0% (0/31)	RR 2.62 (95% Cl 0.13, 53.01)	NSS
Opioids	Hypotension	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Hypothyroidism	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Hypoventilation	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Imbalance	Zin 2010	Oxycodone 2 mg/ml twice daily Placebo	1	62	6.9% (2/29)	6.1% (2/33)	RR 1.14 (95% Cl 0.17, 7.57)	NSS
Opioids	Increased Blood Alkaline Phosphatase	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS

Opioids	Increased Blood Creatine Phosphokinase	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	3.3% (2/60)	0% (0/31)	RR 2.62 (95% Cl 0.13, 53.01)	NSS
Opioids	Increased Blood Pressure	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	3.2% (1/31)	RR 0.52 (95% Cl 0.03, 7.98)	NSS
Opioids	Increased Eosinophil Percentage	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Increased Gamma- glutamyltransferase	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Increased Glycosylated Haemoglobin	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Increased Neutrophil Count	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Increased White Blood Cell Count	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Ingrown Nail	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Injury, Poisoning, and Procedural Complications	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	7.1% (12/169)	9.5% (16/169)	RR 0.75 (95% Cl 0.37, 1.54)	NSS

Opioids	Insomnia	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	8.3% (5/60)	0% (0/31)	RR 5.77 (95% Cl 0.33, 101.10)	NSS
Opioids	Iron Deficiency Anaemia	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Irritability	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Irritable Bowel Syndrome	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Listlessness	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Loss of Consciousness (SAE)	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Macular Oedema	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Malaise	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	5% (3/60)	3.2% (1/31)	RR 1.55 (95% Cl 0.17, 14.29)	NSS
Opioids	Motion Sickness	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS

Opioids	MSK and Connective Tissue Disorders	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	18.3% (31/169)	15.4% (26/169)	RR 1.19 (95% Cl 0.74, 1.92)	NSS
Opioids	Muscular Weakness	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Nasopharyngitis	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	11.7% (7/60)	12.9% (4/31)	RR 0.90 (95% Cl 0.29, 2.85)	NSS
Opioids	Neoplasms benign, malignant and unspecified (including cysts and polyps)	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	1.8% (3/169)	1.2% (2/169)	RR 1.50 (95% Cl 0.25, 8.86)	NSS
Opioids	Ocular Hyperaemia	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Oedema	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Oropharyngeal Pain	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	3.3% (2/60)	0% (0/31)	RR 2.62 (95% Cl 0.13, 53.01)	NSS
Opioids	Otitis Media	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Pain in Extremity	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS

Opioids	Periodontitis	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Peripheral Edema	Zin 2010	Oxycodone 2 mg/ml twice daily Placebo	1	62	3.4% (1/29)	9.1% (3/33)	RR 0.38 (95% Cl 0.04, 3.45)	NSS
Opioids	Postural Dizziness	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Protein Urine Present	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	3.3% (2/60)	0% (0/31)	RR 2.62 (95% Cl 0.13, 53.01)	NSS
Opioids	Prurigo	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Pruritus, generalized	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Pyrexia	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	3.3% (2/60)	0% (0/31)	RR 2.62 (95% Cl 0.13, 53.01)	NSS
Opioids	Radial Nerve Palsy	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Rash	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	3.3% (2/60)	0% (0/31)	RR 2.62 (95% Cl 0.13, 53.01)	NSS

Opioids	Renal and Urinary Problems	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	4.1% (7/169)	2.4% (4/169)	RR 1.75 (95% Cl 0.52, 5.87)	NSS
Opioids	Reproductive System and Breast Disorders	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	1.8% (3/169)	0% (0/169)	RR 7.00 (95% Cl 0.36, 134.49)	NSS
Opioids	Respiratory, Thoracic and Mediastinal Disorders	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	1.8% (3/169)	0% (0/169)	RR 7.00 (95% Cl 0.36, 134.49)	NSS
Opioids	Retinal Haemorrhage	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	3.2% (1/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Rhinitis Allergic	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Sinusitis	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Spinal OA	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Stomatitis	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Surgical and Medical Procedures	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	5.3% (9/169)	3.0% (5/169)	RR 1.80 (95% Cl 0.62, 5.26)	NSS
Opioids	Sweating	Zin 2010	Oxycodone 2 mg/ml twice daily	1	62	6.9% (2/29)	0% (0/33)	RR 5.67 (95% Cl	NSS

			Placebo					0.28, 113.42)	
Opioids	Tachypnoea	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Thirst	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	8.3% (5/60)	0% (0/31)	RR 5.77 (95% Cl 0.33, 101.10)	NSS
Opioids	Tinea Pedis	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Tonsillitis	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Tremor	Zin 2010	Oxycodone 2 mg/ml twice daily Placebo	1	62	6.9% (2/29)	3.0% (1/33)	RR 2.28 (95% Cl 0.22, 23.82)	NSS
Opioids	Trichiasis	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Urinary Tract Infection (SAE)	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	0% (0/60)	3.2% (1/31)	RR 0.17 (95% Cl 0.01, 4.17)	NSS
Opioids	Vascular Disorders	Hanna 2008	Oxycodone 10- 80 mg daily Placebo	1	338	4.7% (8/169)	2.4% (4/169)	RR 2.00 (95% Cl 0.61, 6.52)	NSS
Opioids	Visual Disturbances	Zin 2010	Oxycodone 2 mg/ml twice daily Placebo	1	62	10.3% (3/29)	6.1% (2/33)	RR 1.71 (95% Cl 0.31, 9.52)	NSS

Opioids	Vomiting (SAE)	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Wound	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	1.7% (1/60)	0% (0/31)	RR 1.57 (95% Cl 0.07, 37.54)	NSS
Opioids	Xeroderma	NCTT01124617 2010	Tapentadol 25- 250 mg twice daily Placebo	1	91	3.3% (2/60)	3.2% (1/31)	RR 1.03 (95% Cl 0.10, 10.96)	NSS
Rubefacients	≥1 Treatment- emergent Adverse Event	Irving 2011	8% Capsaicin Patch; Applied for one, 60- minute session 0.04% Capsaicin Placebo Patch	1	416	98.1% (208/212)	86.8% (177/204)	RR 1.13 (95% Cl 1.07, 1.20)	9
Rubefacients	≥1 Treatment- emergent Adverse Event	Webster 2010	8% Capsaicin Patch; Applied for one, 60- minute session 0.04% Capsaicin Placebo Patch	1	155	74.5% (76/102)	52.8% (28/53)	RR 1.41 (95% Cl 1.07, 1.86)	5
Rubefacients	Any adverse event	Backonja 2008	8% Capsaicin Patch applied once for 60 minutes 0.04% Placebo Patch	1	402	99.0% (203/205)	88.3% (174/197)	RR 1.12 (95% Cl 1.06, 1.18)	10
Rubefacients	Any adverse event	Vinik 2015	8% Capsaicin Patch; applied for 60 minutes, 1-7 times during intervention	1	468	69.4% (109/157)	48.1% (37/77)	RR 1.44 (95% Cl 1.12, 1.86)	5

			period (separated by 8 week intervals) Standard of Care						
Rubefacients	Any adverse event	Vinik 2015	8% Capsaicin Patch; applied for 30 minutes, 1-7 times during intervention period (separated by 8 week intervals) Standard of Care	1	468	67.3% (105/156)	48.7% (38/78)	RR 1.38 (95% Cl 1.07, 1.78)	6
Rubefacients	Treatment-related Adverse Events	Simpson 2017	8% Capsaicin Patch (applied once for 30 minutes) Placebo Patch	1	369	46.8% (87/186)	33.9% (62/183)	RR 1.38 (95% Cl 1.07, 1.78)	8
Rubefacients	Application Site Discoloration	Webster 2010	8% Capsaicin Patch; Applied for one, 60- minute session 0.04% Capsaicin Placebo Patch	1	155	0% (0/102)	5.7% (3/53)	RR 0.07 (95% Cl 0.00, 1.42)	NSS
Rubefacients	Application Site Dryness	Webster 2010	8% Capsaicin Patch; Applied for one, 60- minute session	1	155	9.8% (10/102)	3.8% (2/53)	RR 2.60 (95% Cl 0.59, 11.43)	NSS

			0.04% Capsaicin Placebo Patch						
Rubefacients	Application Site Urticaria	Webster 2010	8% Capsaicin Patch; Applied for one, 60- minute session 0.04% Capsaicin Placebo Patch	1	155	2.9% (3/102)	0% (0/53)	RR 3.67 (95% Cl 0.19, 69.76)	NSS
Rubefacients	Application Site Vesicles	Webster 2010	8% Capsaicin Patch; Applied for one, 60- minute session 0.04% Capsaicin Placebo Patch	1	155	4.9% (5/102)	1.9% (1/53)	RR 2.60 (95% Cl 0.31, 21.67)	NSS
Rubefacients	Arthralgia	Watson 1993	0.075% Capsaicin Cream applied four times daily Vehicle Cream	1	143	1.4% (1/74)	0% (0/69)	RR 2.8 (95% Cl 0.12, 67.60)	NSS
Rubefacients	Asthenia	Watson 1993	0.075% Capsaicin Cream applied four times daily Vehicle Cream	1	143	4.1% (3/74)	0% (0/69)	RR 6.53 (95% Cl 0.34, 124.24)	NSS
Rubefacients	Bone Disorder	Watson 1993	0.075% Capsaicin Cream applied four times daily Vehicle Cream	1	143	1.4% (1/74)	1.4% (1/69)	RR 0.93 (95% Cl 0.06, 14.62)	NSS
Rubefacients	Bronchitis	Webster 2010	8% Capsaicin Patch; Applied	1	155	2.9% (3/102)	0% (0/53)	RR 3.67 (95% Cl	NSS

			for one, 60- minute session 0.04% Capsaicin Placebo Patch					0.19 <i>,</i> 69.76)	
Rubefacients	Cerebrovascular Accident	Watson 1993	0.075% Capsaicin Cream applied four times daily Vehicle Cream	1	143	2.7% (2/74)	0% (0/69)	RR 4.67 (95% Cl 0.23, 95.52)	NSS
Rubefacients	Diarrhea	Watson 1993	0.075% Capsaicin Cream applied four times daily Vehicle Cream	1	143	0% (0/74)	2.9% (2/69)	RR 0.19 (95% Cl 0.01, 3.82)	NSS
Rubefacients	Dry Skin	Capsaicin Study Group 1992	0.075% Capsaicin Cream applied four times daily Vehicle Cream	1	277	3.6% (5/138)	4.3% (6/139)	RR 0.84 (95% Cl 0.26, 2.69)	NSS
Rubefacients	Epistaxis	Watson 1993	0.075% Capsaicin Cream applied four times daily Vehicle Cream	1	143	0% (0/74)	1.4% (1/69)	RR 0.31 (95% Cl 0.01, 7.51)	NSS
Rubefacients	Erythema (Location not specified)	Irving 2011	8% Capsaicin Patch; Applied for one, 60- minute session 0.04% Capsaicin Placebo Patch	1	416	6.1% (13/212)	7.8% (16/204)	RR 0.78 (95% Cl 0.39, 1.58)	NSS

Rubefacients	Evidence of Irritation	Simpson 2017	8% Capsaicin Patch (applied once for 30 minutes) Placebo Patch	1	369	8.6% (16/186)	5.5% (10/183)	RR 1.57 (95% Cl 0.73, 3.38)	NSS
Rubefacients	Facial Edema	Watson 1993	0.075% Capsaicin Cream applied four times daily Vehicle Cream	1	143	0% (0/74)	1.4% (1/69)	RR 0.31 (95% Cl 0.01, 7.51)	NSS
Rubefacients	Fever	Watson 1993	0.075% Capsaicin Cream applied four times daily Vehicle Cream	1	143	1.4% (1/74)	0% (0/69)	RR 2.8 (95% Cl 0.12, 67.60)	NSS
Rubefacients	Heart Failure	Watson 1993	0.075% Capsaicin Cream applied four times daily Vehicle Cream	1	143	0% (0/74)	1.4% (1/69)	RR 0.31 (95% Cl 0.01, 7.51)	NSS
Rubefacients	Herpes Zoster	Webster 2010	8% Capsaicin Patch; Applied for one, 60- minute session 0.04% Capsaicin Placebo Patch	1	155	2.9% (3/102)	3.8% (2/53)	RR 0.78 (95% Cl 0.13, 4.52)	NSS
Rubefacients	Injury	Webster 2010	8% Capsaicin Patch; Applied for one, 60- minute session 0.04% Capsaicin Placebo Patch	1	155	0.98% (1/102)	3.8% (2/53)	RR 0.26 (95% Cl 0.02, 2.80)	NSS

Rubefacients	Musculoskeletal and Connective Tissue Disorders	Irving 2011	8% Capsaicin Patch; Applied for one, 60- minute session 0.04% Capsaicin Placebo Patch	1	416	6.6% (14/212)	7.8% (16/204)	RR 0.84 (95% Cl 0.42, 1.68)	NSS
Rubefacients	Pruritus (Location not specified)	Irving 2011	8% Capsaicin Patch; Applied for one, 60- minute session 0.04% Capsaicin Placebo Patch	1	416	3.3% (7/212)	0.98% (2/204)	RR 3.37 (95% Cl 0.71, 16.02)	NSS
Rubefacients	Respiratory, thoracic and mediastinal disorders	Irving 2011	8% Capsaicin Patch; Applied for one, 60- minute session 0.04% Capsaicin Placebo Patch	1	416	3.3% (7/212)	6.9% (14/204)	RR 0.48 (95% Cl 0.20, 1.17)	NSS
Rubefacients	Worsening of PHN	Backonja 2008	8% Capsaicin Patch applied once for 60 minutes 0.04% Placebo Patch	1	402	2.9% (6/205)	5.1% (10/197)	RR 0.58 (95% Cl 0.21, 1.56)	NSS
Rubefacients	Worsening of Postherpetic Neuralgia	Irving 2011	8% Capsaicin Patch; Applied for one, 60- minute session 0.04% Capsaicin Placebo Patch	1	416	7.1% (15/212)	5.9% (12/204)	RR 1.20 (95% Cl 0.58, 2.51)	NSS
SNRIs	>1 treatment- emergent adverse event	Gao 2014	Duloxetine 60 mg daily Placebo	1	404	46.5% (94/202)	35.6% (72/202)	RR 1.31 (95% Cl 1.03, 1.65)	10

SNRIs	≥1 treatment- emergent adverse event	Wernicke 2006	Duloxetine 60 mg daily Placebo	1	168	89.5% (102/114)	72.2% (39/54)	RR 1.24 (95% Cl 1.04, 1.48)	6
SNRIs	Adverse Events	Yasuda 2011	Duloxetine 60 mg daily Placebo	1	170	84.9% (73/86)	72.6% (61/84)	RR 1.17 (95% Cl 1.00, 1.37)	9
SNRIs	Dysuria	Gao 2010	Duloxetine 60- 120 mg daily Placebo	1	215	8.5% (9/106)	0.92% (1/109)	RR 9.25 (95% Cl 1.19, 71.79)	14
SNRIs	Treatment- emergent adverse events	Rowbotham 2005	Venlafaxine 150-225 mg daily Placebo	1	123	89.0% (73/82)	73.2% (30/41)	RR 1.22 (95% Cl 1.00, 1.49)	7
SNRIs	≥1 treatment- emergent adverse event	Gao 2010	Duloxetine 60- 120 mg daily Placebo	1	215	81.1% (86/106)	71.6% (78/109)	RR 1.13 (95% Cl 0.98, 1.32)	NSS
SNRIs	≥1 treatment- emergent adverse event	Wernicke 2006	Duloxetine 60 mg twice daily Placebo	1	166	85.7% (96/112)	74.1% (40/54)	RR 1.16 (95% Cl 0.97, 1.38)	NSS
SNRIs	Abdominal Distension	Gao 2010	Duloxetine 60- 120 mg daily Placebo	1	215	8.5% (9/106)	6.4% (7/109)	RR 1.32 (95% Cl 0.51, 3.42)	NSS
SNRIs	Abdominal Discomfort	Gao 2010	Duloxetine 60- 120 mg daily Placebo	1	215	3.8% (4/106)	5.5% (6/109)	RR 0.69 (95% Cl 0.20, 2.36)	NSS
SNRIs	Adverse Events	Yasuda 2011	Duloxetine 40 mg daily Placebo	1	168	84.7% (72/85)	74.7% (62/83)	RR 1.13 (95% Cl 0.97, 1.32)	NSS
SNRIs	Adverse Reaction	Rowbotham 2005	Venlafaxine 75 mg daily Placebo	1	122	7.3% (6/82)	5.0% (2/40)	RR 1.46 (95% Cl 0.31, 6.93)	NSS
SNRIs	Adverse Reaction	Rowbotham 2005	Venlafaxine 150-225 mg daily Placebo	1	123	9.8% (8/82)	2.4% (1/41)	RR 4.00 (95% Cl 0.52, 30.91)	NSS

SNRIs	ALT Increased	Yasuda 2011	Duloxetine 40 mg daily Placebo	1	168	5.9% (5/85)	3.6% (3/83)	RR 1.63 (95% Cl 0.40, 6.59)	NSS
SNRIs	ALT Increased	Yasuda 2011	Duloxetine 60 mg daily Placebo	1	170	5.8% (5/86)	3.6% (3/84)	RR 1.63 (95% Cl 0.40, 6.60)	NSS
SNRIs	Any adverse event	Allen 2014	Desvenlafaxine 50 mg daily Placebo	1	85	74.6% (47/63)	77.3% (17/22)	RR 0.97 (95% Cl 0.74, 1.26)	NSS
SNRIs	Any adverse event	Allen 2014	Desvenlafaxine 100 mg daily Placebo	1	109	74.7% (65/87)	77.3% (17/22)	RR 0.97 (95% Cl 0.75, 1.25)	NSS
SNRIs	Any adverse event	Allen 2014	Desvenlafaxine 200 mg daily Placebo	1	122	82.8% (82/99)	73.9% (17/23)	RR 1.12 (95% Cl 0.87, 1.45)	NSS
SNRIs	Any adverse event	Allen 2014	Desvenlafaxine 400 mg daily Placebo	1	92	91.3% (63/69)	73.9% (17/23)	RR 1.24 (95% Cl 0.96, 1.59)	NSS
SNRIs	AST Increased	Yasuda 2011	Duloxetine 40 mg daily Placebo	1	168	5.9% (5/85)	3.6% (3/83)	RR 1.63 (95% Cl 0.40, 6.59)	NSS
SNRIs	AST Increased	Yasuda 2011	Duloxetine 60 mg daily Placebo	1	170	9.3% (8/86)	3.6% (3/84)	RR 2.60 (95% Cl 0.72, 9.49)	NSS
SNRIs	Chest Pain (SAE)	Goldstein 2005	Duloxetine 20 mg daily Placebo	1	153	0.87% (1/115)	0% (0/38)	RR 1.01 (95% Cl 0.04, 24.26)	NSS
SNRIs	Chest Pain (SAE)	Goldstein 2005	Duloxetine 60 mg daily Placebo	1	152	0% (0/114)	0% (0/38)	-	-
SNRIs	Chest Pain (SAE)	Goldstein 2005	Duloxetine 120 mg daily Placebo	1	152	0% (0/113)	2.6% (1/39)	RR 0.12 (95% Cl 0.00, 2.81)	NSS
SNRIs	CK Increased	Yasuda 2011	Duloxetine 40 mg daily Placebo	1	168	7.1% (6/85)	3.6% (3/83)	RR 1.95 (95% Cl 0.51, 7.55)	NSS

SNRIs	CK Increased	Yasuda 2011	Duloxetine 60 mg daily Placebo	1	170	0% (0/86)	3.6% (3/84)	RR 0.14 (95% Cl 0.01, 2.66)	NSS
SNRIs	Clinically important ECG changes during treatment	Rowbotham 2005	Venlafaxine 75 mg daily Placebo	1	122	4.9% (4/82)	0% (0/40)	RR 4.45 (95% Cl 0.25, 80.62)	NSS
SNRIs	Clinically important ECG changes during treatment	Rowbotham 2005	Venlafaxine 150-225 mg daily Placebo	1	123	3.7% (3/82)	0% (0/41)	RR 3.54 (95% Cl 0.19, 67.00)	NSS
SNRIs	Dyspepsia	Rowbotham 2005	Venlafaxine 75 mg daily Placebo	1	122	8.5% (7/82)	2.5% (1/40)	RR 3.41 (95% Cl 0.43, 26.82)	NSS
SNRIs	Dyspepsia	Rowbotham 2005	Venlafaxine 150-225 mg daily Placebo	1	123	9.8% (8/82)	0% (0/41)	RR 8.60 (95% Cl 0.51, 145.48)	NSS
SNRIs	ECG Rhythm Changes	Rowbotham 2005	Venlafaxine 75 mg daily Placebo	1	122	6.1% (5/82)	2.5% (1/40)	RR 2.44 (95% Cl 0.29, 20.19)	NSS
SNRIs	ECG Rhythm Changes	Rowbotham 2005	Venlafaxine 150-225 mg daily Placebo	1	123	4.9% (4/82)	0% (0/41)	RR 4.55 (95% Cl 0.25, 82.61)	NSS
SNRIs	Flatulence	Rowbotham 2005	Venlafaxine 75 mg daily Placebo	1	122	1.2% (1/82)	2.5% (1/40)	RR 0.49 (95% Cl 0.03, 7.60)	NSS
SNRIS	Flatulence	Rowbotham 2005	Venlafaxine 150-225 mg daily Placebo	1	123	6.1% (5/82)	2.4% (1/41)	RR 2.50 (95% Cl 0.30, 20.71)	NSS
SNRIs	GGT Increased	Yasuda 2011	Duloxetine 40 mg daily Placebo	1	168	2.4% (2/85)	3.6% (3/83)	RR 0.65 (95% Cl 0.11, 3.80)	NSS

SNRIs	GGT Increased	Yasuda 2011	Duloxetine 60 mg daily Placebo	1	170	5.8% (5/86)	2.4% (2/84)	RR 2.44 (95% Cl 0.49, 12.24)	NSS
SNRIs	HbA1c Increased	Yasuda 2011	Duloxetine 40 mg daily Placebo	1	168	1.2% (1/85)	2.4% (2/83)	RR 0.49 (95% Cl 0.05, 5.28)	NSS
SNRIs	HbA1c Increased	Yasuda 2011	Duloxetine 60 mg daily Placebo	1	170	5.8% (5/86)	2.4% (2/84)	RR 2.44 (95% Cl 0.49, 12.24)	NSS
SNRIs	Hyperglycemia (SAE)	Goldstein 2005	Duloxetine 20 mg daily Placebo	1	153	0% (0/115)	0% (0/38)	-	-
SNRIs	Hyperglycemia (SAE)	Goldstein 2005	Duloxetine 60 mg daily Placebo	1	152	0% (0/114)	0% (0/38)	-	-
SNRIs	Hyperglycemia (SAE)	Goldstein 2005	Duloxetine 120 mg daily Placebo	1	152	0.88% (1/113)	2.6% (1/39)	RR 0.35 (95% Cl 0.02, 5.39)	NSS
SNRIs	Hypoglycemia	Gao 2010	Duloxetine 60- 120 mg daily Placebo	1	215	9.4% (10/106)	4.6% (5/109)	RR 2.06 (95% Cl 0.73, 5.82)	NSS
SNRIs	Impotence (males only)	Rowbotham 2005	Venlafaxine 75 mg daily Placebo	1	79	5.5% (3/55)	0% (0/24)	RR 3.13 (95% Cl 0.17, 58.26)	NSS
SNRIs	Impotence (males only)	Rowbotham 2005	Venlafaxine 150-225 mg daily Placebo	1	66	4.8% (2/42)	0% (0/24)	RR 2.91 (95% Cl 0.15, 58.16)	NSS
SNRIs	LDH Increased	Yasuda 2011	Duloxetine 40 mg daily Placebo	1	168	2.4% (2/85)	2.4% (2/83)	RR 0.98 (95% Cl 0.14, 6.77)	NSS
SNRIs	LDH Increased	Yasuda 2011	Duloxetine 60 mg daily Placebo	1	170	5.8% (5/86)	2.4% (2/84)	RR 2.44 (95% Cl	NSS

								0.49 <i>,</i> 12.24)	
SNRIs	Malaise	Yasuda 2011	Duloxetine 40 mg daily Placebo	1	168	3.5% (3/85)	2.4% (2/83)	RR 1.46 (95% Cl 0.25, 8.54)	NSS
SNRIs	Malaise	Yasuda 2011	Duloxetine 60 mg daily Placebo	1	170	7.0% (6/86)	1.2% (1/84)	RR 5.86 (95% Cl 0.72, 47.65)	NSS
SNRIs	Muscle Spasms	Allen 2014	Desvenlafaxine 50 mg daily Placebo	1	85	9.5% (6/63)	4.5% (1/22)	RR 2.10 (95% Cl 0.27, 16.45)	NSS
SNRIs	Muscle Spasms	Allen 2014	Desvenlafaxine 100 mg daily Placebo	1	109	4.6% (4/87)	4.5% (1/22)	RR 1.01 (95% Cl 0.12, 8.60)	NSS
SNRIs	Muscle Spasms	Allen 2014	Desvenlafaxine 200 mg daily Placebo	1	122	4.0% (4/99)	4.3% (1/23)	RR 0.93 (95% Cl 0.11, 7.93)	NSS
SNRIs	Muscle Spasms	Allen 2014	Desvenlafaxine 400 mg daily Placebo	1	92	4.3% (3/69)	4.3% (1/23)	RR 1.00 (95% Cl 0.11, 9.15)	NSS
SNRIs	Myalgia	Rowbotham 2005	Venlafaxine 75 mg daily Placebo	1	122	4.9% (4/82)	0% (0/40)	RR 4.45 (95% Cl 0.25, 60.62)	NSS
SNRIs	Myalgia	Rowbotham 2005	Venlafaxine 150-225 mg daily	1	123	6.1% (5/82)	0% (0/41)	RR 5.57 (95% Cl 0.32, 98.29)	NSS
SNRIs	Myocardial Infarction (SAE)	Goldstein 2005	Duloxetine 20 mg daily Placebo	1	153	0.87% (1/115)	0% (0/38)	RR 1.01 (95% Cl 0.04, 24.26)	NSS
SNRIs	Myocardial Infarction (SAE)	Goldstein 2005	Duloxetine 60 mg daily Placebo	1	152	0% (0/114)	0% (0/38)	-	-

SNRIs	Myocardial Infarction (SAE)	Goldstein 2005	Duloxetine 120 mg daily Placebo	1	152	0.88% (1/113)	0% (0/39)	RR 1.05 (95% Cl 0.04, 25.32)	NSS
SNRIs	Pain in Extremity	Allen 2014	Desvenlafaxine 50 mg daily Placebo	1	85	6.3% (4/63)	0% (0/22)	RR 3.23 (95% Cl 0.18, 57.77)	NSS
SNRIs	Pain in Extremity	Allen 2014	Desvenlafaxine 100 mg daily Placebo	1	109	1.1% (1/87)	0% (0/22)	RR 0.78 (95% Cl 0.03, 18.62)	NSS
SNRIs	Pain in Extremity	Allen 2014	Desvenlafaxine 200 mg daily Placebo	1	122	1.0% (1/99)	0% (0/23)	RR 0.72 (95% Cl 0.03, 17.13)	NSS
SNRIs	Pain in Extremity	Allen 2014	Desvenlafaxine 400 mg daily Placebo	1	92	1.4% (1/69)	0% (0/23)	RR 1.03 (95% Cl 0.04, 24.41)	NSS
SNRIs	Palpitations	Gao 2010	Duloxetine 60- 120 mg daily Placebo	1	215	9.4% (10/106)	4.6% (5/109)	RR 2.06 (95% Cl 0.73, 5.82)	NSS
SNRIs	Postural Decrease in Systolic Blood Pressure >25mmHg	Rowbotham 2005	Venlafaxine 75 mg daily Placebo	1	122	19.5% (16/82)	15.0% (6/40)	RR 1.30 (95% Cl 0.55, 3.07)	NSS
SNRIs	Postural Decrease in Systolic Blood Pressure >25mmHg	Rowbotham 2005	Venlafaxine 150-225 mg daily Placebo	1	123	12.2% (10/82)	12.2% (5/41)	RR 1.00 (95% Cl 0.37, 2.73)	NSS
SNRIs	Pruritis	Gao 2010	Duloxetine 60- 120 mg daily Placebo	1	215	2.8% (3/106)	7.3% (8/109)	RR 0.39 (95% Cl 0.11, 1.41)	NSS
SNRIs	Sinusitis	Rowbotham 2005	Venlafaxine 75 mg daily Placebo	1	122	2.4% (2/82)	2.5% (1/40)	RR 0.98 (95% Cl 0.09, 10.44)	NSS

SNRIs	Sinusitis	Rowbotham 2005	Venlafaxine 150-225 mg daily Placebo	1	123	7.3% (6/82)	2.4% (1/41)	RR 3.00 (95% Cl 0.37, 24.10)	NSS
SNRIs	Stomach Discomfort	Gao 2010	Duloxetine 60- 120 mg daily Placebo	1	215	6.6% (7/106)	4.6% (5/109)	RR 1.44 (95% Cl 0.47, 4.40)	NSS
SNRIs	Treatment- emergent adverse events	Rowbotham 2005	Venlafaxine 75 mg daily Placebo	1	122	87.8% (72/82)	77.5% (31/40)	RR 1.13 (95% Cl 0.94, 1.36)	NSS
SNRIs	WBC Increased	Yasuda 2011	Duloxetine 40 mg daily Placebo	1	168	4.7% (4/85)	2.4% (2/83)	RR 1.95 (95% Cl 0.37, 10.38)	NSS
SNRIs	WBC Increased	Yasuda 2011	Duloxetine 60 mg daily Placebo	1	170	5.8% (5/86)	2.4% (2/84)	RR 2.44 (95% Cl 0.49, 12.24)	NSS
SNRIs	Weakness	Goldstein 2005	Duloxetine 20 mg daily Placebo	1	153	0.87% (1/115)	0% (0/38)	RR 1.01 (95% Cl 0.04, 24.26)	NSS
SNRIs	Weakness	Goldstein 2005	Duloxetine 60 mg daily Placebo	1	152	2.6% (3/114)	0% (0/38)	RR 2.37 (95% Cl 0.13, 44.95)	NSS
SNRIs	Weakness	Goldstein 2005	Duloxetine 120 mg daily Placebo	1	152	7.1% (8/113)	0% (0/39)	RR 5.96 (95% Cl 0.35, 101.02)	NSS
SNRIs	Weight Decreased	Allen 2014	Desvenlafaxine 50 mg daily Placebo	1	85	0% (0/63)	0% (0/22)	-	-
SNRIs	Weight Decreased	Allen 2014	Desvenlafaxine 100 mg daily Placebo	1	109	0% (0/87)	0% (0/22)	-	-

SNRIs	Weight Decreased	Allen 2014	Desvenlafaxine 200 mg daily Placebo	1	122	1.0% (1/99)	0% (0/23)	RR 0.72 (95% Cl 0.03, 17.13)	NSS
SNRIs	Weight Decreased	Allen 2014	Desvenlafaxine 400 mg daily Placebo	1	92	5.8% (4/69)	0% (0/23)	RR 3.09 (95% Cl 0.17, 55.23)	NSS
TCAs	Dizziness	Achar 2010	Amitriptyline 25 mg daily + Pregabalin 75 mg twice daily Pregabalin 75 mg twice daily	1	30	33.3% (5/15)	26.7% (4/15)	RR 1.25 (95% Cl 0.41, 3.77)	NSS
TCAs	Drowsiness	Achar 2010	Amitriptyline 25 mg daily + Pregabalin 75 mg twice daily Pregabalin 75 mg twice daily	1	30	33.3% (5/15)	26.7% (4/15)	RR 1.25 (95% Cl 0.41, 3.77)	NSS
TCAs	Dry Mouth	Achar 2010	Amitriptyline 25 mg daily + Pregabalin 75 mg twice daily Pregabalin 75 mg twice daily	1	30	46.7% (7/15)	33.3% (5/15)	RR 1.40 (95% Cl 0.57, 3.43)	NSS

\*PEER calculated using medcalc.org/calc/relative\_risk.php;

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CI: Confidence Interval; CK: Creatine Phosphokinase; COPD: Chronic Obstructive Pulmonary Disease; ECG: Electrocardiogram; GGT: Gamma-Glutamyl Transferase; HbA1c: Glycosylated Hemoglobin; LDH: Lactate Dehydrogenase; MSK: Musculoskeletal; NNT: Number Needed to Treat; NSS: Not Statistically Significant; OA: Osteoarthritis; PHN: Postherpetic Neuralgia; RCTs: Randomized Controlled Trials; RR: Risk Ratio; SAE: Serious Adverse Event; SNRIs: Serotonin–Norepinephrine Reuptake Inhibitors; TCAs: Tricyclic Antidepressants; WBC = White Blood Cell

## Table 12: Individual Meta-Analyzed Adverse Events

Intervention	Type of Adverse	Randomized Controlled	# of	# of	Intervention	Control	Risk Ratio (95%	NNH
Type Anticonvulsants (Gabapentin)	Event Dizziness	Trials Backonja 1998 Backonja 2011 Rauck 2012 Rice 2001 Rowbotham 1998 Sandercock 2012 Sang 2013 Wallace 2010 Zhang 2013	9	Participants 2477	Event Rate 19% (300/1566)	Event Rate 11% (102/911)	Confidence Interval) RR 3.18 (95% Cl 2.41, 4.20)	13
Anticonvulsants (Gabapentin)	Peripheral Edema	Rauck 2012 Rice 2001 Rowbotham 1998 Sang 2013 Wallace 2010 Zhang 2013	6	2115	6% (79/1339)	1% (8/776)	RR 3.83 (95% Cl 2.08, 7.04)	21
Anticonvulsants (Gabapentin)	Somnolence and Fatigue	Backonja 1998 Backonja 2011 Rauck 2012 Rice 2001 Rowbotham 1998 Sandercock 2012 Sang 2013 Wallace 2010 Zhang 20139	9	2528	13% (211/1566)	5% (47/962)	RR 2.60 (95% Cl 1.92, 3.53)	12
Anticonvulsants (Gabapentin)	Arthralgia	Rauck 2012 Zhang 2013	2	695	4% (21/510)	3% (6/185)	RR 1.23 (95% Cl 0.50, 3.03)	NSS
Anticonvulsants (Gabapentin)	Back Pain	Rauck 2012 Zhang 2013	2	695	3% (15/510)	3% (5/185)	RR 1.00 (95% Cl 0.38, 2.63)	NSS
Anticonvulsants (Gabapentin)	Blurred Vision	Rauck 2012 Zhang 2013	2	695	3% (13/510)	2% (3/185)	RR 1.17 (95% Cl 0.43, 3.19)	NSS
Anticonvulsants (Gabapentin)	Constipation	Rauck 2012 Zhang 2013	2	695	5% (26/510)	4% (8/185)	RR 1.20 (95% Cl 0.55, 2.61)	NSS

Anticonvulsants (Gabapentin)	Diarrhea	Backonja 1998 Backonja 2011 Rauck 2012 Rice 2001 Zhang 2013	5	1295	6% (49/864)	4% (18/431)	RR 1.43 (95% Cl 0.85, 2.41)	NSS
Anticonvulsants (Gabapentin)	Dry Mouth	Rauck 2012 Rice 2001 Zhang 2013	3	1029	4% (26/733)	2% (6/296)	RR 1.60 (95% Cl 0.73, 3.51)	NSS
Anticonvulsants (Gabapentin)	Headache	Backonja 1998 Backonja 2011 Rauck 2012 Sandercock 2012 Sang 2013 Wallace 2010 Zhang 2013	7	1965	6% (78/1230)	5% (40/735)	RR 1.11 (95% Cl 0.77, 1.61)	NSS
Anticonvulsants (Gabapentin)	Increased Weight	Rauck 2012 Zhang 2013	2	695	4% (18/510)	0.5% (1/185)	RR 2.37 (95% Cl 0.71, 7.87)	NSS
Anticonvulsants (Gabapentin)	Insomnia	Backonja 2011 Zhang 2013	2	472	4% (13/323)	4% (6/149)	RR 0.97 (95% Cl 0.34, 2.74)	NSS
Anticonvulsants (Gabapentin)	Nasopharyngitis	Rauck 2012 Sang 2013 Zhang 2013	3	1147	3% (25/731)	3% (14/416)	RR 0.88 (95% Cl 0.45, 1.72)	NSS
Anticonvulsants (Gabapentin)	Nausea	Backonja 1998 Backonja 2011 Rauck 2012 Sandercock 2012 Sang 2013 Zhang 2013	6	1560	7% (64/958)	5% (28/602)	RR 1.35 (95% Cl 0.87, 2.08)	NSS
Anticonvulsants (Gabapentin)	Serious Adverse Events	Backonja 2011 Rice 2001 Sang 2013 Wallace 2010 Zhang 2013	5	1663	2% (25/1039)	3% (17/624)	RR 0.91 (95% Cl 0.48, 1.72)	NSS
Anticonvulsants (Gabapentin)	Urinary Tract Infection	Rauck 2012 Zhang 2013	2	695	5% (24/510)	3% (6/185)	RR 1.43 (95% Cl 0.59, 3.48)	NSS
Anticonvulsants (Oxcarbazepine)	Back Pain	CTRI476G2301 Dogra 2005	2	266	8% (10/126)	2% (3/140)	RR 3.82 (95% Cl 1.06, 13.71)	18

Anticonvulsants (Oxcarbazepine)	Dizziness	Beydoun 2006 CTRI476G2301 Dogra 2005	3	610	19% (74/381)	3% (8/229)	RR 5.24 (95% Cl 2.54, 10.80)	7
Anticonvulsants (Oxcarbazepine)	Headache	Beydoun 2006 CTRI476G2301 Dogra 2005	3	610	11% (41/381)	5% (12/229)	RR 1.83 (95% Cl 1.00, 3.37)	19
Anticonvulsants (Oxcarbazepine)	Nausea	Beydoun 2006 CTRI476G2301 Dogra 2005	3	610	13% (49/381)	3% (7/229)	RR 3.62 (95% Cl 1.73, 7.59)	11
Anticonvulsants (Oxcarbazepine)	Serious Adverse Events	Beydoun 2006 CTRI476G2301 Dogra 2005	3	631	8% (33/395)	3% (6/236)	RR 3.05 (95% Cl 1.32, 7.06)	18
Anticonvulsants (Oxcarbazepine)	Somnolence or Fatigue	Beydoun 2006 CTRI476G2301 Dogra 2005	3	610	15% (57/381)	5% (11/229)	RR 2.41 (95% Cl 1.33, 4.34)	10
Anticonvulsants (Oxcarbazepine)	Diarrhea	CTRI476G2301 Dogra 2005	2	266	4% (5/126)	6% (8/140)	RR 0.67 (95% Cl 0.22, 2.05)	NSS
Anticonvulsants (Oxcarbazepine)	Tremor	Beydoun 2006 Dogra 2005	2	469	5% (15/310)	2% (3/159)	RR 2.01 (95% Cl 0.63, 6.39)	NSS
Anticonvulsants (Pregabalin)	Abnormal Coordination	Baba 2020 Dworkin 2003 Stacey 2008 Van-Seventer 2006	4	983	4% (26/628)	0.6% (2/355)	RR 4.09 (95% Cl 1.45, 11.52)	28
Anticonvulsants (Pregabalin)	Amblyopia	Dworkin 2003 Lesser 2004 Richter 2005 Rosenstock 2004 Van-Seventer 2006	5	1270	5% (46/841)	2% (9/429)	RR 2.32 (95% Cl 1.23, 4.35)	30
Anticonvulsants (Pregabalin)	Asthenia	Arezzo 2008 Freynhagen 2005 Lesser 2004 Richter 2005 Rosenstock 2004 Sabatowski 2004 Tolle 2008 Van-Seventer 2006	8	2235	6% (87/1563)	3% (18/672)	RR 1.88 (95% Cl 1.17, 3.02)	35

Anticonvulsants (Pregabalin)	Ataxia	Arezzo 2008 Dworkin 2003 Lesser 2004 Van-Seventer 2006	4	1045	7% (45/686)	0.6% (2/359)	RR 4.55 (95% Cl 1.86, 11.09)	17
Anticonvulsants (Pregabalin)	Balance Disorder	Stacey 2008 Vinik 2014	2	427	4% (9/229)	0% (0/198)	RR 5.35 (95% Cl 1.01, 28.42)	26
Anticonvulsants (Pregabalin)	Confusion	Dworkin 2003 Lesser 2004 Stacey 2008 Van-Seventer 2006	4	1147	4% (32/783)	0.8% (3/364)	RR 2.54 (95% Cl 1.14, 5.65)	31
Anticonvulsants (Pregabalin)	Constipation	Huffman 2015 Lesser 2004 Liu 2017 McDonnell 2018 NCT00394901 2006 Rauck 2012 Richter 2005 Rosenstock 2004 Satoh 2011 Smith 2014 Van-Seventer 2006 Vinik 2014 Ziegler 2015	13	3054	5% (99/1843)	3% (32/1211)	RR 1.56 (95% Cl 1.05, 2.32)	37
Anticonvulsants (Pregabalin)	Dizziness	Arezzo 2008         Baba 2020         Dworkin 2003         Freynhagen 2005         Guan 2011         Huffman 2015         Lesser 2004         Liu 2017         McDonnell 2018         Mu 2018         NCT00394901 2006         NCT02215252 2014         Rauck 2012         Richter 2005         Rosenstock 2004	22	5696	20% (687/3503)	6% (122/2193)	RR 3.25 (95% Cl 2.69, 3.92)	8

		Sabatowski 2004 Satoh 2011 Smith 2014 Stacey 2008 Tolle 2008 Van-Seventer 2006 Vinik 2014						
Anticonvulsants (Pregabalin)	Dry Mouth	Achar 2010 Arezzo 2008 Dworkin 2003 Freynhagen 2005 Huffman 2015 Lesser 2004 Liu 2017 Rauck 2012 Richter 2005 Sabatowski 2004 Tolle 2008 Van-Seventer 2006	12	2992	6% (111/1966)	2% (23/1026)	RR 2.24 (95% Cl 1.49, 3.38)	30
Anticonvulsants (Pregabalin)	Euphoria	Arezzo 2008 Lesser 2004 Rosenstock 2004 Stacey 2008	4	919	3% (20/577)	0% (0/342)	RR 4.51 (95% Cl 1.39, 14.60)	29
Anticonvulsants (Pregabalin)	Generalized Edema	Arezzo 2008 Guan 2011 Satoh 2011 Tolle 2008 Van-Seventer 2006	5	1552	5% (54/1041)	1% (6/511)	RR 3.03 (95% Cl 1.48, 6.19)	25
Anticonvulsants (Pregabalin)	Peripheral Edema	Arezzo 2008 Baba 2020 Dworkin 2003 Freynhagen 2005 Huffman 2015 Lesser 2004 Liu 2017 Mu 2018 NCT00394901 2006 Rauck 2012	20	5338	10% (320/3275)	3% (69/2063)	RR 2.68 (95% Cl 2.09, 3.44)	16

		Richter 2005 Rosenstock 2004 Sabatowski 2004 Satoh 2011 Smith 2014 Stacey 2008 Tolle 2008 Van-Seventer 2006 Vinik 2014 Ziegler 2015						
Anticonvulsants (Pregabalin)	Somnolence and Fatigue	Arezzo 2008 Baba 2020 Dworkin 2003 Freynhagen 2005 Guan 2011 Huffman 2015 Lesser 2004 Liu 2017 Mu 2018 NCT00394901 2006 Rauck 2012 Richter 2005 Rosenstock 2004 Sabatowski 2004 Sabatowski 2004 Satoh 2011 Smith 2014 Stacey 2008 Tolle 2008 Van-Seventer 2006 Vinik 2014 Ziegler 2015	21	5646	15% (507/3481)	4% (90/2165)	RR 3.38 (95% Cl 2.71, 4.21)	10
Anticonvulsants (Pregabalin)	Vertigo	Freynhagen 2005 Stacey 2008 Tolle 2008	3	1002	6% (43/751)	0.4% (1/251)	RR 3.56 (95% Cl 1.29, 9.85)	19
Anticonvulsants (Pregabalin)	Weight Gain	Arezzo 2008 Baba 2020 Freynhagen 2005 Guan 2011	13	3283	8% (161/2073)	1% (12/1210)	RR 4.84 (95% Cl 2.94, 7.95)	15

		Huffman 2015 McDonnell 2018 NCT003934901 2006 Rauck 2012 Richter 2005 Satoh 2011 Stacey 2008 Van-Seventer 2006 Vinik 2014						
Anticonvulsants (Pregabalin)	Abnormal Thinking	Arezzo 2008 Van-Seventer 2006	2	535	3% (11/357)	0.6% (1/178)	RR 2.35 (95% Cl 0.65, 8.49)	NSS
Anticonvulsants (Pregabalin)	Amnesia	Lesser 2004 Stacey 2008	2	606	2% (9/419)	0.5% (1/187)	RR 2.17 (95% Cl 0.49, 9.71)	NSS
Anticonvulsants (Pregabalin)	Back Pain	McDonnell 2018 NCT00394901 2006 Rauck 2012	3	559	1% (5/386)	0.6% (1/173)	RR 1.60 (95% Cl 0.34, 7.57)	NSS
Anticonvulsants (Pregabalin)	Contusion	NCT00394901 2006 Stacey 2008	2	640	3% (14/452)	1% (2/188)	RR 1.92 (95% Cl 0.57, 6.51)	NSS
Anticonvulsants (Pregabalin)	Diarrhea	Dworkin 2003 Huffman 2015 Lesser 2004 Liu 2017 Rauck 2012 Richter 2005 Rosenstock 2004 Sabatowski 2004 Smith 2014 Van-Seventer 2006 Vinik 2014 Ziegler 2015	12	2689	3% (55/1591)	3% (38/1098)	RR 0.95 (95% Cl 0.64, 1.42)	NSS
Anticonvulsants (Pregabalin)	Diplopia	NCT0039401 2006 Stacey 2008 Van-Seventer 2006	3	1008	2% (15/727)	0% (0/281)	RR 2.81 (95% Cl 0.75, 10.52)	NSS
Anticonvulsants (Pregabalin)	Disturbance in Attention	Rauck 2012 Smith 2014	2	287	3% (5/164)	0.8% (1/123)	RR 2.28 (95% Cl 0.41, 12.78)	NSS
Anticonvulsants (Pregabalin)	Facial Edema	NCT00394901 2006 Satoh 2011	3	1053	3% (25/727)	0.6% (2/326)	RR 2.36 (95% Cl 0.93, 5.98)	NSS

		Van-Seventer 2006						
Anticonvulsants (Pregabalin)	Falls	NCT00394901 2006 Rauck 2012 Stacey 2008 Vinik 2014	4	894	4% (21/568)	2% (5/326)	RR 1.67 (95% Cl 0.68, 4.10)	NSS
Anticonvulsants (Pregabalin)	Flatulence	Rosenstock 2004 Van-Seventer 2006	2	514	2% (7/351)	2% (3/163)	RR 0.99 (95% Cl 0.32, 3.03)	NSS
Anticonvulsants (Pregabalin)	Headache	Baba 2020 Dworkin 2003 Freynhagen 2005 Huffman 2015 Lesser 2004 McDonnell 2018 NCT00394901 2006 NCT02215252 2014 Rauck 2012 Richter 2005 Rosenstock 2004 Sabatowski 2004 Smith 2014 Tolle 2008 Van-Seventer 2006 Vinik 2014 Ziegler 2015	17	3928	5% (134/2502)	6% (81/1426)	RR 0.97 (95% Cl 0.73, 1.27)	NSS
Anticonvulsants (Pregabalin)	Hyperglycemia	Rosenstock 2004 Vinik 2014	2	304	2% (3/126)	0.6% (1/178)	RR 2.74 (95% Cl 0.41, 18.48)	NSS
Anticonvulsants (Pregabalin)	Increased Appetite	Rauck 2012 Stacey 2008	2	365	3% (7/245)	2% (2/120)	RR 1.45 (95% Cl 0.35, 5.98)	NSS
Anticonvulsants (Pregabalin)	Increased Pain	Huffman 2015 Lesser 2004 Rauck 2012 Richter 2005 Van-Seventer 2006	5	1431	4% (36/940)	3% (16/491)	RR 1.04 (95% Cl 0.60, 1.80)	NSS
Anticonvulsants (Pregabalin)	Increased Sweating	Stacey 2008 Van-Seventer 2006	2	637	0.7% (3/454)	2% (4/183)	RR 0.36 (95% Cl 0.11, 1.11)	NSS
Anticonvulsants (Pregabalin)	Infection	Lesser 2004 Richter 2005	5	1125	7% (51/684)	6% (27/441)	RR 1.34 (95% Cl 0.86, 2.09)	NSS

		Rosenstock 2004 Sabatowski 2004 Vinik 2014						
Anticonvulsants (Pregabalin)	Injury	Lesser 2004 Richter 2005 Rosenstock 2004 Vinik 2014	4	887	5% (26/527)	5% (17/360)	RR 1.15 (95% Cl 0.61, 2.17)	NSS
Anticonvulsants (Pregabalin)	Lethargy	Guan 2011 Stacey 2008	2	577	5% (18/385)	2% (3/192)	RR 2.63 (95% Cl 0.86, 8.09)	NSS
Anticonvulsants (Pregabalin)	Muscle Spasms	Rauck 2012 Ziegler 2015	2	228	4% (6/136)	2% (2/92)	RR 1.93 (95% Cl 0.41, 9.14)	NSS
Anticonvulsants (Pregabalin)	Nasopharyngitis	Baba 2020 Liu 2017 NCT00394901 2006 Rauck 2012 Smith 2014 Ziegler 2015	6	1183	5% (36/703)	6% (27/480)	RR 0.74 (95% Cl 0.45, 1.21)	NSS
Anticonvulsants (Pregabalin)	Nausea	Freynhagen 2005 Huffman 2015 McDonnell 2018 NCT00394901 2006 NCT02215252 2014 Rauck 2012 Rosenstock 2004 Smith 2014 Van-Seventer 2006 Vinik 2014	10	2234	4% (62/1401)	4% (32/833)	RR 1.01 (95% Cl 0.65, 1.55)	NSS
Anticonvulsants (Pregabalin)	Serious Adverse Events	Arezzo 2008 Guan 2011 Huffman 2015 Lesser 2004 Liu 2017 McDonnell 2018 Moon 2010 Mu 2018 NCT00394901 2006 NCT02215252 2014 Satoh 2011	16	4290	3% (88/2553)	3% (54/1737)	RR 1.01 (95% Cl 0.73, 1.41)	NSS

		Smith 2014 Stacey 2008 Tolle 2008 Vinik 2014 Ziegler 2015						
Anticonvulsants (Pregabalin)	Upper Respiratory Tract Infection	Huffman 2015 NCT02215252 2014	2	475	2% (6/244)	5% (11/231)	RR 0.52 (95% Cl 0.19, 1.38)	NSS
Anticonvulsants (Pregabalin)	Urinary Tract Infection	Mu 2018 Rauck 2012 Smith 2014 Vinik 2014 Ziegler 2015	5	1199	4% (21/598)	5% (28/601)	RR 0.76 (95% Cl 0.44, 1.31)	NSS
Anticonvulsants (Pregabalin)	Vision Problems	Huffman 2015 Rauck 2012 Van-Seventer 2006 Vinik 2014 Zhang 2013	5	1377	3% (23/865)	1.0% (5/512)	RR 1.95 (95% Cl 0.85, 4.47)	NSS
Anticonvulsants (Pregabalin)	Vomiting	Baba 2020 Rauck 2012 Rosenstock 2004 Vinik 2014	4	573	4% (8/227)	2% (7/296)	RR 1.29 (95% Cl 0.48, 3.46)	NSS
Opioids	Constipation	Freeman 2007 Hanna 2008 Jensen 2006 NCT01124617 2010 Zin 2010	5	963	24% (122/500)	7% (31/463)	RR 3.72 (95% Cl 2.58, 5.35)	6
Opioids	Dizziness	Freeman 2007 Hanna 2008 Jensen 2006 NCT01124617 2010 Zin 2010	5	963	18% (88/500)	8% (35/463)	RR 2.49 (95% Cl 1.78, 3.50)	10
Opioids	Dry Mouth	Jensen 2006 NCT01124617 2010	2	250	10% (14/142)	2% (2/108)	RR 5.01 (95% Cl 1.38, 18.25)	13
Opioids	Nausea	Freeman 2007 Hanna 2008 Jensen 2006	5	963	25% (124/500)	8% (37/463)	RR 3.15 (95% Cl 2.23, 4.45)	6

		NCT01124617 2010 Zin 2010						
Opioids	Pruritus	Jensen 2006 NCT01124617 2010 Zin 2010	3	312	16% (27/171)	4% (6/141)	RR 3.68 (95% Cl 1.68, 8.06)	9
Opioids	Somnolence and Fatigue	Freeman 2007 Hanna 2008 Jensen 2006 NCT01124617 2010 Zin 2010	5	963	27% (137/500)	8% (36/463)	RR 3.54 (95% Cl 2.52, 4.97)	6
Opioids	Vomiting	Hanna 2008 Jensen 2006 NCT01124617 2010 Zin 2010	4	650	14% (48/340)	4% (12/310)	RR 3.58 (95% Cl 1.90, 6.72)	11
Opioids	Asthenia	Jensen 2006 NCT01124617 2010	2	250	8% (12/142)	6% (6/108)	RR 1.68 (95% Cl 0.70, 4.06)	NSS
Opioids	Diarrhea	Freeman 2007 NCT01124617 2010 Zin 2010	3	466	5% (13/249)	4% (8/217)	RR 1.36 (95% Cl 0.57, 3.26)	NSS
Opioids	Generalized Pain	Freeman 2007 NCT01124617 2010	2	404	2% (4/220)	5% (9/184)	RR 0.38 (95% Cl 0.12, 1.24)	NSS
Opioids	Headache	Freeman 2007 Hanna 2008 Jensen 2006 NCT01124617 2010 Zin 2010	5	963	9% (45/500)	12% (54/463)	RR 0.79 (95% Cl 0.55, 1.15)	NSS
Opioids	Serious Adverse Events	Freeman 2007 Jensen 2006 NCT01124617 2010 Simpson 2016	4	749	6% (24/395)	7% (25/354)	RR 0.85 (95% Cl 0.50, 1.46)	NSS
Opioids	Upper Respiratory Tract Infection	Freeman 2007 NCT01124617 2010	2	404	5% (10/220)	4% (8/184)	RR 1.11 (95% Cl 0.46, 2.71)	NSS
Rubefacients	Application Site Pain	Backonja 2008 Capsaicin Study Group 1992	5	1619	35% (292/843)	15% (117/776)	RR 2.38 (95% Cl 1.99, 2.84)	6

		Irving 2011 Simpson 2017 Webster 2010						
Rubefacients	Coughing and/or Sneezing	Capsaicin Study Group 1992 Watson 1993 Webster 2010	3	575	8% (26/314)	1% (3/261)	RR 6.85 (95% Cl 2.29, 20.43)	15
Rubefacients	Increased Blood Pressure	Backonja 2008 Simpson 2017 Webster 2010	3	926	5% (26/493)	2% (9/433)	RR 2.57 (95% Cl 1.23, 5.35)	32
Rubefacients	Local Reaction (Burning, Stinging, and/or Erythema)	Backonja 2008 Bernstein 1989 Capsaicin Study Group 1992 Irving 2011 Tandan 1992 Watson 1993 Webster 2010	7	1447	72% (547/758)	47% (323/689)	RR 1.63 (95% Cl 1.50, 1.76)	4
Rubefacients	Nausea	Backonja 2008 Irving 2011 Watson 1993 Webster 2010	4	1116	4% (26/593)	2% (8/523)	RR 2.73 (95% Cl 1.27, 5.87)	36
Rubefacients	Papules at Application Site	Backonja 2008 Irving 2011 Webster 2010	3	973	8% (39/519)	3% (13/454)	RR 2.68 (95% Cl 1.46, 4.91)	22
Rubefacients	Sinusitis	Backonja 2008 Irving 2011	2	818	3% (12/417)	0.5% (2/401)	RR 5.77 (95% Cl 1.30, 25.62)	43
Rubefacients	Swelling at Application Site	Backonja 2008 Irving 2011 Webster 2010	3	973	7% (35/519)	0.7% (3/454)	RR 8.24 (95% Cl 2.80, 24.24)	17
Rubefacients	Unspecified Application Site Reaction	Simpson 2017 Watson 1993	2	512	29% (76/260)	6% (16/252)	RR 4.64 (95% Cl 2.79, 7.72)	5
Rubefacients	Vomiting	Backonja 2008 Irving 2011	2	818	3% (12/417)	0.7% (3/401)	RR 3.43 (95% Cl 1.06, 11.14)	47
Rubefacients	Back Pain	Backonja 2008 Webster 2010	2	557	3% (9/307)	2% (5/250)	RR 1.47 (95% Cl 0.49, 4.38)	NSS

Rubefacients	Dizziness	Backonja 2008 Irving 2011 Watson 1993 Webster 2010	4	1116	2% (10/593)	3% (15/523)	RR 0.60 (95% Cl 0.28, 1.28)	NSS
Rubefacients	Headache	Backonja 2008 Irving 2011 Watson 1993	3	961	3% (13/491)	4% (18/470)	RR 0.70 (95% Cl 0.35, 1.40)	NSS
Rubefacients	Nasopharyngitis	Backonja 2008 Watson 1993 Webster 2010	3	700	3% (12/381)	4% (12/319)	RR 0.79 (95% Cl 0.36, 1.71)	NSS
Rubefacients	Pruritus at Application Site	Backonja 2008 Irving 2011 Webster 2010	3	973	6% (33/519)	3% (15/454)	RR 1.60 (95% Cl 0.89, 2.89)	NSS
Rubefacients	Serious Adverse Events	Backonja 2008 Irving 2011 Simpson 2017 Vinik 2015 Webster 2010	5	1810	6% (63/1018)	4% (32/792)	RR 1.38 (95% Cl 0.90, 2.11)	NSS
Rubefacients	Upper Respiratory Tract Infection	Irving 2011 Watson 1993 Webster 2010	3	714	3% (12/388)	2% (8/326)	RR 1.29 (95% Cl 0.56, 2.97)	NSS
SNRIS	Anorexia	Gao 2010 Goldstein 2005 Rowbotham 2005	3	917	6% (36/612)	2% (5/305)	RR 3.40 (95% Cl 1.47, 7.86)	24
SNRIs	Asthenia	Gao 2010 Gao 2014	2	619	5% (16/308)	0.3% (1/311)	RR 11.16 (95% Cl 2.11, 59.13)	21
SNRIS	Constipation	Allen 2014 Gao 2010 Gao 2014 Goldstein 2005 Wernicke 2006 Yasuda 2011	6	2156	8% (115/1365)	4% (28/791)	RR 2.31 (95% Cl 1.52, 3.52)	21
SNRIs	Diarrhea	Gao 2010 Wernicke 2006 Yasuda 2011	3	887	8% (39/503)	4% (14/384)	RR 2.22 (95% Cl 1.19, 4.13)	25

SNRIs	Dizziness	Allen 2014 Gao 2010 Gao 2014 Goldstein 2005 Wernicke 2006 Yasuda 2011	6	2156	12% (161/1365)	6% (44/791)	RR 1.93 (95% Cl 1.39, 2.68)	17
SNRIs	Increased Sweating	Gao 2010 Goldstein 2005 Rowbotham 2005 Wernicke 2006	4	1251	7% (60/838)	2% (10/413)	RR 2.94 (95% Cl 1.53, 5.63)	22
SNRIs	Insomnia	Allen 2014 Rowbotham 2005 Wernicke 2006	3	987	6% (42/708)	2% (6/279)	RR 2.43 (95% Cl 1.14, 5.19)	27
SNRIs	Nausea	Allen 2014 Gao 2010 Gao 2014 Goldstein 2005 Rowbotham 2005 Wernicke 2006 Yasuda 2011	7	2401	19% (296/1529)	5% (47/872)	RR 3.36 (95% Cl 2.50, 4.52)	8
SNRIs	Somnolence and Fatigue	Allen 2014 Gao 2010 Gao 2014 Goldstein 2005 Rowbotham 2005 Wernicke 2006 Yasuda 2011	7	2401	18% (272/1529)	6% (52/872)	RR 3.09 (95% Cl 2.31, 4.13)	9
SNRIs	Vomiting	Allen 2014 Gao 2010 Rowbotham 2005 Yasuda 2011	4	1206	6% (42/759)	2% (9/447)	RR 2.30 (95% Cl 1.17, 4.49)	29
SNRIs	Decreased Appetite	Allen 2014 Gao 2014 Goldstein 2005	3	1269	5% (43/862)	2% (10/407)	RR 1.87 (95% Cl 0.97, 3.60)	NSS
SNRIs	Dry Mouth	Allen 2014 Gao 2010 Goldstein 2005	3	1080	8% (58/766)	4% (12/314)	RR 1.76 (95% Cl 0.97, 3.17)	NSS

SNRIs	Headache	Gao 2010 Wernicke 2006	2	549	10% (33/332)	6% (13/217)	RR 1.53 (95% Cl 0.81, 2.91)	NSS
SNRIs	Lethargy	Allen 2014 Gao 2010	2	623	5% (21/424)	2% (4/199)	RR 2.33 (95% Cl 0.96, 5.66)	NSS
SNRIs	Nasopharyngitis	Allen 2014 Wernicke 2006 Yasuda 2011	3	1080	8% (55/715)	8% (30/365)	RR 1.18 (95% Cl 0.76, 1.82)	NSS
SNRIS	Serious Adverse Events	Allen 2014 Gao 2010 Gao 2014 Goldstein 2005 Raskin 2005 Rowbotham 2005 Wernicke 2006 Yasuda 2011	8	2749	3% (50/1761)	4% (35/988)	RR 0.75 (95% Cl 0.50, 1.13)	NSS
SNRIs	Sustained Hypertension	Goldstein 2005 Raskin 2005	2	805	5% (26/574)	4% (10/231)	RR 1.06 (95% Cl 0.51, 2.20)	NSS

Cl: Confidence Interval; NNT: Number Needed to Treat; NSS: Not Statistically Significant; RCTs: Randomized Controlled Trials; RR: Risk Ratio; SNRIs: Serotonin– Norepinephrine Reuptake Inhibitors

Intervention Type	Type of Adverse Event	Randomized Controlled Trials	# of RCTs	# of Participants	Intervention Event Rate	Control Event Rate	Risk Ratio (95% Confidence Interval)	NNH
Anticonvulsants (Gabapentin)	Dizziness	Backonja 1998 Backonja 2011 Rauck 2012 Rice 2001 Rowbotham 1998 Sandercock 2012 Sang 2013 Wallace 2010 Zhang 2013	9	2477	19% (300/1566)	11% (102/911)	RR 3.18 (95% Cl 2.41, 4.20)	13
Anticonvulsants (Gabapentin)	Somnolence and Fatigue	Backonja 1998 Backonja 2011 Rauck 2012 Rice 2001 Rowbotham 1998 Sandercock 2012 Sang 2013 Wallace 2010 Zhang 20139	9	2528	13% (211/1566)	5% (47/962)	RR 2.60 (95% Cl 1.92, 3.53)	12
Anticonvulsants (Oxcarbazepine)	Dizziness	Beydoun 2006 CTRI476G2301 Dogra 2005	3	610	19% (74/381)	3% (8/229)	RR 5.24 (95% Cl 2.54, 10.80)	7
Anticonvulsants (Oxcarbazepine)	Headache	Beydoun 2006 CTRI476G2301 Dogra 2005	3	610	11% (41/381)	5% (12/229)	RR 1.83 (95% Cl 1.00, 3.37)	19
Anticonvulsants (Oxcarbazepine)	Nausea	Beydoun 2006 CTRI476G2301 Dogra 2005	3	610	13% (49/381)	3% (7/229)	RR 3.62 (95% Cl 1.73, 7.59)	11
Anticonvulsants (Oxcarbazepine)	Somnolence or Fatigue	Beydoun 2006 CTRI476G2301 Dogra 2005	3	610	15% (57/381)	5% (11/229)	RR 2.41 (95% Cl 1.33, 4.34)	10
Anticonvulsants (Pregabalin)	Dizziness	Arezzo 2008 Baba 2020 Dworkin 2003 Freynhagen 2005 Guan 2011	22	5696	20% (687/3503)	6% (122/2193)	RR 3.25 (95% Cl 2.69, 3.92)	8

## Table 13: Statistically Significant Meta-Analyzed Adverse Events Occurring in >10% of Patients Treated with Intervention

		Huffman 2015 Lesser 2004 Liu 2017 McDonnell 2018 Mu 2018 NCT00394901 2006 NCT02215252 2014 Rauck 2012 Richter 2005 Rosenstock 2004 Sabatowski 2004 Sabatowski 2004 Satoh 2011 Smith 2014 Stacey 2008 Tolle 2008 Van-Seventer 2006 Vinik 2014						
Anticonvulsants (Pregabalin)	Somnolence and Fatigue	Arezzo 2008 Baba 2020 Dworkin 2003 Freynhagen 2005 Guan 2011 Huffman 2015 Lesser 2004 Liu 2017 Mu 2018 NCT00394901 2006 Rauck 2012 Richter 2005 Rosenstock 2004 Sabatowski 2004 Sabatowski 2004 Satoh 2011 Smith 2014 Stacey 2008 Tolle 2008 Van-Seventer 2006 Vinik 2014 Ziegler 2015	21	5646	15% (507/3481)	4% (90/2165)	RR 3.38 (95% Cl 2.71, 4.21)	10
Opioids	Constipation	Freeman 2007 Hanna 2008	5	963	24% (122/500)	7% (31/463)	RR 3.72 (95% Cl 2.58, 5.35)	6

		Jensen 2006 NCT01124617 2010 Zin 2010						
Opioids	Dizziness	Freeman 2007 Hanna 2008 Jensen 2006 NCT01124617 2010 Zin 2010	5	963	18% (88/500)	8% (35/463)	RR 2.49 (95% Cl 1.78, 3.50)	10
Opioids	Nausea	Freeman 2007 Hanna 2008 Jensen 2006 NCT01124617 2010 Zin 2010	5	963	25% (124/500)	8% (37/463)	RR 3.15 (95% Cl 2.23, 4.45)	6
Opioids	Pruritus	Jensen 2006 NCT01124617 2010 Zin 2010	3	312	16% (27/171)	4% (6/141)	RR 3.68 (95% Cl 1.68, 8.06)	9
Opioids	Somnolence and Fatigue	Freeman 2007 Hanna 2008 Jensen 2006 NCT01124617 2010 Zin 2010	5	963	27% (137/500)	8% (36/463)	RR 3.54 (95% Cl 2.52, 4.97)	6
Opioids	Vomiting	Hanna 2008 Jensen 2006 NCT01124617 2010 Zin 2010	4	650	14% (48/340)	4% (12/310)	RR 3.58 (95% Cl 1.90, 6.72)	11
Rubefacients	Application Site Pain	Backonja 2008 Capsaicin Study Group 1992 Irving 2011 Simpson 2017 Webster 2010	5	1619	35% (292/843)	15% (117/776)	RR 2.38 (95% Cl 1.99, 2.84)	6
Rubefacients	Local Reaction (Burning, Stinging, and/or Erythema)	Backonja 2008 Bernstein 1989 Capsaicin Study Group 1992 Irving 2011 Tandan 1992 Watson 1993	7	1447	72% (547/758)	47% (323/689)	RR 1.63 (95% Cl 1.50, 1.76)	4

		Webster 2010						
Rubefacients	Unspecified Application Site Reaction	Simpson 2017 Watson 1993	2	512	29% (76/260)	6% (16/252)	RR 4.64 (95% Cl 2.79, 7.72)	5
SNRIS	Dizziness	Allen 2014 Gao 2010 Gao 2014 Goldstein 2005 Wernicke 2006 Yasuda 2011	6	2156	12% (161/1365)	6% (44/791)	RR 1.93 (95% Cl 1.39, 2.68)	17
SNRIs	Nausea	Allen 2014 Gao 2010 Gao 2014 Goldstein 2005 Rowbotham 2005 Wernicke 2006 Yasuda 2011	7	2401	19% (296/1529)	5% (47/872)	RR 3.36 (95% Cl 2.50, 4.52)	8
SNRIS	Somnolence and Fatigue	Allen 2014 Gao 2010 Gao 2014 Goldstein 2005 Rowbotham 2005 Wernicke 2006 Yasuda 2011	7	2401	18% (272/1529)	6% (52/872)	RR 3.09 (95% Cl 2.31, 4.13)	9

### Table 14: Withdrawals Due to Adverse Events

Intervention Type	Number of RCTs	Intervention Event Rate	Control Event Rate	Risk Ratio (95% Cl)	NNH
Acupuncture	1	7% (2/28)	3% (1/31)	RR 2.21 (95% Cl 0.21, 23.11)	NSS
Anticonvulsants (Gabapentin)	8	13% (184/1470)	8% (72/911)	RR 1.47 (95% Cl 1.13, 1.91)	22
Anticonvulsants (Oxcarbazepine)	3	26% (102/395)	7% (16/234)	RR 3.82 (95% Cl 2.28, 6.39)	6
Anticonvulsants (Pregabalin)	24	11% (399/3701)	5% (105/2240)	RR 2.15 (95% Cl 1.74, 2.65)	17
Anticonvulsants (Topiramate)	1	24% (52/214)	8.3% (9/109)	RR 2.94 (95% Cl 1.51, 5.75)	7
Opioids	6	14% (84/593)	6% (31/556)	RR 2.55 (95% Cl 1.73, 3.76)	12
SNRIs	7	13% (207/1655)	5% (42/879)	RR 2.48 (95% Cl 1.78, 3.45)	13
Rubefacients	3	6% (36/599)	2% (8/428)	RR 3.31 (95% Cl 1.56, 7.01)	25

Cl: Confidence Interval; NNT: Number Needed to Treat; NSS: Not Statistically Significant; RCTs: Randomized Controlled Trials; RR: Risk Ratio; SNRIs: Serotonin-Norepinephrine Reuptake Inhibitors

## Data Analysis of Adverse Events

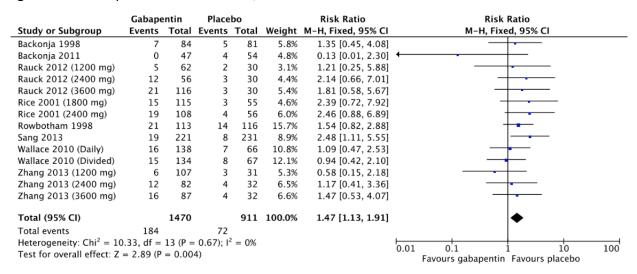
## Acupuncture

## Figure 11.1 Acupuncture versus control; Withdrawals due to Adverse Events

	Acupun	cture	Cont	rol		<b>Risk Ratio</b>	Risk Ratio
<b>Study or Subgroup</b>	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Garrow 2014	2	28	1	31	100.0%	2.21 [0.21, 23.11]	
Total (95% CI)		28		31	100.0%	2.21 [0.21, 23.11]	
Total events	2		1				
Heterogeneity: Not ap	oplicable						0.01 0.1 1 10 100
Test for overall effect	: Z = 0.66	(P = 0.	51)				Favours acupuncture Favours control

#### Anticonvulsants (Gabapentin)

#### Figure 12.1 Gabapentin versus control; Withdrawals due to Adverse Events



#### Figure 12.2 Gabapentin versus control; Adverse Event: Arthralgia

	Gabape	entin	Place	bo		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Rauck 2012 (1200 mg)	1	62	1	30	15.5%	0.48 [0.03, 7.47]	
Rauck 2012 (2400 mg)	2	56	1	30	15.0%	1.07 [0.10, 11.34]	
Rauck 2012 (3600 mg)	5	116	1	30	18.3%	1.29 [0.16, 10.66]	
Zhang 2013 (1200 mg)	6	107	1	31	17.8%	1.74 [0.22, 13.90]	
Zhang 2013 (2400 mg)	4	82	1	32	16.6%	1.56 [0.18, 13.44]	
Zhang 2013 (3600 mg)	3	87	1	32	16.8%	1.10 [0.12, 10.23]	
Total (95% CI)		510		185	100.0%	1.23 [0.50, 3.03]	-
Total events	21		6				
Heterogeneity: $Chi^2 = 0.6$	62, df = 5	(P = 0)	.99); I <sup>2</sup> =	0%			
Test for overall effect: Z	= 0.44 (P	= 0.66	)				0.01 0.1 1 10 100 Favours gabapentin Favours placebo

#### Figure 12.3 Gabapentin versus control; Adverse Event: Back Pain

	Gabape	ntin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Rauck 2012 (1200 mg)	1	62	0	30	8.4%	1.48 [0.06, 35.20]	· · · · · · · · · · · · · · · · · · ·
Rauck 2012 (2400 mg)	1	56	1	30	16.3%	0.54 [0.03, 8.26]	
Rauck 2012 (3600 mg)	3	116	1	30	19.8%	0.78 [0.08, 7.20]	
Zhang 2013 (1200 mg)	4	107	1	31	19.4%	1.16 [0.13, 9.99]	
Zhang 2013 (2400 mg)	4	82	1	32	18.0%	1.56 [0.18, 13.44]	
Zhang 2013 (3600 mg)	2	87	1	32	18.2%	0.74 [0.07, 7.84]	
Total (95% CI)		510		185	100.0%	1.00 [0.38, 2.63]	-
Total events	15		5				
Heterogeneity: $Chi^2 = 0$ .	56, df = 5	(P = 0)	.99); I <sup>2</sup> =	0%		H	0.01 0.1 1 10 100
Test for overall effect: Z	= 0.01 (P	= 0.99	)				Favours gabapentin Favours placebo

## Figure 12.4 Gabapentin versus control; Adverse Event: Blurred Vision

	Gabape	entin	Place	bo		<b>Risk Ratio</b>		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% Cl
Rauck 2012 (1200 mg)	0	62	1	30	28.3%	0.16 [0.01, 3.91]	+	
Rauck 2012 (2400 mg)	3	56	1	30	18.3%	1.61 [0.17, 14.79]		
Rauck 2012 (3600 mg)	2	116	1	30	22.3%	0.52 [0.05, 5.51]		
Zhang 2013 (1200 mg)	2	107	0	31	10.8%	1.48 [0.07, 30.07]		
Zhang 2013 (2400 mg)	4	82	0	32	10.1%	3.58 [0.20, 64.63]		
Zhang 2013 (3600 mg)	2	87	0	32	10.2%	1.88 [0.09, 38.03]		
Total (95% CI)		510		185	100.0%	1.17 [0.43, 3.19]		
Total events	13		3					
Heterogeneity: $Chi^2 = 2$ .	70, df = 5	(P = 0)	.75); I <sup>2</sup> =	0%			- 01	
Test for overall effect: Z	= 0.30 (P	= 0.76	)				0.01	0.1 1 10 10 Favours gabapentin Favours placebo

## Figure 12.5 Gabapentin versus control; Adverse Event: Constipation

	Gabape	entin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Rauck 2012 (1200 mg)	3	62	1	30	11.6%	1.45 [0.16, 13.38]	
Rauck 2012 (2400 mg)	4	56	1	30	11.2%	2.14 [0.25, 18.32]	
Rauck 2012 (3600 mg)	4	116	1	30	13.7%	1.03 [0.12, 8.92]	
Zhang 2013 (1200 mg)	7	107	1	31	13.4%	2.03 [0.26, 15.86]	
Zhang 2013 (2400 mg)	4	82	2	32	24.8%	0.78 [0.15, 4.05]	
Zhang 2013 (3600 mg)	4	87	2	32	25.2%	0.74 [0.14, 3.82]	
Total (95% CI)		510		185	100.0%	1.20 [0.55, 2.61]	-
Total events	26		8				
Heterogeneity: $Chi^2 = 1.2$	18, df = 5	(P = 0)	.95); I <sup>2</sup> =	0%			0.01 0.1 1 10 100
Test for overall effect: Z	= 0.46 (P	= 0.64	)				Favours gabapentin Favours placebo

## Figure 12.6 Gabapentin versus control; Adverse Event: Diarrhea

	Gabape	ntin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Backonja 1998	9	84	7	81	30.7%	1.24 [0.48, 3.17]	
Backonja 2011	3	47	1	54	4.0%	3.45 [0.37, 32.03]	
Rauck 2012 (1200 mg)	3	62	1	30	5.8%	1.45 [0.16, 13.38]	
Rauck 2012 (2400 mg)	2	56	1	30	5.6%	1.07 [0.10, 11.34]	
Rauck 2012 (3600 mg)	6	116	2	30	13.7%	0.78 [0.16, 3.65]	
Rice 2001 (1800 mg)	7	115	0	55	2.9%	7.24 [0.42, 124.55]	
Rice 2001 (2400 mg)	5	108	1	56	5.7%	2.59 [0.31, 21.66]	
Zhang 2013 (1200 mg)	6	107	1	31	6.7%	1.74 [0.22, 13.90]	
Zhang 2013 (2400 mg)	2	82	2	32	12.4%	0.39 [0.06, 2.65]	
Zhang 2013 (3600 mg)	6	87	2	32	12.6%	1.10 [0.23, 5.19]	
Total (95% CI)		864		431	100.0%	1.43 [0.85, 2.41]	•
Total events	49		18				
Heterogeneity: $Chi^2 = 4.8$	80, df = 9	(P = 0)	.85); I <sup>2</sup> =	0%			
Test for overall effect: Z	= 1.34 (P	= 0.18	)				0.01 0.1 1 10 100 Favours gabapentin Favours placebo

	Gabape	entin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Backonja 1998	20	84	4	81	6.3%	4.82 [1.72, 13.49]	
Backonja 2011	10	47	3	54	4.3%	3.83 [1.12, 13.10]	
Rauck 2012 (1200 mg)	9	62	1	30	2.1%	4.35 [0.58, 32.81]	
Rauck 2012 (2400 mg)	8	56	2	30	4.0%	2.14 [0.49, 9.46]	
Rauck 2012 (3600 mg)	16	116	2	30	4.9%	2.07 [0.50, 8.51]	
Rice 2001 (1800 mg)	36	115	5	55	10.5%	3.44 [1.43, 8.29]	
Rice 2001 (2400 mg)	36	108	6	56	12.2%	3.11 [1.40, 6.94]	
Rowbotham 1998	27	113	6	116	9.2%	4.62 [1.98, 10.76]	
Sandercock 2012 (Daily)	8	47	25	0		Not estimable	
Sandercock 2012 (Divided)	6	49	26	0		Not estimable	
Sang 2013	25	221	4	231	6.1%	6.53 [2.31, 18.47]	
Wallace 2010 (Daily)	14	138	2	66	4.2%	3.35 [0.78, 14.30]	
Wallace 2010 (Divided)	20	134	2	67	4.1%	5.00 [1.20, 20.76]	
Zhang 2013 (1200 mg)	18	107	4	31	9.6%	1.30 [0.48, 3.57]	
Zhang 2013 (2400 mg)	21	82	5	32	11.1%	1.64 [0.68, 3.97]	
Zhang 2013 (3600 mg)	26	87	5	32	11.3%	1.91 [0.80, 4.55]	
Total (95% CI)		1566		911	100.0%	3.18 [2.41, 4.20]	•
Total events	300		102				
Heterogeneity: Chi <sup>2</sup> = 10.94	, df = 13	(P = 0.6)	52); $I^2 = ($	0%			
Test for overall effect: $Z = 8$	.16 (P < 0	.00001	)				0.01 0.1 1 10 10
Test for overall effect. $Z = 8$	.10 (P < 0	.00001	,				Favours gabapentin Favours placebo

## Figure 12.7 Gabapentin versus control; Adverse Event: Dizziness

### Figure 12.8 Gabapentin versus control; Adverse Event: Dry Mouth

	Gabape	ntin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% CI
Rauck 2012 (1200 mg)	0	62	1	30	19.0%	0.16 [0.01, 3.91]	· · · · · · · · · · · · · · · · · · ·
Rauck 2012 (2400 mg)	4	56	1	30	12.3%	2.14 [0.25, 18.32]	
Rauck 2012 (3600 mg)	1	116	1	30	15.0%	0.26 [0.02, 4.02]	
Rice 2001 (1800 mg)	7	115	0	55	6.4%	7.24 [0.42, 124.55]	
Rice 2001 (2400 mg)	5	108	1	56	12.5%	2.59 [0.31, 21.66]	
Zhang 2013 (1200 mg)	1	107	0	31	7.3%	0.89 [0.04, 21.29]	
Zhang 2013 (2400 mg)	4	82	1	32	13.6%	1.56 [0.18, 13.44]	
Zhang 2013 (3600 mg)	4	87	1	32	13.8%	1.47 [0.17, 12.68]	
Total (95% CI)		733		296	100.0%	1.60 [0.73, 3.51]	-
Total events	26		6				
Heterogeneity: $Chi^2 = 5.1$	L7, df = 7	(P = 0)	.64); I <sup>2</sup> =	0%			0.01 0.1 1 10 100
Test for overall effect: Z	= 1.17 (P	= 0.24	)				0.01 0.1 1 10 100 Favours gabapentin Favours placebo

## Figure 12.9 Gabapentin versus control; Adverse Event: Headache

	Gabape	ntin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Backonja 1998	9	84	3	81	6.2%	2.89 [0.81, 10.31]	
Backonja 2011	4	47	4	54	7.5%	1.15 [0.30, 4.34]	
Rauck 2012 (1200 mg)	3	62	3	30	8.2%	0.48 [0.10, 2.26]	
Rauck 2012 (2400 mg)	4	56	2	30	5.3%	1.07 [0.21, 5.51]	
Rauck 2012 (3600 mg)	4	116	2	30	6.4%	0.52 [0.10, 2.69]	
Sandercock 2012 (Daily)	2	47	1	25	2.6%	1.06 [0.10, 11.17]	
Sandercock 2012 (Divided)	3	49	1	26	2.6%	1.59 [0.17, 14.55]	
Sang 2013	10	221	9	231	17.8%	1.16 [0.48, 2.80]	
Wallace 2010 (Daily)	5	138	3	66	8.2%	0.80 [0.20, 3.24]	
Wallace 2010 (Divided)	9	134	3	67	8.1%	1.50 [0.42, 5.36]	
Zhang 2013 (1200 mg)	11	107	3	31	9.4%	1.06 [0.32, 3.57]	
Zhang 2013 (2400 mg)	8	82	3	32	8.7%	1.04 [0.29, 3.68]	
Zhang 2013 (3600 mg)	6	87	3	32	8.9%	0.74 [0.20, 2.77]	
Total (95% CI)		1230		735	100.0%	1.11 [0.77, 1.61]	<b>↓</b>
Total events	78		40				
Heterogeneity: $Chi^2 = 5.06$ ,	df = 12 (P	P = 0.96	5); $I^2 = 09$	6			0.01 0.1 1 10 100
Test for overall effect: $Z = 0$ .	58 (P = 0)	.57)					0.01 0.1 1 10 100 Favours gabapentin Favours placebo

	Gabape	ntin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% CI
Rauck 2012 (1200 mg)	0	62	0	30		Not estimable	
Rauck 2012 (2400 mg)	2	56	0	30	14.8%	2.72 [0.13, 54.88]	
Rauck 2012 (3600 mg)	5	116	0	30	18.0%	2.91 [0.17, 51.29]	
Zhang 2013 (1200 mg)	3	107	0	31	17.6%	2.07 [0.11, 39.11]	
Zhang 2013 (2400 mg)	4	82	0	32	16.3%	3.58 [0.20, 64.63]	
Zhang 2013 (3600 mg)	4	87	1	32	33.3%	1.47 [0.17, 12.68]	
Total (95% CI)		510		185	100.0%	2.37 [0.71, 7.87]	
Total events	18		1				_
Heterogeneity: $Chi^2 = 0$ .	30, df = 4	(P = 0)	.99); I <sup>2</sup> =	0%			0.01 0.1 1 10 100
Test for overall effect: Z	= 1.40 (P	= 0.16	)				Favours gabapentin Favours placebo

## Figure 12.10 Gabapentin versus control; Adverse Event: Increased Weight

### Figure 12.11 Gabapentin versus control; Adverse Event: Insomnia

	Gabape	entin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Backonja 2011	0	47	4	54	53.3%	0.13 [0.01, 2.30]	←
Zhang 2013 (1200 mg)	3	107	0	31	9.8%	2.07 [0.11, 39.11]	
Zhang 2013 (2400 mg)	4	82	1	32	18.3%	1.56 [0.18, 13.44]	
Zhang 2013 (3600 mg)	6	87	1	32	18.6%	2.21 [0.28, 17.63]	
Total (95% CI)		323		149	100.0%	0.97 [0.34, 2.74]	
Total events	13		6				
Heterogeneity: $Chi^2 = 2$ .	94, df = 3	B (P = 0)					
Test for overall effect: Z	= 0.06 (P	= 0.95	)				0.01 0.1 1 10 100 Favours gabapentin Favours placebo

### Figure 12.12 Gabapentin versus control; Adverse Event: Nasopharyngitis

	Gabape	ntin	Place	bo		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Rauck 2012 (1200 mg)	1	62	1	30	7.7%	0.48 [0.03, 7.47]	· · · · · · · · · · · · · · · · · · ·
Rauck 2012 (2400 mg)	2	56	1	30	7.5%	1.07 [0.10, 11.34]	S
Rauck 2012 (3600 mg)	4	116	1	30	9.1%	1.03 [0.12, 8.92]	· · · · · · · · · · · · · · · · · · ·
Sang 2013	5	221	6	231	33.6%	0.87 [0.27, 2.81]	<b>_</b>
Zhang 2013 (1200 mg)	5	107	1	31	8.9%	1.45 [0.18, 11.94]	
Zhang 2013 (2400 mg)	3	82	2	32	16.5%	0.59 [0.10, 3.34]	
Zhang 2013 (3600 mg)	5	87	2	32	16.8%	0.92 [0.19, 4.50]	
Total (95% CI)		731		416	100.0%	0.88 [0.45, 1.72]	•
Total events	25		14				
Heterogeneity: $Chi^2 = 0$ .	66, df = 6	(P = 1)	$.00); I^2 =$	0%			
Test for overall effect: Z	= 0.36 (P	= 0.72	)				0.01 0.1 1 10 100 Favours gabapentin Favours placebo

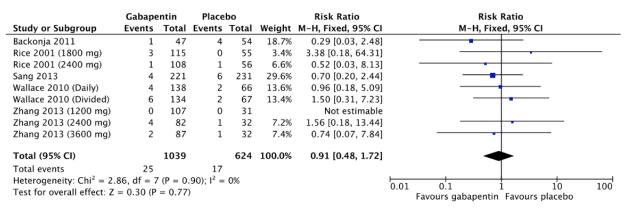
### Figure 12.13 Gabapentin versus control; Adverse Event: Nausea

	Gabape	ntin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Backonja 1998	7	84	4	81	12.0%	1.69 [0.51, 5.55]	
Backonja 2011	4	47	5	54	13.7%	0.92 [0.26, 3.23]	
Rauck 2012 (1200 mg)	7	62	3	30	11.9%	1.13 [0.31, 4.06]	
Rauck 2012 (2400 mg)	4	56	2	30	7.6%	1.07 [0.21, 5.51]	
Rauck 2012 (3600 mg)	7	116	2	30	9.3%	0.91 [0.20, 4.14]	
Sandercock 2012 (Daily)	2	47	0	25	1.9%	2.71 [0.14, 54.32]	
Sandercock 2012 (Divided)	3	49	0	26	1.9%	3.78 [0.20, 70.51]	
Sang 2013	10	221	7	231	20.1%	1.49 [0.58, 3.85]	- <b>+</b>
Zhang 2013 (1200 mg)	9	107	1	31	4.6%	2.61 [0.34, 19.79]	
Zhang 2013 (2400 mg)	3	82	2	32	8.5%	0.59 [0.10, 3.34]	
Zhang 2013 (3600 mg)	8	87	2	32	8.6%	1.47 [0.33, 6.56]	
Total (95% CI)		958		602	100.0%	1.35 [0.87, 2.08]	•
Total events	64		28				
Heterogeneity: $Chi^2 = 2.94$ ,	df = 10 (P	P = 0.98	8); $I^2 = 09$	6			
Test for overall effect: $Z = 1$	.34 (P = 0)	.18)					0.01 0.1 1 10 100 Favours gabapentin Favours placebo

	Gabape	entin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Rauck 2012 (1200 mg)	2	62	1	30	9.2%	0.97 [0.09, 10.25]	
Rauck 2012 (2400 mg)	0	56	1	30	13.2%	0.18 [0.01, 4.32]	· · · · · · · · · · · · · · · · · · ·
Rauck 2012 (3600 mg)	11	116	1	30	10.8%	2.84 [0.38, 21.18]	
Rice 2001 (1800 mg)	6	115	0	55	4.6%	6.28 [0.36, 109.44]	
Rice 2001 (2400 mg)	12	108	0	56	4.5%	13.07 [0.79, 216.82]	
Rowbotham 1998	11	113	4	116	26.9%	2.82 [0.93, 8.61]	
Sang 2013	7	221	1	231	6.7%	7.32 [0.91, 58.99]	
Wallace 2010 (Daily)	7	138	0	66	4.6%	7.23 [0.42, 124.72]	
Wallace 2010 (Divided)	6	134	0	67	4.5%	6.55 [0.37, 114.53]	
Zhang 2013 (1200 mg)	6	107	0	31	5.3%	3.85 [0.22, 66.54]	
Zhang 2013 (2400 mg)	6	82	0	32	4.9%	5.17 [0.30, 89.18]	
Zhang 2013 (3600 mg)	5	87	0	32	5.0%	4.13 [0.23, 72.56]	
Total (95% CI)		1339		776	100.0%	3.83 [2.08, 7.04]	◆
Total events	79		8				
Heterogeneity: $Chi^2 = 6$ .	82, df = 1	1 (P =	0.81); I <sup>2</sup>	= 0%			
Test for overall effect: Z							0.01 0.1 1 10 100 Favours gabapentin Favours placebo
							ravours gabapentin Favours placebo

#### Figure 12.14 Gabapentin versus control; Adverse Event: Peripheral Edema

#### Figure 12.15 Gabapentin versus control; Adverse Event: Serious Adverse Events



#### Figure 12.16 Gabapentin versus control; Adverse Event: Somnolence and Fatigue

	Gabape	entin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Backonja 1998	19	84	5	81	8.8%	3.66 [1.44, 9.35]	
Backonja 2011	2	47	4	54	6.4%	0.57 [0.11, 3.00]	
Rauck 2012 (1200 mg)	5	62	2	30	4.6%	1.21 [0.25, 5.88]	
Rauck 2012 (2400 mg)	10	56	2	30	4.5%	2.68 [0.63, 11.44]	
Rauck 2012 (3600 mg)	19	116	2	30	5.5%	2.46 [0.61, 9.97]	
Rice 2001 (1800 mg)	20	115	3	55	7.0%	3.19 [0.99, 10.27]	
Rice 2001 (2400 mg)	22	108	4	56	9.1%	2.85 [1.03, 7.87]	
Rowbotham 1998	31	113	6	116	10.2%	5.30 [2.30, 12.22]	
Sandercock 2012 (Daily)	6	47	0	25	1.1%	7.04 [0.41, 120.11]	<b></b>
Sandercock 2012 (Divided)	2	49	0	26	1.1%	2.70 [0.13, 54.23]	
Sang 2013	12	221	7	231	11.8%	1.79 [0.72, 4.47]	+
Wallace 2010 (Daily)	4	138	1	66	2.3%	1.91 [0.22, 16.78]	
Wallace 2010 (Divided)	9	134	2	67	4.6%	2.25 [0.50, 10.12]	
Zhang 2013 (1200 mg)	16	107	3	31	8.0%	1.55 [0.48, 4.96]	
Zhang 2013 (2400 mg)	13	82	3	32	7.4%	1.69 [0.52, 5.54]	
Zhang 2013 (3600 mg)	21	87	3	32	7.6%	2.57 [0.82, 8.05]	+
Total (95% CI)		1566		962	100.0%	2.60 [1.92, 3.53]	•
Total events	211		47				
Heterogeneity: $Chi^2 = 10.08$	, df = 15	(P = 0.8)	$(31); I^2 = 0$	0%			0.01 0.1 1 10 100
Test for overall effect: $Z = 6$	.18 (P < 0	.00001	)				0.01 0.1 1 10 100 Favours gabapentin Favours placebo

# Figure 12.17 Gabapentin versus control; Adverse Event: Urinary Tract Infection

	Gabape	entin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Rauck 2012 (1200 mg)	3	62	1	30	15.5%	1.45 [0.16, 13.38]	
Rauck 2012 (2400 mg)	4	56	1	30	15.0%	2.14 [0.25, 18.32]	
Rauck 2012 (3600 mg)	6	116	1	30	18.3%	1.55 [0.19, 12.40]	
Zhang 2013 (1200 mg)	8	107	1	31	17.8%	2.32 [0.30, 17.83]	
Zhang 2013 (2400 mg)	2	82	1	32	16.6%	0.78 [0.07, 8.31]	
Zhang 2013 (3600 mg)	1	87	1	32	16.8%	0.37 [0.02, 5.71]	
Total (95% CI)		510		185	100.0%	1.43 [0.59, 3.48]	
Total events	24		6				
Heterogeneity: $Chi^2 = 1$ .	55, df = 5	5 (P = 0)	.91); I <sup>2</sup> =	0%			0.01 0.1 1 10 100
Test for overall effect: Z	= 0.80 (P	= 0.42	)				Favours gabapentin Favours placebo

## Anticonvulsants (Oxcarbazepine)

## Figure 13.1 Oxcarbazepine versus control; Withdrawals due to Adverse Events

	Oxcarbaz	epine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Beydoun 2006 (1200 mg)	20	85	2	30	15.9%	3.53 [0.88, 14.21]	
Beydoun 2006 (1800 mg)	36	87	2	30	15.9%	6.21 [1.59, 24.23]	
Beydoun 2006 (600 mg)	9	83	2	29	15.9%	1.57 [0.36, 6.86]	•
CTRI476G2301	18	71	4	68	21.9%	4.31 [1.54, 12.09]	
Dogra 2005	19	69	6	77	30.4%	3.53 [1.50, 8.34]	
Total (95% CI)		395		234	100.0%	3.82 [2.28, 6.39]	•
Total events	102		16				
Heterogeneity: $Chi^2 = 1.98$	, df = 4 (P =	0.74);	$I^2 = 0\%$				
Test for overall effect: Z =	5.10 (P < 0.	00001)					0.01 0.1 1 10 100 Favours oxcarbazepine Favours placebo

## Figure 13.2 Oxcarbazepine versus control; Adverse Event: Back Pain

	Oxcarbap	ezine	Place	bo		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl	
CTRI476G2301	5	71	1	70	36.4%	4.93 [0.59, 41.13]		_
Dogra 2005	5	55	2	70	63.6%	3.18 [0.64, 15.78]		
Total (95% CI)		126		140	100.0%	3.82 [1.06, 13.71]		
Total events	10		3					
Heterogeneity: Chi <sup>2</sup> =	0.11, df =	1 (P = 0)	).75); I <sup>2</sup> =	= 0%			0.01 0.1 1 10	100
Test for overall effect	: Z = 2.05 (F	P = 0.04	4)				Favours oxcarbapezine Favours placebo	100

## Figure 13.3 Oxcarbazepine versus control; Adverse Event: Diarrhea

	Oxcarbape	ezine	Place	bo		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
CTRI476G2301	4	71	4	70	53.4%	0.99 [0.26, 3.79]	<b>_</b>
Dogra 2005	1	55	4	70	46.6%	0.32 [0.04, 2.77]	
Total (95% CI)		126		140	100.0%	0.67 [0.22, 2.05]	
Total events	5		8				
Heterogeneity: Chi <sup>2</sup> =	= 0.77, df = 1	1 (P = 0)	).38); I <sup>2</sup> =	= 0%			0.01 0.1 1 10 100
Test for overall effect	t: Z = 0.69 (P	P = 0.49	<b>)</b> )				Favours oxcarbapezine Favours placebo

## Figure 13.4 Oxcarbazepine versus control; Adverse Event: Dizziness

	Oxcarbaz	epine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Beydoun 2006 (1200 mg)	16	85	1	30	15.4%	5.65 [0.78, 40.78]	
Beydoun 2006 (1800 mg)	30	87	1	30	15.5%	10.34 [1.47, 72.61]	
Beydoun 2006 (600 mg)	5	83	0	29	7.7%	3.93 [0.22, 68.94]	
CTRI476G2301	16	71	5	70	52.4%	3.15 [1.22, 8.14]	
Dogra 2005	7	55	1	70	9.1%	8.91 [1.13, 70.27]	
Total (95% CI)		381		229	100.0%	5.24 [2.54, 10.80]	
Total events	74		8				
Heterogeneity: Chi <sup>2</sup> = 1.86	, df = 4 (P =	0.76);	$l^2 = 0\%$				
Test for overall effect: Z =	4.48 (P < 0.	00001)					0.01 0.1 1 10 100 Favours oxcarbazepine Favours placebo

## Figure 13.5 Oxcarbazepine versus control; Adverse Event: Headache

	Oxcarbaz	epine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Beydoun 2006 (1200 mg)	9	85	2	30	19.3%	1.59 [0.36, 6.94]	
Beydoun 2006 (1800 mg)	10	87	3	30	29.2%	1.15 [0.34, 3.90]	
Beydoun 2006 (600 mg)	9	83	2	29	19.4%	1.57 [0.36, 6.86]	
CTRI476G2301	8	71	4	70	26.3%	1.97 [0.62, 6.25]	
Dogra 2005	5	55	1	70	5.8%	6.36 [0.77, 52.90]	
Total (95% CI)		381		229	100.0%	1.83 [1.00, 3.37]	-
Total events	41		12				
Heterogeneity: $Chi^2 = 1.98$	, df = 4 (P =	= 0.74);	$I^2 = 0\%$				
Test for overall effect: Z =	1.95 (P = 0.	05)					0.01 0.1 1 10 100 Favours oxcarbazepine Favours placebo

## Figure 13.6 Oxcarbazepine versus control; Adverse Event: Nausea

	Oxcarbaz	epine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Beydoun 2006 (1200 mg)	13	85	2	30	31.8%	2.29 [0.55, 9.58]	
Beydoun 2006 (1800 mg)	17	87	2	30	32.0%	2.93 [0.72, 11.95]	
Beydoun 2006 (600 mg)	2	83	1	29	15.9%	0.70 [0.07, 7.42]	
CTRI476G2301	15	71	1	70	10.8%	14.79 [2.01, 108.96]	
Dogra 2005	2	55	1	70	9.5%	2.55 [0.24, 27.35]	
Total (95% CI)		381		229	100.0%	3.62 [1.73, 7.59]	•
Total events	49		7				
Heterogeneity: $Chi^2 = 4.33$	, df = 4 (P =	0.36);	$l^2 = 8\%$				
Test for overall effect: $Z = 2$							0.01 0.1 1 10 100 Favours oxcarbazepine Favours placebo

## Figure 13.7 Oxcarbazepine versus control; Adverse Event: Serious Adverse Events

	Oxcarbaz	epine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Beydoun 2006 (1200 mg)	9	85	0	30	9.4%	6.85 [0.41, 114.22]	
Beydoun 2006 (1800 mg)	10	87	1	30	19.0%	3.45 [0.46, 25.82]	
Beydoun 2006 (600 mg)	2	83	0	29	9.4%	1.79 [0.09, 36.14]	
CTRI476G2301	5	71	2	70	25.8%	2.46 [0.49, 12.28]	
Dogra 2005	7	69	3	77	36.3%	2.60 [0.70, 9.68]	
Total (95% CI)		395		236	100.0%	3.05 [1.32, 7.06]	•
Total events	33		6				
Heterogeneity: $Chi^2 = 0.58$	, df = 4 (P =	0.97);	$l^2 = 0\%$				
Test for overall effect: Z =	2.61 (P = 0.)	009)					0.01 0.1 1 10 100 Favours oxcarbazepine Favours placebo

## Figure 13.8 Oxcarbazepine versus control; Adverse Event: Somnolence and Fatigue

	Oxcarbaze	epine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Beydoun 2006 (1200 mg)	16	85	3	30	29.1%	1.88 [0.59, 6.01]	
Beydoun 2006 (1800 mg)	22	87	3	30	29.3%	2.53 [0.81, 7.85]	
Beydoun 2006 (600 mg)	6	83	3	29	29.2%	0.70 [0.19, 2.62]	
CTRI476G2301	5	71	1	70	6.6%	4.93 [0.59, 41.13]	
Dogra 2005	8	55	1	70	5.8%	10.18 [1.31, 78.98]	
Total (95% CI)		381		229	100.0%	2.41 [1.33, 4.34]	◆
Total events	57		11				
Heterogeneity: $Chi^2 = 5.90$	, df = 4 (P =	0.21);	$I^2 = 32\%$				
Test for overall effect: $Z = 2$	2.92 (P = 0.0)	003)					0.01 0.1 1 10 100 Favours oxcarbazepine Favours placebo

## Figure 13.9 Oxcarbazepine versus control; Adverse Event: Tremor

	Oxcarbaz	epine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Beydoun 2006 (1200 mg)	1	85	1	30	32.3%	0.35 [0.02, 5.47]	
Beydoun 2006 (1800 mg)	11	87	1	30	32.5%	3.79 [0.51, 28.16]	
Beydoun 2006 (600 mg)	1	83	0	29	16.1%	1.07 [0.04, 25.59]	<b>_</b>
Dogra 2005	2	55	1	70	19.2%	2.55 [0.24, 27.35]	
Total (95% CI)		310		159	100.0%	2.01 [0.63, 6.39]	
Total events	15		3				
Heterogeneity: $Chi^2 = 2.12$	, df = 3 (P =	0.55);	$I^2 = 0\%$				
Test for overall effect: Z =	1.18 (P = 0.1)	24)					0.01 0.1 1 10 100 Favours oxcarbazepine Favours placebo

## Anticonvulsants (Pregabalin)

	Pregab		Place			Risk Ratio	Risk Ratio
Study or Subgroup					Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Achar 2010	0	15	0	15		Not estimable	
Arezzo 2008	14	82	10	85	7.8%	1.45 [0.68, 3.08]	
Baba 2020	8	85	1	88	0.8%	8.28 [1.06, 64.81]	
Dworkin 2003	28	89	4	84	3.3%	6.61 [2.42, 18.04]	
Freynhagen 2005 (Fixed)	33	132	2	32	2.5%	4.00 [1.01, 15.81]	
Freynhagen 2005 (Flexed)	24	141	3	33	3.8%	1.87 [0.60, 5.85]	
Guan 2011	11	206	4	102	4.2%	1.36 [0.44, 4.17]	
Huffman 2015	9	198	5	186	4.1%	1.69 [0.58, 4.95]	
Lesser 2004 (300 mg)	3	81	1	32	1.1%	1.19 [0.13, 10.98]	
Lesser 2004 (600 mg)	10	82	1	32	1.1%	3.90 [0.52, 29.26]	
Lesser 2004 (75 mg)	2	77	1	33	1.1%	0.86 [0.08, 9.13]	
Liu 2017	6	111	2	109	1.6%	2.95 [0.61, 14.28]	
McDonnell 2018	5	46	2	45	1.6%	2.45 [0.50, 11.96]	
Moon 2010	8	162	6	78	6.4%	0.64 [0.23, 1.79]	
Mu 2018	11	314	9	308	7.2%	1.20 [0.50, 2.85]	
NCT00394901 2006 (150 mg)	7	87	1	32	1.2%	2.57 [0.33, 20.12]	
NCT00394901 2006 (300 mg)	16	90	2	33	2.3%	2.93 [0.71, 12.07]	
NCT00394901 2006 (600 mg)	20	97	2	33	2.4%	3.40 [0.84, 13.78]	
NCT02215252 2014	5	46	2	45	1.6%	2.45 [0.50, 11.96]	
Rauck 2012 (300 mg)	6	66	3	30	3.3%	0.91 [0.24, 3.39]	
Richter 2005 (150 mg)	2	79	2	42	2.1%	0.53 [0.08, 3.64]	
Richter 2005 (600 mg)	7	82	2	43	2.1%	1.84 [0.40, 8.46]	
Rosenstock 2004	8	76	2	70	1.6%	3.68 [0.81, 16.76]	
Sabatowski 2004 (150 mg)	9	81	4	40	4.2%	1.11 [0.36, 3.39]	
Sabatowski 2004 (300 mg)	12	76	4	41	4.1%	1.62 [0.56, 4.70]	
Satoh 2011 (300 mg)	17	134	3	67	3.2%	2.83 [0.86, 9.33]	
Satoh 2011 (600 mg)	13	45	4	68	2.5%	4.91 [1.71, 14.11]	
Smith 2014	10	98	8	93	6.5%	1.19 [0.49, 2.88]	
Stacey 2008 (Fixed)	17	88	2	45	2.1%	4.35 [1.05, 17.99]	
Stacey 2008 (Flexed)	4	91	3	45	3.2%	0.66 [0.15, 2.82]	
Tolle 2008 (150 mg)	5	99	1	32	1.2%	1.62 [0.20, 13.33]	
Tolle 2008 (300 mg)	11	99	1	32	1.2%	3.56 [0.48, 26.48]	
Tolle 2008 (600 mg)	13	101	1	32	1.2%	4.12 [0.56, 30.27]	
Van-Seventer 2006 (150 mg)	7	87	1	31	1.2%	2.49 [0.32, 19.47]	
Van-Seventer 2006 (300 mg)	15	98	2	31	2.4%	2.37 [0.57, 9.81]	
Van-Seventer 2006 (300 mg)	15	98 90	2	31	2.4%		
	19	90 70	2	62		3.27 [0.81, 13.25]	
Ziegler 2015	4	70	2	62	1.7%	1.77 [0.34, 9.34]	
Total (95% CI)		3701		2240	100.0%	2.15 [1.74, 2.65]	◆
Total events	399		105				
Heterogeneity: $Chi^2 = 33.02$ , df			$I^{2} = 0\%$				0.01 0.1 1 10
Test for overall effect: Z = 7.07	(P < 0.00)	001)					Favours pregabalin Favours placebo

## Figure 14.1 Pregabalin versus control; Withdrawals due to Adverse Events

## Figure 14.2 Pregabalin versus control; Adverse Event: Abnormal Coordination

	Pregat	oalin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Baba 2020	4	85	1	88	20.1%	4.14 [0.47, 36.30]	
Dworkin 2003	7	89	1	84	21.0%	6.61 [0.83, 52.57]	
Stacey 2008 (Fixed)	2	88	0	45	13.5%	2.58 [0.13, 52.71]	
Stacey 2008 (Flexed)	0	91	0	45		Not estimable	
Van-Seventer 2006 (150 mg)	3	87	0	31	15.0%	2.55 [0.14, 47.93]	
Van-Seventer 2006 (300 mg)	3	98	0	31	15.4%	2.26 [0.12, 42.64]	
Van-Seventer 2006 (600 mg)	7	90	0	31	15.1%	5.27 [0.31, 89.76]	
Total (95% CI)		628		355	100.0%	4.09 [1.45, 11.52]	
Total events	26		2				
Heterogeneity: $Chi^2 = 0.58$ , df	= 5 (P =	0.99); I	$^{2} = 0\%$				
Test for overall effect: $Z = 2.67$	7 (P = 0.0)	08)					0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.3 Pregabalin versus control; Adverse Event: Abnormal Thinking

	Pregat	oalin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Arezzo 2008	3	82	0	85	14.2%	7.25 [0.38, 138.27]	• • • •
Van-Seventer 2006 (150 mg)	2	87	0	31	21.1%	1.82 [0.09, 36.86]	
Van-Seventer 2006 (300 mg)	2	98	0	31	21.8%	1.62 [0.08, 32.79]	
Van-Seventer 2006 (600 mg)	4	90	1	31	42.9%	1.38 [0.16, 11.86]	
Total (95% CI)		357		178	100.0%	2.35 [0.65, 8.49]	
Total events	11		1				
Heterogeneity: $Chi^2 = 0.89$ , df	= 3 (P =	0.83); I	$^{2} = 0\%$				
Test for overall effect: $Z = 1.3$	1 (P = 0.1)	9)					0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.4 Pregabalin versus control; Adverse Event: Amblyopia

	Pregat	balin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Dworkin 2003	10	89	1	84	7.1%	9.44 [1.23, 72.14]	
Lesser 2004 (300 mg)	4	81	0	32	4.9%	3.62 [0.20, 65.41]	
Lesser 2004 (600 mg)	7	82	0	32	5.0%	5.96 [0.35, 101.48]	
Lesser 2004 (75 mg)	2	77	1	33	9.7%	0.86 [0.08, 9.13]	
Richter 2005 (150 mg)	2	79	2	42	18.1%	0.53 [0.08, 3.64]	
Richter 2005 (600 mg)	7	82	3	43	27.3%	1.22 [0.33, 4.49]	
Rosenstock 2004	4	76	1	70	7.2%	3.68 [0.42, 32.17]	
Van-Seventer 2006 (150 mg)	2	87	0	31	5.1%	1.82 [0.09, 36.86]	
Van-Seventer 2006 (300 mg)	3	98	0	31	5.2%	2.26 [0.12, 42.64]	
Van-Seventer 2006 (600 mg)	5	90	1	31	10.3%	1.72 [0.21, 14.18]	
Total (95% CI)		841		429	100.0%	2.32 [1.23, 4.35]	•
Total events	46		9				
Heterogeneity: $Chi^2 = 6.48$ , df	= 9 (P =	0.69); I	$^{2} = 0\%$				
Test for overall effect: $Z = 2.6$	1 (P = 0.0)	09)					0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.5 Pregabalin versus control; Adverse Event: Amnesia

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Lesser 2004 (300 mg)	0	81	0	32		Not estimable	
Lesser 2004 (600 mg)	5	82	0	32	25.8%	4.37 [0.25, 76.89]	
Lesser 2004 (75 mg)	2	77	1	33	50.5%	0.86 [0.08, 9.13]	
Stacey 2008 (Fixed)	2	88	0	45	23.8%	2.58 [0.13, 52.71]	
Stacey 2008 (Flexed)	0	91	0	45		Not estimable	
Total (95% CI)		419		187	100.0%	2.17 [0.48, 9.81]	
Total events	9		1				
Heterogeneity: $Chi^2 = 0$	.84, df =	2 (P =	0.66); I <sup>2</sup>	= 0%			
Test for overall effect: Z	2 = 1.01 (	P = 0.3	1)				0.01 0.1 1 10 100 Favours pregabalin Favours placebo

0							
	Pregał	balin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Arezzo 2008	8	82	1	85	3.5%	8.29 [1.06, 64.84]	
Freynhagen 2005 (Fixed)	12	132	0	32	2.9%	6.20 [0.38, 102.10]	
Freynhagen 2005 (Flexed)	9	141	0	33	2.9%	4.55 [0.27, 76.25]	
Lesser 2004 (300 mg)	4	81	1	32	5.1%	1.58 [0.18, 13.60]	
Lesser 2004 (600 mg)	6	82	1	32	5.2%	2.34 [0.29, 18.69]	
Lesser 2004 (75 mg)	3	77	1	33	5.0%	1.29 [0.14, 11.91]	
Richter 2005 (150 mg)	3	79	1	42	4.7%	1.59 [0.17, 14.86]	
Richter 2005 (600 mg)	10	82	2	43	9.4%	2.62 [0.60, 11.43]	
Rosenstock 2004	3	76	2	70	7.5%	1.38 [0.24, 8.03]	
Sabatowski 2004 (150 mg)	5	81	2	40	9.6%	1.23 [0.25, 6.09]	
Sabatowski 2004 (300 mg)	2	76	2	41	9.3%	0.54 [0.08, 3.69]	
Tolle 2008 (150 mg)	1	99	0	32	2.7%	0.99 [0.04, 23.72]	
Tolle 2008 (300 mg)	4	99	0	32	2.7%	2.97 [0.16, 53.71]	
Tolle 2008 (600 mg)	5	101	0	32	2.7%	3.56 [0.20, 62.66]	
Van-Seventer 2006 (150 mg)	4	87	1	31	5.3%	1.43 [0.17, 12.27]	
Van-Seventer 2006 (300 mg)	3	98	2	31	10.9%	0.47 [0.08, 2.71]	
Van-Seventer 2006 (600 mg)	5	90	2	31	10.7%	0.86 [0.18, 4.22]	
Total (95% CI)		1563		672	100.0%	1.88 [1.17, 3.02]	◆
Total events	87		18				
Heterogeneity: Chi <sup>2</sup> = 9.32, df	= 16 (P =	= 0.90);	$I^2 = 0\%$				0.01 0.1 1 10 10
Test for overall effect: $Z = 2.67$	2 (P = 0.0)	09)					0.01 0.1 1 10 10 Favours pregabalin Favours placebo
							Favours pregaballit Favours placebo

## Figure 14.6 Pregabalin versus control; Adverse Event: Asthenia

Figure 14.7 Pregabalin versus control; Adverse Event: Ataxia

	Pregat	balin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Arezzo 2008	4	82	0	85	7.2%	9.33 [0.51, 170.52]	
Dworkin 2003	6	89	0	84	7.6%	12.28 [0.70, 214.63]	
Lesser 2004 (300 mg)	3	81	0	32	10.5%	2.82 [0.15, 53.05]	
Lesser 2004 (600 mg)	7	82	1	32	21.2%	2.73 [0.35, 21.33]	
Lesser 2004 (75 mg)	5	77	1	33	20.6%	2.14 [0.26, 17.64]	
Van-Seventer 2006 (150 mg)	3	87	0	31	10.8%	2.55 [0.14, 47.93]	
Van-Seventer 2006 (300 mg)	6	98	0	31	11.1%	4.20 [0.24, 72.55]	
Van-Seventer 2006 (600 mg)	11	90	0	31	10.9%	8.09 [0.49, 133.35]	
Total (95% CI)		686		359	100.0%	4.55 [1.86, 11.09]	
Total events	45		2				
Heterogeneity: $Chi^2 = 1.84$ , df	= 7 (P =	0.97); I	$^{2} = 0\%$				0.01 0.1 1 10 100
Test for overall effect: $Z = 3.33$	B (P = 0.0)	009)					0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.8 Pregabalin versus control; Adverse Event: Back Pain

	Pregat	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
McDonnell 2018	1	46	0	45	19.4%	2.94 [0.12, 70.23]	
NCT00394901 2006 (150 mg)	0	87	0	32		Not estimable	
NCT00394901 2006 (300 mg)	1	90	0	33	27.9%	1.12 [0.05, 26.85]	<b>_</b>
NCT00394901 2006 (600 mg)	0	97	0	33		Not estimable	
Rauck 2012 (300 mg)	3	66	1	30	52.7%	1.36 [0.15, 12.58]	
Total (95% CI)		386		173	100.0%	1.60 [0.34, 7.57]	
Total events	5		1				
Heterogeneity: $Chi^2 = 0.21$ , df =	= 2 (P = 0	.90); I <sup>2</sup>	= 0%				0.01 0.1 1 10 100
Test for overall effect: $Z = 0.59$	(P = 0.55	)					0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.9 Pregabalin versus control; Adverse Event: Balance Disorder

	Pregat	oalin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Stacey 2008 (Fixed)	4	88	0	45	40.1%	4.65 [0.26, 84.54]	
Stacey 2008 (Flexed)	3	91	0	45	40.5%	3.50 [0.18, 66.34]	
Vinik 2014	2	50	0	108	19.4%	10.69 [0.52, 218.56]	
Total (95% CI)		229		198	100.0%	5.35 [1.01, 28.42]	
Total events	9		0				
Heterogeneity: Chi <sup>2</sup> =	0.29, df =	= 2 (P =	= 0.86); I	$^{2} = 0\%$			
Test for overall effect:	Z = 1.97	(P = 0	.05)				0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.10 Pregabalin versus control; Adverse Event: Confusion

	Pregat	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Dworkin 2003	6	89	0	84	5.7%	12.28 [0.70, 214.63]	· · · · · ·
Lesser 2004 (300 mg)	4	81	0	32	7.9%	3.62 [0.20, 65.41]	
Lesser 2004 (600 mg)	7	82	1	32	15.9%	2.73 [0.35, 21.33]	
Lesser 2004 (75 mg)	0	77	1	33	23.1%	0.15 [0.01, 3.48]	←
Stacey 2008 (Fixed)	3	88	0	45	7.3%	3.62 [0.19, 68.56]	
Stacey 2008 (Flexed)	3	91	0	45	7.4%	3.50 [0.18, 66.34]	
Van-Seventer 2006 (150 mg)	3	87	0	31	8.1%	2.55 [0.14, 47.93]	
Van-Seventer 2006 (300 mg)	3	98	0	31	8.3%	2.26 [0.12, 42.64]	
Van-Seventer 2006 (600 mg)	3	90	1	31	16.4%	1.03 [0.11, 9.57]	
Total (95% CI)		783		364	100.0%	2.54 [1.14, 5.65]	•
Total events	32		3				
Heterogeneity: $Chi^2 = 5.08$ , df	= 8 (P =	0.75); I	$ ^2 = 0\%$				0.01 0.1 1 10 100
Test for overall effect: $Z = 2.2$	7 (P = 0.0)	2)					0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.11 Pregabalin versus control; Adverse Event: Constipation

	Pregat	oalin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Huffman 2015	3	198	4	186	9.8%	0.70 [0.16, 3.11]	
Lesser 2004 (300 mg)	3	81	0	32	1.7%	2.82 [0.15, 53.05]	
Lesser 2004 (600 mg)	7	82	0	32	1.7%	5.96 [0.35, 101.48]	
Lesser 2004 (75 mg)	0	77	1	33	5.0%	0.15 [0.01, 3.48]	· · · · · · · · · · · · · · · · · · ·
Liu 2017	5	111	1	109	2.4%	4.91 [0.58, 41.35]	
McDonnell 2018	0	46	0	45		Not estimable	
NCT00394901 2006 (150 mg)	12	87	2	32	7.0%	2.21 [0.52, 9.32]	
NCT00394901 2006 (300 mg)	11	89	2	33	6.9%	2.04 [0.48, 8.72]	
NCT00394901 2006 (600 mg)	14	97	2	33	7.1%	2.38 [0.57, 9.93]	
Rauck 2012 (300 mg)	6	66	1	30	3.3%	2.73 [0.34, 21.67]	
Richter 2005 (150 mg)	3	79	2	42	6.2%	0.80 [0.14, 4.59]	
Richter 2005 (600 mg)	5	82	2	43	6.2%	1.31 [0.27, 6.48]	
Rosenstock 2004	4	76	0	70	1.2%	8.30 [0.45, 151.41]	
Satoh 2011 (300 mg)	4	134	0	67	1.6%	4.53 [0.25, 82.98]	
Satoh 2011 (600 mg)	2	45	1	68	1.9%	3.02 [0.28, 32.35]	
Smith 2014	2	98	6	93	14.7%	0.32 [0.07, 1.53]	
Van-Seventer 2006 (150 mg)	1	87	0	31	1.7%	1.09 [0.05, 26.10]	
Van-Seventer 2006 (300 mg)	8	98	1	31	3.6%	2.53 [0.33, 19.45]	
Van-Seventer 2006 (600 mg)	8	90	1	31	3.5%	2.76 [0.36, 21.16]	
Vinik 2014	1	50	2	108	3.0%	1.08 [0.10, 11.63]	
Ziegler 2015	0	70	4	62	11.4%	0.10 [0.01, 1.80]	· · · · · · · · · · · · · · · · · · ·
Total (95% CI)		1843		1211	100.0%	1.56 [1.05, 2.32]	◆
Total events	99		32				
Heterogeneity: $Chi^2 = 17.12$ , df	= 19 (P =	= 0.58);	$I^2 = 0\%$				
Test for overall effect: $Z = 2.19$							0.01 0.1 1 10 100 Favours pregabalin Favours placebo
							ravours pregaballit ravours placebo

## Figure 14.12 Pregabalin versus control; Adverse Event: Contusion

	Pregat	balin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% CI
NCT00394901 2006 (150 mg)	5	87	0	32	16.7%	4.13 [0.23, 72.56]	· · · · · · · · · · · · · · · · · · ·
NCT00394901 2006 (300 mg)	4	89	1	33	33.6%	1.48 [0.17, 12.79]	<b>_</b>
NCT00394901 2006 (600 mg)	3	97	1	33	34.3%	1.02 [0.11, 9.48]	↓                                 •
Stacey 2008 (Fixed)	0	88	0	45		Not estimable	
Stacey 2008 (Flexed)	2	91	0	45	15.3%	2.50 [0.12, 51.01]	
Total (95% CI)		452		188	100.0%	1.92 [0.57, 6.51]	
Total events	14		2				
Heterogeneity: $Chi^2 = 0.67$ , df =	= 3 (P = 0	.88); I <sup>2</sup>	= 0%				
Test for overall effect: Z = 1.05	(P = 0.29)	))					0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.13 Pregabalin versus control; Adverse Event: Diarrhea

	Pregab	oalin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Dworkin 2003	6	89	4	84	9.0%	1.42 [0.41, 4.84]	
Huffman 2015	2	198	5	186	11.3%	0.38 [0.07, 1.91]	
Lesser 2004 (300 mg)	1	81	2	32	6.3%	0.20 [0.02, 2.10]	
Lesser 2004 (600 mg)	3	82	2	32	6.3%	0.59 [0.10, 3.34]	
Lesser 2004 (75 mg)	4	77	3	33	9.2%	0.57 [0.14, 2.41]	
Liu 2017	5	111	2	109	4.4%	2.45 [0.49, 12.39]	
Rauck 2012 (300 mg)	5	66	2	30	6.0%	1.14 [0.23, 5.53]	<b>_</b>
Richter 2005 (150 mg)	4	79	1	42	2.9%	2.13 [0.25, 18.42]	
Richter 2005 (600 mg)	2	82	2	43	5.7%	0.52 [0.08, 3.59]	
Rosenstock 2004	3	76	2	70	4.6%	1.38 [0.24, 8.03]	
Sabatowski 2004 (150 mg)	4	81	2	40	5.9%	0.99 [0.19, 5.17]	
Sabatowski 2004 (300 mg)	4	76	2	41	5.7%	1.08 [0.21, 5.64]	
Smith 2014	2	98	1	93	2.2%	1.90 [0.18, 20.58]	
Van-Seventer 2006 (150 mg)	5	87	0	31	1.6%	4.00 [0.23, 70.31]	
Van-Seventer 2006 (300 mg)	0	98	0	31		Not estimable	
Van-Seventer 2006 (600 mg)	0	90	1	31	4.9%	0.12 [0.00, 2.81]	· · · · · · · · · · · · · · · · · · ·
Vinik 2014	0	50	3	108	4.9%	0.31 [0.02, 5.80]	
Ziegler 2015	5	70	4	62	9.3%	1.11 [0.31, 3.94]	
Total (95% CI)		1591		1098	100.0%	0.95 [0.64, 1.42]	<b>•</b>
Total events	55		38				
Heterogeneity: $Chi^2 = 10.18$ , c	lf = 16 (P	= 0.86	); $I^2 = 09$	6			
Test for overall effect: $Z = 0.2$							0.01 0.1 1 10 100
		_,					Favours pregabalin Favours placebo

## Figure 14.14 Pregabalin versus control; Adverse Event: Diplopia

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
NCT00394901 2006 (150 mg)	0	87	0	32		Not estimable	
NCT00394901 2006 (300 mg)	2	89	0	33	20.5%	1.89 [0.09, 38.34]	
NCT00394901 2006 (600 mg)	6	97	0	33	21.0%	4.51 [0.26, 77.96]	
Stacey 2008 (Fixed)	3	88	0	45	18.7%	3.62 [0.19, 68.56]	
Stacey 2008 (Flexed)	1	91	0	45	18.9%	1.50 [0.06, 36.11]	
Van–Seventer 2006 (150 mg)	0	87	0	31		Not estimable	
Van-Seventer 2006 (300 mg)	0	98	0	31		Not estimable	
Van-Seventer 2006 (600 mg)	3	90	0	31	20.9%	2.46 [0.13, 46.36]	
Total (95% CI)		727		281	100.0%	2.81 [0.75, 10.52]	
Total events	15		0				
Heterogeneity: Chi <sup>2</sup> = 0.36, df =	= 4 (P = 0	.99); I <sup>2</sup>	= 0%				0.01 0.1 1 10 100
Test for overall effect: $Z = 1.53$	(P = 0.13	)					Favours pregabalin Favours placebo

## Figure 14.15 Pregabalin versus control; Adverse Event: Disturbance in Attention

	Pregab	alin	Place	bo		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Rauck 2012 (300 mg)	3	66	1	30	72.8%	1.36 [0.15, 12.58]	
Smith 2014	2	98	0	93	27.2%	4.75 [0.23, 97.60]	
Total (95% CI)		164		123	100.0%	2.28 [0.41, 12.78]	
Total events	5		1				
Heterogeneity: $Chi^2 = 0$	).43, df =	1 (P =	0.51); I <sup>2</sup>	= 0%			0.01 0.1 1 10 100
Test for overall effect:	Z = 0.94	(P = 0.3)	35)				Favours pregabalin Favours placebo

## Figure 14.16 Pregabalin versus control; Adverse Event: Dizziness

M-H, Fixed, 95% Cl
•
).01 0.1 1 10 10 Favours pregabalin Favours placebo
0

	Pregat		Place			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Achar 2010	5	15	7	15	20.5%	0.71 [0.29, 1.75]	
Arezzo 2008	4	82	1	85	2.9%	4.15 [0.47, 36.32]	
Dworkin 2003	10	89	2	84	6.0%	4.72 [1.07, 20.91]	
Freynhagen 2005 (Fixed)	8	132	1	32	4.7%	1.94 [0.25, 14.95]	
Freynhagen 2005 (Flexed)	4	141	2	33	9.5%	0.47 [0.09, 2.45]	
Huffman 2015	5	198	1	186	3.0%	4.70 [0.55, 39.83]	
esser 2004 (300 mg)	6	81	0	32	2.1%	5.23 [0.30, 90.26]	
esser 2004 (600 mg)	4	82	0	32	2.1%	3.58 [0.20, 64.63]	
_esser 2004 (75 mg)	2	77	0	33	2.0%	2.18 [0.11, 44.20]	
_iu 2017	6	111	3	109	8.9%	1.96 [0.50, 7.66]	
Rauck 2012 (300 mg)	1	66	1	30	4.0%	0.45 [0.03, 7.03]	
Richter 2005 (150 mg)	0	79	1	42	5.7%	0.18 [0.01, 4.30]	· · · · · · · · · · · · · · · · · · ·
Richter 2005 (600 mg)	7	82	1	43	3.8%	3.67 [0.47, 28.87]	
Sabatowski 2004 (150 mg)	9	81	1	40	3.9%	4.44 [0.58, 33.87]	
Sabatowski 2004 (300 mg)	5	76	2	41	7.6%	1.35 [0.27, 6.65]	
Folle 2008 (150 mg)	3	99	0	32	2.2%	2.31 [0.12, 43.56]	
Folle 2008 (300 mg)	5	99	0	32	2.2%	3.63 [0.21, 63.91]	
Folle 2008 (600 mg)	7	101	0	32	2.2%	4.85 [0.28, 82.70]	
/an-Seventer 2006 (150 mg)	5	87	0	31	2.1%	4.00 [0.23, 70.31]	
/an-Seventer 2006 (300 mg)	4	98	0	31	2.2%	2.91 [0.16, 52.58]	
/an-Seventer 2006 (600 mg)	11	90	0	31	2.2%	8.09 [0.49, 133.35]	
Fotal (95% CI)		1966		1026	100.0%	2.24 [1.49, 3.38]	•
Fotal events	111		23				
Heterogeneity: Chi <sup>2</sup> = 18.07, d	f = 20 (P	= 0.58	); $I^2 = 0\%$	6			
Test for overall effect: $Z = 3.85$							0.01 0.1 1 10 10 Favours pregabalin Favours placebo

## Figure 14.17 Pregabalin versus control; Adverse Event: Dry Mouth

## Figure 14.18 Pregabalin versus control; Adverse Event: Euphoria

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Arezzo 2008	3	82	0	85	13.0%	7.25 [0.38, 138.27]	
Lesser 2004 (300 mg)	5	81	0	32	18.9%	4.43 [0.25, 77.82]	
Lesser 2004 (600 mg)	4	82	0	32	19.0%	3.58 [0.20, 64.63]	
Lesser 2004 (75 mg)	0	77	0	33		Not estimable	
Rosenstock 2004	4	76	0	70	13.8%	8.30 [0.45, 151.41]	
Stacey 2008 (Fixed)	2	88	0	45	17.5%	2.58 [0.13, 52.71]	
Stacey 2008 (Flexed)	2	91	0	45	17.7%	2.50 [0.12, 51.01]	
Total (95% CI)		577		342	100.0%	4.51 [1.39, 14.60]	
Total events	20		0				
Heterogeneity: $Chi^2 = 0$	).57, df =	5 (P =	0.99); I <sup>2</sup>	= 0%			
Test for overall effect: 2	Z = 2.51 (	P = 0.0	)1)				0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.19 Pregabalin versus control; Adverse Event: Facial Edema

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
NCT00394901 2006 (150 mg)	4	87	0	32	10.4%	3.38 [0.19, 60.98]	
NCT00394901 2006 (300 mg)	1	89	0	33	10.4%	1.13 [0.05, 27.15]	
NCT00394901 2006 (600 mg)	6	97	0	33	10.6%	4.51 [0.26, 77.96]	
Satoh 2011 (300 mg)	5	134	0	67	9.5%	5.54 [0.31, 98.74]	
Satoh 2011 (600 mg)	1	45	0	68	5.7%	4.50 [0.19, 108.08]	
Van-Seventer 2006 (150 mg)	3	87	0	31	10.5%	2.55 [0.14, 47.93]	
Van-Seventer 2006 (300 mg)	1	98	1	31	21.7%	0.32 [0.02, 4.91]	
Van-Seventer 2006 (600 mg)	4	90	1	31	21.2%	1.38 [0.16, 11.86]	
Total (95% CI)		727		326	100.0%	2.36 [0.93, 5.98]	
Total events	25		2				
Heterogeneity: $Chi^2 = 3.26$ , df =	= 7 (P = 0	.86); I <sup>2</sup>	= 0%				
Test for overall effect: $Z = 1.81$	(P = 0.07)	)					0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.20 Pregabalin versus control; Adverse Event: Falls

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
NCT00394901 2006 (150 mg)	6	87	1	32	18.6%	2.21 [0.28, 17.63]	
NCT00394901 2006 (300 mg)	7	89	1	33	18.6%	2.60 [0.33, 20.30]	
NCT00394901 2006 (600 mg)	4	97	2	33	37.9%	0.68 [0.13, 3.55]	
Rauck 2012 (300 mg)	0	66	0	30		Not estimable	
Stacey 2008 (Fixed)	1	88	0	45	8.4%	1.55 [0.06, 37.31]	
Stacey 2008 (Flexed)	2	91	0	45	8.5%	2.50 [0.12, 51.01]	
Vinik 2014	1	50	1	108	8.0%	2.16 [0.14, 33.84]	
Total (95% CI)		568		326	100.0%	1.67 [0.68, 4.10]	
Total events	21		5				
Heterogeneity: Chi <sup>2</sup> = 1.48, df =	= 5 (P = 0)	.91); I <sup>2</sup>	= 0%				0.01 0.1 1 10 100
Test for overall effect: $Z = 1.11$	(P = 0.27)	)					0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.21 Pregabalin versus control; Adverse Event: Flatulence

	Pregat	balin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Rosenstock 2004	3	76	1	70	18.8%	2.76 [0.29, 25.95]	
Van-Seventer 2006 (150 mg)	1	87	0	31	13.3%	1.09 [0.05, 26.10]	
Van-Seventer 2006 (300 mg)	0	98	1	31	41.0%	0.11 [0.00, 2.58]	<
Van-Seventer 2006 (600 mg)	3	90	1	31	26.9%	1.03 [0.11, 9.57]	
Total (95% CI)		351		163	100.0%	0.99 [0.32, 3.03]	
Total events	7		3				
Heterogeneity: $Chi^2 = 2.69$ , df	= 3 (P =	0.44); I	$ ^2 = 0\%$				
Test for overall effect: $Z = 0.02$	2 (P = 0.9)	(8)					0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.22 Pregabalin versus control; Adverse Event: Generalized Edema

	Pregat	balin	Place	bo		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Arezzo 2008	3	82	0	85	4.3%	7.25 [0.38, 138.27]	
Guan 2011	15	206	2	102	23.5%	3.71 [0.87, 15.93]	
Satoh 2011 (300 mg)	3	134	0	67	5.8%	3.53 [0.18, 67.29]	
Satoh 2011 (600 mg)	2	45	1	68	7.0%	3.02 [0.28, 32.35]	
Tolle 2008 (150 mg)	4	99	0	32	6.6%	2.97 [0.16, 53.71]	
Tolle 2008 (300 mg)	12	99	0	32	6.6%	8.25 [0.50, 135.56]	
Tolle 2008 (600 mg)	4	101	0	32	6.6%	2.91 [0.16, 52.67]	
Van-Seventer 2006 (150 mg)	3	87	1	31	13.0%	1.07 [0.12, 9.90]	
Van-Seventer 2006 (300 mg)	3	98	1	31	13.4%	0.95 [0.10, 8.80]	
Van-Seventer 2006 (600 mg)	5	90	1	31	13.1%	1.72 [0.21, 14.18]	
Total (95% CI)		1041		511	100.0%	3.03 [1.48, 6.19]	•
Total events	54		6				
Heterogeneity: Chi <sup>2</sup> = 3.08, df	= 9 (P =	0.96); I	$^{2} = 0\%$				
Test for overall effect: $Z = 3.04$							0.01 0.1 1 10 100 Favours pregabalin Favours placebo

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Baba 2020	5	85	2	88	2.0%	2.59 [0.52, 12.98]	
Dworkin 2003	7	89	7	84	7.5%	0.94 [0.35, 2.58]	
Freynhagen 2005 (Fixed)	3	132	1	32	1.7%	0.73 [0.08, 6.76]	
Freynhagen 2005 (Flexed)	7	141	1	33	1.7%	1.64 [0.21, 12.86]	
Huffman 2015	5	198	8	186	8.5%	0.59 [0.20, 1.76]	
Lesser 2004 (300 mg)	7	81	3	32	4.5%	0.92 [0.25, 3.35]	
Lesser 2004 (600 mg)	8	82	3	32	4.5%	1.04 [0.29, 3.68]	
Lesser 2004 (75 mg)	5	77	4	33	5.8%	0.54 [0.15, 1.87]	
McDonnell 2018	3	46	4	45	4.2%	0.73 [0.17, 3.09]	
NCT00394901 2006 (150 mg)	2	87	0	32	0.8%	1.88 [0.09, 38.03]	
NCT00394901 2006 (300 mg)	1	89	0	33	0.8%	1.13 [0.05, 27.15]	
NCT00394901 2006 (600 mg)	5	97	1	33	1.5%	1.70 [0.21, 14.04]	
NCT02215252 2014	3	46	4	45	4.2%	0.73 [0.17, 3.09]	
Rauck 2012 (300 mg)	6	66	2	30	2.8%	1.36 [0.29, 6.37]	
Richter 2005 (150 mg)	6	79	4	42	5.4%	0.80 [0.24, 2.67]	
Richter 2005 (600 mg)	13	82	5	43	6.8%	1.36 [0.52, 3.57]	
Rosenstock 2004	5	76	7	70	7.5%	0.66 [0.22, 1.98]	
Sabatowski 2004 (150 mg)	9	81	1	40	1.4%	4.44 [0.58, 33.87]	
Sabatowski 2004 (300 mg)	8	76	2	41	2.7%	2.16 [0.48, 9.69]	
Smith 2014	4	98	7	93	7.4%	0.54 [0.16, 1.79]	
Tolle 2008 (150 mg)	5	99	1	32	1.6%	1.62 [0.20, 13.33]	
Folle 2008 (300 mg)	3	99	2	32	3.1%	0.48 [0.08, 2.77]	
Tolle 2008 (600 mg)	1	101	2	32	3.1%	0.16 [0.01, 1.69]	
Van-Seventer 2006 (150 mg)	4	87	1	31	1.5%	1.43 [0.17, 12.27]	
Van-Seventer 2006 (300 mg)	1	98	1	31	1.6%	0.32 [0.02, 4.91]	
Van-Seventer 2006 (600 mg)	4	90	1	31	1.5%	1.38 [0.16, 11.86]	
Vinik 2014	2	50	4	108	2.6%	1.08 [0.20, 5.70]	
Ziegler 2015	2	70	3	62	3.3%	0.59 [0.10, 3.42]	
Fotal (95% CI)		2502		1426	100.0%	0.97 [0.73, 1.27]	. ↓
Total events	134		81				
Heterogeneity: Chi <sup>2</sup> = 13.84, df	= 27 (P =	= 0.98);	$I^2 = 0\%$				0.01 0.1 1 10 100
Test for overall effect: $Z = 0.24$	(P = 0.81)	)					0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.23 Pregabalin versus control; Adverse Event: Headache

## Figure 14.24 Pregabalin versus control; Adverse Event: Hyperglycemia

	Pregat	balin	Place	bo		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Rosenstock 2004	3	76	0	70	35.2%	6.45 [0.34, 122.78]	<b>_</b>
Vinik 2014	0	50	1	108	64.8%	0.71 [0.03, 17.19]	
Total (95% CI)		126		178	100.0%	2.74 [0.41, 18.48]	
Total events	3		1				
Heterogeneity: Chi <sup>2</sup> =	,		, ,	$I^2 = 1\%$			0.01 0.1 1 10 100
Test for overall effect	t: Z = 1.0	3 (P = 0)	).30)				Favours pregabalin Favours placebo

## Figure 14.25 Pregabalin versus control; Adverse Event: Increased Appetite

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Rauck 2012 (300 mg)	3	66	1	30	40.9%	1.36 [0.15, 12.58]	
Stacey 2008 (Fixed)	1	88	1	45	39.3%	0.51 [0.03, 7.99]	
Stacey 2008 (Flexed)	3	91	0	45	19.8%	3.50 [0.18, 66.34]	
Total (95% CI)		245		120	100.0%	1.45 [0.35, 5.98]	
Total events	7		2				
Heterogeneity: Chi <sup>2</sup> = (	0.90, df =	2 (P =	0.64); I <sup>2</sup>	= 0%			0.01 0.1 1 10 100
Test for overall effect:	Z = 0.52	(P = 0.6)	51)				0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.26 Pregabalin versus control; Adverse Event: Increased Pain

	Pregat	oalin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Huffman 2015	5	198	1	186	4.5%	4.70 [0.55, 39.83]	
Lesser 2004 (300 mg)	4	81	1	32	6.2%	1.58 [0.18, 13.60]	
Lesser 2004 (600 mg)	6	82	2	32	12.4%	1.17 [0.25, 5.50]	
Lesser 2004 (75 mg)	4	77	2	33	12.1%	0.86 [0.16, 4.45]	
Rauck 2012 (300 mg)	3	66	1	30	5.9%	1.36 [0.15, 12.58]	
Richter 2005 (150 mg)	3	79	3	42	16.9%	0.53 [0.11, 2.52]	
Richter 2005 (600 mg)	6	82	4	43	22.7%	0.79 [0.23, 2.64]	
Van-Seventer 2006 (150 mg)	2	87	0	31	3.2%	1.82 [0.09, 36.86]	
Van-Seventer 2006 (300 mg)	3	98	1	31	6.6%	0.95 [0.10, 8.80]	
Van-Seventer 2006 (600 mg)	0	90	1	31	9.6%	0.12 [0.00, 2.81]	· · · · · · · · · · · · · · · · · · ·
Total (95% CI)		940		491	100.0%	1.04 [0.60, 1.80]	•
Total events	36		16				
Heterogeneity: $Chi^2 = 5.06$ , df	= 9 (P =	0.83); I	$^{2} = 0\%$				
Test for overall effect: $Z = 0.13$	B (P = 0.9)	0)					0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.27 Pregabalin versus control; Adverse Event: Increased Sweating

	Pregab	balin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Stacey 2008 (Fixed)	2	88	0	45	7.6%	2.58 [0.13, 52.71]	
Stacey 2008 (Flexed)	0	91	1	45	23.2%	0.17 [0.01, 4.01]	← ■
Van-Seventer 2006 (150 mg)	1	87	1	31	17.1%	0.36 [0.02, 5.53]	
Van-Seventer 2006 (300 mg)	0	98	1	31	26.3%	0.11 [0.00, 2.58]	← ■
Van-Seventer 2006 (600 mg)	0	90	1	31	25.7%	0.12 [0.00, 2.81]	• • • • • • • • • • • • • • • • • • •
Total (95% CI)		454		183	100.0%	0.36 [0.11, 1.11]	
Total events	3		4				
Heterogeneity: $Chi^2 = 2.89$ , df	= 4 (P =	0.58); I	$ ^2 = 0\%$				
Test for overall effect: $Z = 1.78$	B (P = 0.0)	7)					0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.28 Pregabalin versus control; Adverse Event: Infection

	Pregab	alin	Placel	00		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Lesser 2004 (300 mg)	3	77	2	32	9.1%	0.62 [0.11, 3.56]	
Lesser 2004 (600 mg)	8	81	2	32	9.3%	1.58 [0.35, 7.04]	
Lesser 2004 (75 mg)	1	82	3	33	13.8%	0.13 [0.01, 1.24]	
Richter 2005 (150 mg)	10	79	4	42	16.9%	1.33 [0.44, 3.98]	
Richter 2005 (600 mg)	5	82	4	43	16.9%	0.66 [0.19, 2.32]	
Rosenstock 2004	11	76	4	70	13.4%	2.53 [0.85, 7.59]	+
Sabatowski 2004 (150 mg)	2	81	0	40	2.2%	2.50 [0.12, 50.88]	
Sabatowski 2004 (300 mg)	5	76	0	41	2.1%	6.00 [0.34, 105.88]	
Vinik 2014	6	50	8	108	16.3%	1.62 [0.59, 4.42]	- <b>-</b>
Total (95% CI)		684		441	100.0%	1.34 [0.86, 2.09]	◆
Total events	51		27				
Heterogeneity: $Chi^2 = 8.77$ ,	df = 8 (P	= 0.36	); I <sup>2</sup> = 9%				0.01 0.1 1 10 100
Test for overall effect: $Z = 1$ .	.29 (P = 0	).20)					Favours pregabalin Favours placebo

## Figure 14.29 Pregabalin versus control; Adverse Event: Injury

	Pregat	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Lesser 2004 (300 mg)	2	81	0	32	4.0%	2.01 [0.10, 40.80]	
Lesser 2004 (600 mg)	4	82	0	32	4.0%	3.58 [0.20, 64.63]	
Lesser 2004 (75 mg)	4	77	0	33	3.9%	3.92 [0.22, 70.86]	
Richter 2005 (150 mg)	2	79	2	42	14.6%	0.53 [0.08, 3.64]	
Richter 2005 (600 mg)	8	82	3	43	22.0%	1.40 [0.39, 5.00]	
Rosenstock 2004	3	76	4	70	23.3%	0.69 [0.16, 2.98]	
Vinik 2014	3	50	8	108	28.3%	0.81 [0.22, 2.92]	
Total (95% CI)		527		360	100.0%	1.15 [0.61, 2.17]	-
Total events	26		17				
Heterogeneity: $Chi^2 = 2$ .	.88, df =	6 (P = 0	0.82); I <sup>2</sup> :	= 0%			0.01 0.1 1 10 100
Test for overall effect: Z	= 0.43 (	P = 0.6	7)				0.01 0.1 1 10 100 Favours pregabalin Favours placebo

Figure 14.30 Pregabalin versus control; Adverse Event: Lethargy
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	Pregat	balin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Guan 2011	16	206	3	102	85.9%	2.64 [0.79, 8.86]	+- <b>-</b>
Stacey 2008 (Fixed)	2	88	0	45	14.1%	2.58 [0.13, 52.71]	
Stacey 2008 (Flexed)	0	91	0	45		Not estimable	
Total (95% CI)		385		192	100.0%	2.63 [0.86, 8.09]	
Total events	18		3				
Heterogeneity: Chi <sup>2</sup> =	0.00, df	= 1 (P =	= 0.99); I	$^{2} = 0\%$			
Test for overall effect:	Z = 1.69	(P = 0)	.09)				0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.31 Pregabalin versus control; Adverse Event: Muscle Spasm

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Rauck 2012 (300 mg)	3	66	1	30	56.5%	1.36 [0.15, 12.58]	
Ziegler 2015	3	70	1	62	43.5%	2.66 [0.28, 24.89]	
Total (95% CI)		136		92	100.0%	1.93 [0.41, 9.14]	
Total events	6		2				
Heterogeneity: Chi <sup>2</sup> = 0	.17, df =	1 (P =	0.68); I <sup>2</sup>	= 0%			
Test for overall effect: 2	2 = 0.83 (	(P = 0.4)	11)				0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.32 Pregabalin versus control; Adverse Event: Nasopharyngitis

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Baba 2020	2	85	3	88	9.0%	0.69 [0.12, 4.03]	
Liu 2017	5	111	9	109	27.8%	0.55 [0.19, 1.58]	
NCT00394901 2006 (150 mg)	8	87	3	32	13.4%	0.98 [0.28, 3.47]	
NCT00394901 2006 (300 mg)	10	89	3	33	13.4%	1.24 [0.36, 4.22]	
NCT00394901 2006 (600 mg)	5	97	4	33	18.3%	0.43 [0.12, 1.49]	
Rauck 2012 (300 mg)	3	66	2	30	8.4%	0.68 [0.12, 3.87]	
Smith 2014	2	98	2	93	6.3%	0.95 [0.14, 6.60]	
Ziegler 2015	1	70	1	62	3.3%	0.89 [0.06, 13.86]	
Total (95% CI)		703		480	100.0%	0.74 [0.45, 1.21]	•
Total events	36		27				
Heterogeneity: $Chi^2 = 2.02$ , df =	= 7 (P = 0	.96); I <sup>2</sup>	= 0%				0.01 0.1 1 10 100
Test for overall effect: $Z = 1.20$	(P = 0.23	)					0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.33 Pregabalin versus control; Adverse Event: Nausea

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Freynhagen 2005 (Fixed)	14	132	0	32	2.0%	7.20 [0.44, 117.54]	
Freynhagen 2005 (Flexed)	7	141	1	33	4.1%	1.64 [0.21, 12.86]	
Huffman 2015	5	198	6	186	15.6%	0.78 [0.24, 2.52]	
McDonnell 2018	3	46	1	45	2.6%	2.93 [0.32, 27.17]	
NCT00394901 2006 (150 mg)	2	87	1	32	3.7%	0.74 [0.07, 7.84]	
NCT00394901 2006 (300 mg)	6	89	2	33	7.4%	1.11 [0.24, 5.24]	
NCT00394901 2006 (600 mg)	7	97	2	33	7.5%	1.19 [0.26, 5.45]	
NCT02215252 2014	3	46	1	45	2.6%	2.93 [0.32, 27.17]	
Rauck 2012 (300 mg)	3	66	2	30	7.0%	0.68 [0.12, 3.87]	
Rosenstock 2004	6	76	6	70	15.8%	0.92 [0.31, 2.72]	
Smith 2014	2	98	3	93	7.8%	0.63 [0.11, 3.70]	
Van-Seventer 2006 (150 mg)	1	87	1	31	3.7%	0.36 [0.02, 5.53]	
Van-Seventer 2006 (300 mg)	0	98	2	31	9.6%	0.06 [0.00, 1.31]	· · · · · · · · · · · · · · · · · · ·
Van-Seventer 2006 (600 mg)	2	90	2	31	7.5%	0.34 [0.05, 2.34]	
Vinik 2014	1	50	2	108	3.2%	1.08 [0.10, 11.63]	
Total (95% CI)		1401		833	100.0%	1.01 [0.65, 1.55]	★
Total events	62		32				
Heterogeneity: Chi <sup>2</sup> = 9.64, df =	= 14 (P =	0.79); I	$^{2} = 0\%$				
Test for overall effect: $Z = 0.03$							0.01 0.1 i 10 100 Favours pregabalin Favours placebo

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Arezzo 2008	30	82	27	85	31.2%	1.15 [0.76, 1.76]	
Baba 2020	5	85	1	88	1.2%	5.18 [0.62, 43.40]	
Dworkin 2003	17	89	2	84	2.4%	8.02 [1.91, 33.67]	
Freynhagen 2005 (Fixed)	10	132	1	32	1.9%	2.42 [0.32, 18.26]	
Freynhagen 2005 (Flexed)	22	141	1	33	1.9%	5.15 [0.72, 36.84]	
Huffman 2015	9	198	2	186	2.4%	4.23 [0.93, 19.31]	
Lesser 2004 (300 mg)	6	81	0	32	0.8%	5.23 [0.30, 90.26]	
Lesser 2004 (600 mg)	11	82	1	32	1.7%	4.29 [0.58, 31.91]	
Lesser 2004 (75 mg)	3	77	1	33	1.6%	1.29 [0.14, 11.91]	
Liu 2017	7	111	2	109	2.4%	3.44 [0.73, 16.18]	
Mu 2018	10	314	1	308	1.2%	9.81 [1.26, 76.16]	· · · · · · · · · · · · · · · · · · ·
NCT00394901 2006 (150 mg)	4	87	0	32	0.9%	3.38 [0.19, 60.98]	
NCT00394901 2006 (300 mg)	12	89	0	33	0.9%	9.44 [0.57, 155.16]	
NCT00394901 2006 (600 mg)	18	97	1	33	1.8%	6.12 [0.85, 44.11]	· · · · · · · · · · · · · · · · · · ·
Rauck 2012 (300 mg)	11	66	2	30	3.2%	2.50 [0.59, 10.59]	
Richter 2005 (150 mg)	3	79	2	42	3.1%	0.80 [0.14, 4.59]	
Richter 2005 (600 mg)	14	82	2	43	3.1%	3.67 [0.87, 15.41]	
Rosenstock 2004	8	76	1	70	1.2%	7.37 [0.95, 57.43]	
Sabatowski 2004 (150 mg)	2	81	0	40	0.8%	2.50 [0.12, 50.88]	
Sabatowski 2004 (300 mg)	10	76	0	41		11.45 [0.69, 190.64]	
Satoh 2011 (300 mg)	17	134	3	67	4.7%	2.83 [0.86, 9.33]	
Satoh 2011 (600 mg)	- 6	45	3	68	2.8%	3.02 [0.80, 11.47]	
Smith 2014	7	98	2	93	2.4%	3.32 [0.71, 15.58]	
Stacey 2008 (Fixed)	3	88	0	45	0.8%	3.62 [0.19, 68.56]	
Stacey 2008 (Flexed)	3	91	1	45	1.6%	1.48 [0.16, 13.86]	
Tolle 2008 (150 mg)	5	99	0	32	0.9%	3.63 [0.21, 63.91]	
Tolle 2008 (300 mg)	9	99	1	32	1.8%	2.91 [0.38, 22.09]	
Tolle 2008 (600 mg)	10	101	1	32	1.8%	3.17 [0.42, 23.81]	
Van-Seventer 2006 (150 mg)	11	87	3	31	5.2%	1.31 [0.39, 4.38]	
Van-Seventer 2006 (300 mg)	14	98	3	31	5.4%	1.48 [0.45, 4.80]	
Van-Seventer 2006 (600 mg)	12	90	4	31	7.0%	1.03 [0.36, 2.97]	
Vinik 2014	4	50	1	108	0.7%	8.64 [0.99, 75.33]	
Ziegler 2015	7	70	0	62		13.31 [0.78, 228.39]	+
Total (95% CI)		3275		2063	100.0%	2.68 [2.09, 3.44]	•
Total events	320		69				
Heterogeneity: $Chi^2 = 35.08$ , df		= 0.32)					
Test for overall effect: $Z = 7.80$			570				0.01 0.1 1 10 1

## Figure 14.34 Pregabalin versus control; Adverse Event: Peripheral Edema

## Figure 14.35 Pregabalin versus control; Adverse Event: Serious Adverse Events

Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Fixed, 95% CI         M-H, Fixed, 95% CI           Arezzo 2008         4         82         8         85         11.7%         0.52 (0.16, 1.66]         Image: Comparison of the compa		Pregab	balin	Place	bo		Risk Ratio	Risk Ratio
Guan 2011       3       206       2       102       4.0% $0.74$ [0.13, 4.38]         Huffman 2015       9       198       2       186 $3.1\%$ $4.23$ [0.93, 19.31]         Lesser 2004 (300 mg)       0       81       1       32 $3.2\%$ 0.13 [0.01, 3.21]         Lesser 2004 (600 mg)       4       82       1 $32$ $2.1\%$ 1.56 [0.18, 13.44]         Lesser 2004 (75 mg)       1       77       1 $33$ $2.1\%$ 0.43 [0.03, 6.65]         Liu 2017       2       111       0       109       0.8% $4.91$ [0.24, 101.13]         McDonnell 2018       1       46       0 $45$ 0.8% $2.94$ [0.12, 70.23]         Moon 2010       10       162       5       78       10.1%       0.96 [0.34, 2.72]         Mu 2018       7       314       5       308       7.5%       1.37 [0.44, 4.28]         NCT00394901 2006 (150 mg)       2       87       2.32       4.4%       0.74 [0.14, 3.86]         NCT0215252 2014       1       46       0       45       0.8%       2.94 [0.12, 70.23]         Satch 2011 (600 mg)       2       45       2       68	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Huffman 2015       9       198       2       186 $3.1\%$ $4.23$ [ $0.93, 19.31$ ]         Lesser 2004 (300 mg)       0       81       1 $32$ $3.2\%$ $0.13$ [ $0.01, 3.21$ ]         Lesser 2004 (75 mg)       1       77       1 $33$ $2.1\%$ $1.56$ [ $0.18, 13.44$ ]         Lesser 2004 (75 mg)       1       77       1 $33$ $2.1\%$ $0.43$ [ $0.03, 6.65$ ]         Liu 2017       2       111       0 $109$ $0.8\%$ $4.91$ [ $0.24, 101.13$ ]         McDonnell 2018       1       46       0       45 $0.8\%$ $2.94$ [ $0.12, 70.23$ ]         Mu 2018       7 $314$ $5$ $308$ $7.5\%$ $1.37$ [ $0.04, 4.428$ ]         NCT00394901 2006 (500 mg)       2 $87$ $2$ $32.4\%$ $0.37$ [ $0.05, 2.50$ ]         NCT02394901 2006 (600 mg)       1 $97$ $2$ $33$ $4.5\%$ $0.17$ [ $0.02, 1.82$ ]         NCT02394901 2006 (600 mg)       4 $97$ $2$ $33$ $4.5\%$ $0.74$ [ $0.12, 70.23$ ]         NCT02215252 2014       1       46 $0$ $45$ $0.8\%$ $2.94$ [ $0.16, 53.71$ ]	Arezzo 2008	4	82	8	85	11.7%	0.52 [0.16, 1.66]	
Lesser 2004 (300 mg) 0 81 1 32 3.2% 0.13 [0.01, 3.21] Lesser 2004 (600 mg) 4 82 1 32 2.1% 1.56 [0.18, 13.44] Lesser 2004 (75 mg) 1 77 1 33 2.1% 0.43 [0.03, 6.65] McDonnell 2018 1 46 0 45 0.8% 2.94 [0.12, 70.23] McDonnell 2018 1 46 0 45 0.8% 2.94 [0.12, 70.23] Mon 2010 10 162 5 78 10.1% 0.96 [0.34, 2.72] Mu 2018 7 314 5 308 7.5% 1.37 [0.44, 4.28] NCT00394901 2006 (150 mg) 2 87 2 32 4.4% 0.37 [0.5, 2.50] NCT00394901 2006 (600 mg) 1 97 2 33 4.5% 0.17 [0.02, 1.82] NCT0215252 2014 1 46 0 45 0.8% 2.94 [0.12, 70.23] Satch 2011 (300 mg) 4 134 1 67 2.0% 2.00 [0.23, 17.54] Satch 2011 (300 mg) 2 45 2 68 2.4% 1.51 [0.22, 10.34] Smith 2014 3 98 8 93 12.2% 0.36 [0.10, 1.30] Stacey 2008 (Flexed) 6 91 4 45 8.0% 0.74 [0.22, 2.50] Tolle 2008 (150 mg) 4 99 0 32 1.1% 2.97 [0.16, 53.71] Tolle 2008 (150 mg) 6 101 1 32 2.3% 0.97 [0.10, 9.00] Tolle 2008 (600 mg) 6 101 1 32 2.3% 0.97 [0.10, 9.00] Tolle 2008 (600 mg) 6 101 1 32 2.3% 0.97 [0.10, 9.00] Tolle 2008 (600 mg) 6 101 1 32 2.3% 0.97 [0.10, 9.00] Tolle 2008 (600 mg) 6 101 1 32 2.3% 0.97 [0.10, 9.00] Tolle 2008 (600 mg) 6 101 1 32 2.3% 1.30 [0.23, 7.69] Total (95% CI) 2553 1737 100.0% 1.01 [0.73, 1.41] Total events 88 54 Heterogeneity: Chi <sup>2</sup> = 17.00, df = 23 (P = 0.81); $ ^2 = 0\%$	Guan 2011	3	206	2	102	4.0%	0.74 [0.13, 4.38]	
Lesser 2004 (600 mg)       4       82       1       32       2.1%       1.56 [0.18, 13.44]         Lesser 2004 (75 mg)       1       77       1       33       2.1%       0.43 [0.03, 6.65]         Liu 2017       2       111       0       109       0.8%       4.91 [0.24, 101.13]         McDonnell 2018       1       46       0       45       0.8%       2.94 [0.12, 70.23]         Mu 2018       7       314       5       308       7.5%       1.37 [0.44, 4.28]         NCT00394901 2006 (150 mg)       2       87       2       32       4.4%       0.37 [0.05, 2.50]         NCT00394901 2006 (600 mg)       1       97       2       33       4.5%       0.17 [0.02, 1.82]         NCT00394901 2006 (600 mg)       1       97       2       33       4.5%       0.17 [0.02, 1.82]         NCT0215252 2014       1       46       0       45       0.8%       0.94 [0.12, 70.23]         Satch 2011 (600 mg)       2       45       2       68       2.94 [0.12, 70.23]	Huffman 2015	9	198	2	186	3.1%	4.23 [0.93, 19.31]	
Lesser 2004 (75 mg)       1       77       1       33       2.1%       0.43 [0.03, 6.65]         Liu 2017       2       111       0       109       0.8%       4.91 [0.24, 101.13]         McDonnell 2018       1       46       0       45       0.8%       2.94 [0.12, 70.23]         Mu 2018       7       314       5       308       7.5%       1.37 [0.44, 4.28]         NCT00394901 2006 (150 mg)       2       87       2       32       4.4%       0.37 [0.05, 2.50]         NCT00394901 2006 (300 mg)       4       89       2       33       4.5%       0.17 [0.02, 1.82]         NCT023252 2014       1       46       0       45       0.8%       2.94 [0.12, 70.23]         Satoh 2011 (300 mg)       4       134       1       67       2.0%       2.00 [0.23, 17.54]         Satoh 2011 (600 mg)       2       45       2       68       2.4%       1.51 [0.22, 10.34]         Smith 2014       3       98       93       12.2%       0.36 [0.10, 1.30]       54         Stacey 2008 (Fixed)       6       91       4       5.9%       1.36 [0.38, 4.89]       54         Tolle 2008 (300 mg)       3       99       1       <	Lesser 2004 (300 mg)	0	81	1	32	3.2%	0.13 [0.01, 3.21]	· · · · · · · · · · · · · · · · · · ·
Liu 2017 2 111 0 109 0.8% 4.91 [0.24, 101.13] McDonnell 2018 1 46 0 45 0.8% 2.94 [0.12, 70.23] Moon 2010 10 162 5 78 10.1% 0.96 [0.34, 2.72] Mu 2018 7 314 5 308 7.5% 1.37 [0.44, 4.28] NCT00394901 2006 (150 mg) 2 87 2 32 4.4% 0.37 [0.05, 2.50] NCT00394901 2006 (600 mg) 1 97 2 33 4.5% 0.17 [0.02, 1.82] NCT00215252 2014 1 46 0 45 0.8% 2.94 [0.12, 70.23] Satoh 2011 (300 mg) 4 134 1 67 2.0% 2.00 [0.23, 17.54] Satoh 2011 (600 mg) 2 45 2 68 2.4% 1.51 [0.22, 10.34] Smith 2014 3 98 8 93 12.2% 0.36 [0.10, 1.30] Stacey 2008 (Fixed) 8 88 3 45 5.9% 1.36 [0.38, 4.89] Stacey 2008 (Fixed) 8 88 3 45 5.9% 1.36 [0.38, 4.89] Stacey 2008 (Fixed) 8 88 3 45 5.9% 1.36 [0.38, 4.89] Stacey 2008 (Fixed) 6 91 4 45 8.0% 0.74 [0.22, 2.50] Tolle 2008 (500 mg) 4 99 0 32 1.1% 2.97 [0.10, 9.00] Tolle 2008 (600 mg) 6 101 1 32 2.3% 0.97 [0.10, 9.00] Tolle 2008 (600 mg) 6 101 1 32 2.3% 0.97 [0.10, 9.00] Tolle 2008 (600 mg) 6 101 1 32 2.3% 1.90 [0.24, 15.21] Vinik 2014 0 50 1 108 1.4% 0.71 [0.03, 17.19] Ziegler 2015 3 70 2 62 3.2% 1.33 [0.23, 7.69] Total (95% CI) 2553 1737 100.0% 1.01 [0.73, 1.41] Total events 88 54 Heterogeneity: Chi <sup>2</sup> = 17.00, df = 23 (P = 0.81); l <sup>2</sup> = 0%	Lesser 2004 (600 mg)	4	82	1	32	2.1%	1.56 [0.18, 13.44]	
McDonnell 2018       1       46       0       45       0.8%       2.94 [0.12, 70.23]         Moon 2010       10       162       5       78       10.1%       0.96 [0.34, 2.72]         Mu 2018       7       314       5       308       7.5%       1.37 [0.44, 4.28]         NCT00394901 2006 (150 mg)       2       87       2       32       4.4%       0.37 [0.05, 2.50]         NCT00394901 2006 (600 mg)       1       97       2       33       4.5%       0.17 [0.02, 1.82]         NCT02215252 2014       1       46       0       45       0.8%       2.94 [0.12, 70.23]         Satoh 2011 (600 mg)       2       45       2       68       2.00 [0.23, 17.54]         Satoh 2011 (600 mg)       2       45       2       68       2.4%       1.51 [0.22, 10.34]         Smith 2014       3       98       8       93       12.2%       0.36 [0.10, 1.30]         Stacey 2008 (Fixed)       8       88       3       45       5.9%       1.36 [0.38, 4.89]         Stacey 2008 (Flexed)       6       91       4       45       8.0%       0.77 [0.24, 15.21]         Tolle 2008 (600 mg)       6       101       1.32       2.3%	Lesser 2004 (75 mg)	1	77	1	33	2.1%	0.43 [0.03, 6.65]	
Moon 2010       10       162       5       78       10.1% $0.96[0.34, 2.72]$ Mu 2018       7       314       5       308       7.5%       1.37 [0.44, 4.28]         NCT00394901 2006 (150 mg)       2       87       2       32       4.4% $0.37 [0.05, 2.50]$ NCT00394901 2006 (600 mg)       4       89       2       33       4.5% $0.17 [0.02, 1.82]$ NCT0215252 2014       1       46       0       45       0.8%       2.94 [0.12, 70.23]         Satch 2011 (300 mg)       4       134       1       67       2.0%       2.00 [0.23, 17.54]         Satch 2011 (600 mg)       2       45       2       68       2.4%       1.35 [0.22, 10.34]         Smith 2014       3       98       8       93       12.2%       0.36 [0.10, 1.30]         Stacey 2008 (Fixed)       8       88       3       45       5.9%       1.36 [0.38, 4.89]         Stacey 2008 (Flexed)       6       91       4       45       8.0%       0.74 [0.22, 2.50]         Tolle 2008 (300 mg)       3       99       1       32       2.3%       0.97 [0.10, 9.00]         Tolle 2008 (600 mg)       6       101       132	Liu 2017	2	111	0	109	0.8%	4.91 [0.24, 101.13]	
Mu 2018       7 $314$ 5 $308$ $7.5\%$ $1.37$ [0.44, 4.28]         NCT00394901 2006 (150 mg)       2 $87$ 2 $32$ $4.4\%$ $0.37$ [0.05, 2.50]         NCT00394901 2006 (300 mg)       4 $89$ 2 $33$ $4.4\%$ $0.74$ [0.14, 3.86]         NCT00394901 2006 (600 mg)       1 $97$ 2 $33$ $4.4\%$ $0.74$ [0.12, 70.23]         Satch 2011 (300 mg)       4       134       1 $67$ $2.0\%$ $2.00$ [0.23, 17.54]         Satch 2011 (600 mg)       2 $45$ 2 $68$ $2.4\%$ $1.51$ [0.22, 10.34]         Smith 2014       3 $98$ $8$ $93$ $12.2\%$ $0.36$ [0.10, 1.30]         Stacey 2008 (Fixed) $8$ $88$ $3$ $45$ $5.9\%$ $1.36$ [0.38, 4.89]         Stacey 2008 (Fixed) $6$ $91$ $4$ $45$ $8.0\%$ $0.74$ [0.22, 2.50]         Tolle 2008 (300 mg) $3$ $99$ $132$ $2.3\%$ $0.97$ [0.10, 9.00]         Tolle 2008 (600 mg) $6$ $101$ $132$ $2.3\%$ $1.90$ [0.24, 15.21]	McDonnell 2018	1	46	0	45	0.8%	2.94 [0.12, 70.23]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Moon 2010	10	162	5	78	10.1%	0.96 [0.34, 2.72]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Mu 2018	7	314	5	308	7.5%	1.37 [0.44, 4.28]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	NCT00394901 2006 (150 mg)	2	87	2	32	4.4%	0.37 [0.05, 2.50]	
NCT02215252 2014       1       46       0       45       0.8%       2.94 [0.12, 70.23]         Satoh 2011 (300 mg)       4       134       1       67       2.0%       2.00 [0.23, 17.54]         Satoh 2011 (600 mg)       2       45       2       68       2.4%       1.51 [0.22, 10.34]         Smith 2014       3       98       8       93       12.2%       0.36 [0.10, 1.30]         Stacey 2008 (Fixed)       6       91       4       45       8.0%       0.74 [0.22, 2.50]         Folle 2008 (150 mg)       4       99       0       32       1.1%       2.97 [0.16, 53.71]         Folle 2008 (300 mg)       3       99       1       32       2.3%       0.97 [0.10, 9.00]         Folle 2008 (600 mg)       6       101       1       32       2.3%       1.90 [0.24, 15.21]         Vinik 2014       0       50       1       108       1.4%       0.71 [0.03, 17.19]         Ziegler 2015       3       70       2       62       3.2%       1.33 [0.23, 7.69]         Total (95% Cl)       2553       1737       100.0%       1.01 [0.73, 1.41]       4         Fotal vents       88       54       54       54       54	NCT00394901 2006 (300 mg)	4	89	2	33	4.4%	0.74 [0.14, 3.86]	
Satch 2011 (300 mg)       4       134       1       67       2.0%       2.00 [0.23, 17.54]         Satch 2011 (600 mg)       2       45       2       68       2.4%       1.51 [0.22, 10.34]         Satch 2011 (600 mg)       2       45       2       68       2.4%       1.51 [0.22, 10.34]         Satch 2014       3       98       8       93       12.2%       0.36 [0.10, 1.30]         Stacey 2008 (Fixed)       8       88       3       45       5.9%       1.36 [0.38, 4.89]         Stacey 2008 (Flexed)       6       91       4       45       8.0%       0.74 [0.22, 2.50]         Folle 2008 (150 mg)       4       99       0       32       1.1%       2.97 [0.16, 53.71]         Folle 2008 (300 mg)       3       99       1       32       2.3%       0.97 [0.10, 9.00]         Folle 2008 (600 mg)       6       101       1       32       2.3%       1.90 [0.24, 15.21]         /inik 2014       0       50       1       108       1.4%       0.71 [0.03, 17.19]         Ziegler 2015       3       70       2       62       3.2%       1.33 [0.23, 7.69]         Fotal (95% CI)       2553       1737       100.0%	NCT00394901 2006 (600 mg)	1	97	2	33	4.5%	0.17 [0.02, 1.82]	
Satch 2011 (600 mg)       2       45       2       68       2.4%       1.51 [0.22, 10.34]         Smith 2014       3       98       8       93       12.2%       0.36 [0.10, 1.30]         Stacey 2008 (Fixed)       8       88       3       45       5.9%       1.36 [0.38, 4.89]         Stacey 2008 (Flexed)       6       91       4       45       8.0%       0.74 [0.22, 2.50]         Folle 2008 (150 mg)       4       99       0       32       1.3%       0.97 [0.10, 9.00]         Folle 2008 (300 mg)       3       99       1       32       2.3%       0.97 [0.10, 9.00]         Folle 2008 (600 mg)       6       101       1       32       2.3%       1.90 [0.24, 15.21]         Vinik 2014       0       50       1       108       1.4%       0.71 [0.03, 17.19]         Ziegler 2015       3       70       2       62       3.2%       1.33 [0.23, 7.69]         Total (95% CI)       2553       1737       100.0%       1.01 [0.73, 1.41]       4         Feterogeneity: Chi <sup>2</sup> = 17.00, df = 23 (P = 0.81); l <sup>2</sup> = 0%       0.01       0.1       10	NCT02215252 2014	1	46	0	45	0.8%	2.94 [0.12, 70.23]	
Simith 2014       3       98       8       93 $12.2\%$ $0.36$ [ $0.10, 1.30$ ]         Stacey 2008 (Fixed)       8       88       3 $45$ $5.9\%$ $1.36$ [ $0.38, 4.89$ ]         Stacey 2008 (Flexed)       6       91       4 $45$ $8.0\%$ $0.74$ [ $0.22, 2.50$ ]         Folle 2008 (150 mg)       4       99 $0$ $22$ $1.1\%$ $2.97$ [ $0.16, 53.71$ ]         Folle 2008 (300 mg)       3       99 $1$ $32$ $2.3\%$ $0.97$ [ $0.10, 9.00$ ]         Folle 2008 (600 mg)       6       101 $32$ $2.3\%$ $1.90$ [ $0.24, 15.21$ ]         /inik 2014       0       50       1 $108$ $1.4\%$ $0.71$ [ $0.03, 17.19$ ]         Ziegler 2015       3       70       2 $62$ $3.2\%$ $1.33$ [ $0.23, 7.69$ ]         Fotal (95% CI)       2553       1737 $100.0\%$ $1.01$ [ $0.73, 1.41$ ]         Fotal events       88       54         Heterogeneity: Chi <sup>2</sup> = 17.00, df = 23 (P = $0.81$ ); I <sup>2</sup> = $0\%$ $0.01$ $0.1$ $10$	Satoh 2011 (300 mg)	4	134	1	67	2.0%	2.00 [0.23, 17.54]	
Stacey 2008 (Fixed)       8       88       3       45       5.9% $1.36 [0.38, 4.89]$ Stacey 2008 (Flexed)       6       91       4       45       8.0% $0.74 [0.22, 2.50]$ Tolle 2008 (150 mg)       4       99       0       32 $1.1\%$ $2.97 [0.16, 53.71]$ Tolle 2008 (600 mg)       6       101       1       32 $2.3\%$ $0.97 [0.10, 9.00]$ Tolle 2008 (600 mg)       6       101       1       32 $2.3\%$ $1.90 [0.24, 15.21]$ Vinik 2014       0       50       1       108 $1.4\%$ $0.71 [0.03, 17.19]$ Ziegler 2015       3       70       2       62 $3.2\%$ $1.33 [0.23, 7.69]$ Total (95% Cl)       2553       1737       100.0%       1.01 [0.73, 1.41]         Total events       88       54         Heterogeneity: Chi <sup>2</sup> = 17.00, df = 23 (P = 0.81); I <sup>2</sup> = 0% $0.01$ $0.1$ $10$	Satoh 2011 (600 mg)	2	45	2	68	2.4%	1.51 [0.22, 10.34]	
Stacey 2008 (Flexed)       6       91       4       45       8.0% $0.74 [0.22, 2.50]$ Tolle 2008 (150 mg)       4       99       0       32 $1.1\%$ $2.97 [0.16, 53.71]$ Tolle 2008 (300 mg)       3       99       1       32 $2.3\%$ $0.97 [0.10, 9.00]$ Tolle 2008 (600 mg)       6       101       1       32 $2.3\%$ $1.90 [0.24, 15.21]$ Vinik 2014       0       50       1       108 $1.4\%$ $0.71 [0.03, 17.19]$ Ziegler 2015       3       70       2       62 $3.2\%$ $1.33 [0.23, 7.69]$ Total (95% Cl)       2553       1737       100.0% $1.01 [0.73, 1.41]$ Total events       88       54         Heterogeneity: Chi <sup>2</sup> = 17.00, df = 23 (P = 0.81); I <sup>2</sup> = 0% $0.01$ $0.1$ $10$	Smith 2014	3	98	8	93	12.2%	0.36 [0.10, 1.30]	
Tolle 2008 (150 mg)       4       99       0       32       1.1%       2.97 [0.16, 53.71]         Tolle 2008 (300 mg)       3       99       1       32       2.3%       0.97 [0.10, 9.00]         Tolle 2008 (600 mg)       6       101       1       32       2.3%       1.90 [0.24, 15.21]         Vinik 2014       0       50       1       108       1.4%       0.71 [0.03, 17.19]         Ziegler 2015       3       70       2       62       3.2%       1.33 [0.23, 7.69]         Total (95% Cl)       2553       1737       100.0%       1.01 [0.73, 1.41]         Total events       88       54         Heterogeneity: Chi <sup>2</sup> = 17.00, df = 23 (P = 0.81); l <sup>2</sup> = 0%       0.01       0.1       10	Stacey 2008 (Fixed)	8	88	3	45	5.9%	1.36 [0.38, 4.89]	
Tolle 2008 (300 mg)       3       99       1       32       2.3%       0.97 [0.10, 9.00]         Tolle 2008 (600 mg)       6       101       1       32       2.3%       1.90 [0.24, 15.21]         Vinik 2014       0       50       1       108       1.4%       0.71 [0.03, 17.19]         Ziegler 2015       3       70       2       62       3.2%       1.33 [0.23, 7.69]         Total (95% Cl)       2553       1737       100.0%       1.01 [0.73, 1.41]         Total events       88       54         Heterogeneity: Chi <sup>2</sup> = 17.00, df = 23 (P = 0.81); l <sup>2</sup> = 0%       0.01       0.1       10	Stacey 2008 (Flexed)	6	91	4	45	8.0%	0.74 [0.22, 2.50]	
Folle 2008 (600 mg)       6       101       1       32       2.3%       1.90 [0.24, 15.21]         Vinik 2014       0       50       1       108       1.4%       0.71 [0.03, 17.19]         Ziegler 2015       3       70       2       62       3.2%       1.33 [0.23, 7.69]         Total (95% Cl)       2553       1737       100.0%       1.01 [0.73, 1.41]         Fotal events       88       54         Heterogeneity: Chi <sup>2</sup> = 17.00, df = 23 (P = 0.81); l <sup>2</sup> = 0%       0.01       0.1       10	Tolle 2008 (150 mg)	4	99	0	32	1.1%	2.97 [0.16, 53.71]	
Vinik 2014       0       50       1       108       1.4%       0.71 $[0.03, 17.19]$ Ziegler 2015       3       70       2       62       3.2%       1.33 $[0.23, 7.69]$ Total (95% Cl)       2553       1737       100.0%       1.01 $[0.73, 1.41]$ Fotal events       88       54         Heterogeneity: Chi <sup>2</sup> = 17.00, df = 23 (P = 0.81); l <sup>2</sup> = 0%       0.01       0.1       10	Tolle 2008 (300 mg)	3	99	1	32	2.3%	0.97 [0.10, 9.00]	
Ziegler 2015       3       70       2       62 $3.2\%$ $1.33$ [0.23, 7.69]         Fotal (95% Cl)       2553       1737       100.0%       1.01 [0.73, 1.41]         Fotal events       88       54         Heterogeneity: Chi <sup>2</sup> = 17.00, df = 23 (P = 0.81); l <sup>2</sup> = 0%       0.01       0.1       10	Tolle 2008 (600 mg)	6	101	1	32	2.3%	1.90 [0.24, 15.21]	
Total (95% Cl)       2553       1737       100.0%       1.01 [0.73, 1.41]         Total events       88       54         Heterogeneity: Chi <sup>2</sup> = 17.00, df = 23 (P = 0.81); $I^2 = 0\%$ 0.01       0.1       10	Vinik 2014	0	50	1	108	1.4%	0.71 [0.03, 17.19]	
Total events 88 54 Heterogeneity: $Chi^2 = 17.00$ , df = 23 (P = 0.81); $I^2 = 0\%$	Ziegler 2015	3	70	2	62	3.2%	1.33 [0.23, 7.69]	
Heterogeneity: $\text{Chi}^2 = 17.00$ , $\text{df} = 23$ (P = 0.81); $\text{I}^2 = 0\%$	Total (95% CI)		2553		1737	100.0%	1.01 [0.73, 1.41]	◆
	Total events	88		54				
	Heterogeneity: Chi <sup>2</sup> = 17.00, df	= 23 (P =	= 0.81)	$I^2 = 0\%$				
(est for overall effect: $Z = 0.09$ ( $P = 0.93$ )	Test for overall effect: $Z = 0.09$							0.01 0.1 1 10 10 Favours pregabalin Favours placebo

	Pregat		Place			Risk Ratio	Risk Ratio
Study or Subgroup						M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Arezzo 2008	11	82	5	85	4.6%	2.28 [0.83, 6.28]	
3aba 2020	12	85	5	88	4.6%	2.48 [0.91, 6.75]	
Dworkin 2003	22	89	6	84	5.8%	3.46 [1.48, 8.11]	
Freynhagen 2005 (Fixed)	17	132	0	32		8.68 [0.54, 140.71]	
Freynhagen 2005 (Flexed)	15	141	0	33	0.8%	7.42 [0.46, 120.99]	
Guan 2011	10	206	1	102	1.3%	4.95 [0.64, 38.15]	
Huffman 2015	23	198	7	186	6.8%	3.09 [1.36, 7.02]	
_esser 2004 (300 mg)	19	81	1	32	1.3%	7.51 [1.05, 53.76]	
_esser 2004 (600 mg)	22	82	1	32	1.4%	8.59 [1.21, 61.07]	
_esser 2004 (75 mg)	3	77	2	33	2.6%	0.64 [0.11, 3.67]	
_iu 2017	11	111	6	109	5.7%	1.80 [0.69, 4.70]	<b>—</b>
Mu 2018	18	314	6	308	5.7%	2.94 [1.18, 7.31]	
NCT00394901 2006 (150 mg)	19	87	3	32	4.1%	2.33 [0.74, 7.34]	
NCT00394901 2006 (300 mg)	22	89	3	33	4.1%	2.72 [0.87, 8.49]	+
NCT00394901 2006 (600 mg)	37	97	3	33	4.2%	4.20 [1.39, 12.71]	— — — — — — — — — — — — — — — — — — —
Rauck 2012 (300 mg)	13	66	2	30	2.6%	2.95 [0.71, 12.28]	
Richter 2005 (150 mg)	4	79	1	42	1.2%	2.13 [0.25, 18.42]	
Richter 2005 (600 mg)	18	82	2	43	2.5%	4.72 [1.15, 19.40]	
Rosenstock 2004	15	76	2	70	2.0%	6.91 [1.64, 29.13]	
Sabatowski 2004 (150 mg)	12	81	3	40	3.8%	1.98 [0.59, 6.61]	
Sabatowski 2004 (300 mg)	18	76	3	41	3.7%	3.24 [1.01, 10.34]	
Satoh 2011 (300 mg)	28	134	5	67	6.3%	2.80 [1.13, 6.92]	
Satoh 2011 (600 mg)	18	45	6	68	4.5%	4.53 [1.95, 10.54]	
Smith 2014	13	98	3	93	2.9%	4.11 [1.21, 13.97]	
Stacey 2008 (Fixed)	22	88	1	45	1.2%		· · · · · · · · · · · · · · · · · · ·
Stacey 2008 (Flexed)	18	91	2	45	2.5%	4.45 [1.08, 18.35]	
Folle 2008 (150 mg)	5	99	0	32	0.7%	3.63 [0.21, 63.91]	
Folle 2008 (300 mg)	4	99	0	32	0.7%	2.97 [0.16, 53.71]	
Folle 2008 (600 mg)	8	101	1	32	1.4%	2.53 [0.33, 19.50]	
/an-Seventer 2006 (150 mg)	8	87	1	31	1.4%	2.85 [0.37, 21.88]	
/an-Seventer 2006 (300 mg)	11	98	1	31	1.4%	3.48 [0.47, 25.89]	
/an-Seventer 2006 (600 mg)	23	90	2	31	2.8%	3.96 [0.99, 15.84]	
/inik 2014	6	50	3	108	1.8%	4.32 [1.13, 16.58]	
Ziegler 2015	2	70	3	62	3.0%	0.59 [0.10, 3.42]	
Total (95% CI)		3481		2165	100.0%	3.38 [2.71, 4.21]	•
Total events	507		90				
Heterogeneity: $Chi^2 = 17.81$ , df							

## Figure 14.36 Pregabalin versus control; Adverse Event: Somnolence and Fatigue

## Figure 14.37 Pregabalin versus control; Adverse Event: Upper Respiratory Tract Infection

	Pregat	oalin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Huffman 2015	5	198	8	186	57.6%	0.59 [0.20, 1.76]	]
McDonnell 2018	1	46	3	45	21.2%	0.33 [0.04, 3.02]	]
NCT02215252 2014	1	46	3	45	21.2%	0.33 [0.04, 3.02]	]
Ziegler 2015	0	70	0	62		Not estimable	2
Total (95% CI)		360		338	100.0%	0.48 [0.19, 1.16]	
Total events	7		14				
Heterogeneity: Chi <sup>2</sup> =	0.36, df	= 2 (P =	= 0.83); I	$^{2} = 0\%$			
Test for overall effect:	Z = 1.63	(P = 0	.10)				0.01 0.1 1 10 100 Favours pregabalin Favours placebo

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Mu 2018	7	314	12	308	44.3%	0.57 [0.23, 1.43]	
Rauck 2012 (300 mg)	4	66	2	30	10.1%	0.91 [0.18, 4.69]	
Smith 2014	5	98	7	93	26.3%	0.68 [0.22, 2.06]	
Vinik 2014	4	50	5	108	11.6%	1.73 [0.48, 6.16]	
Ziegler 2015	1	70	2	62	7.8%	0.44 [0.04, 4.77]	
Total (95% CI)		598		601	100.0%	0.76 [0.44, 1.31]	•
Total events	21		28				
Heterogeneity: $Chi^2 = 2$	2.26, df =	4 (P =	0.69); I <sup>2</sup>		0.01 0.1 1 10 100		
Test for overall effect:	Z = 0.99 (	P = 0.3	32)				0.01 0.1 1 10 100 Favours pregabalin Favours placebo

## Figure 14.38 Pregabalin versus control; Adverse Event: Urinary Tract Infection

## Figure 14.39 Pregabalin versus control; Adverse Event: Vertigo

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Freynhagen 2005 (Fixed)	13	132	0	32	13.3%	6.70 [0.41, 109.82]	• • • •
Freynhagen 2005 (Flexed)	11	141	1	33	27.0%	2.57 [0.34, 19.25]	
Stacey 2008 (Fixed)	2	88	0	45	11.0%	2.58 [0.13, 52.71]	
Stacey 2008 (Flexed)	4	91	0	45	11.1%	4.50 [0.25, 81.80]	
Tolle 2008 (150 mg)	2	99	0	32	12.5%	1.65 [0.08, 33.50]	
Tolle 2008 (300 mg)	6	99	0	32	12.5%	4.29 [0.25, 74.12]	
Tolle 2008 (600 mg)	5	101	0	32	12.6%	3.56 [0.20, 62.66]	
Total (95% CI)		751		251	100.0%	3.56 [1.29, 9.85]	
Total events	43		1				
Heterogeneity: Chi <sup>2</sup> = 0.63,	df = 6 (P	= 1.00	0); $I^2 = 0$ %	6			0.01 0.1 1 10 100
Test for overall effect: $Z = 2$	2.45 (P =	0.01)					Favours pregabalin Favours placebo

## Figure 14.40 Pregabalin versus control; Adverse Event: Vision Problems

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Huffman 2015	4	198	1	186	11.8%	3.76 [0.42, 33.31]	
Rauck 2012 (300 mg)	3	66	2	30	31.4%	0.68 [0.12, 3.87]	
Van-Seventer 2006 (150 mg)	0	87	0	31		Not estimable	
Van-Seventer 2006 (300 mg)	2	98	0	31	8.6%	1.62 [0.08, 32.79]	
Van-Seventer 2006 (600 mg)	4	90	0	31	8.4%	3.16 [0.18, 57.17]	
Vinik 2014	2	50	2	108	14.5%	2.16 [0.31, 14.90]	
Zhang 2013 (1200 mg)	2	107	0	31	8.8%	1.48 [0.07, 30.07]	
Zhang 2013 (2400 mg)	4	82	0	32	8.2%	3.58 [0.20, 64.63]	
Zhang 2013 (3600 mg)	2	87	0	32	8.3%	1.88 [0.09, 38.03]	
Total (95% CI)		865		512	100.0%	1.95 [0.85, 4.47]	
Total events	23		5				
Heterogeneity: $Chi^2 = 2.09$ , df	= 7 (P =	0.95); I	$^{2} = 0\%$				
Test for overall effect: $Z = 1.55$	$\Theta (P = 0.1)$	1)					0.01 0.1 İ 10 100 Favours pregabalin Favours placebo

#### Figure 14.41 Pregabalin versus control; Adverse Event: Vomiting

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Baba 2020	5	85	1	88	14.2%	5.18 [0.62, 43.40]	
Rauck 2012 (300 mg)	0	66	1	30	29.5%	0.15 [0.01, 3.68]	←
Rosenstock 2004	3	76	1	70	15.0%	2.76 [0.29, 25.95]	
Vinik 2014	0	50	4	108	41.3%	0.24 [0.01, 4.33]	
Total (95% CI)		277		296	100.0%	1.29 [0.48, 3.46]	
Total events	8		7				
Heterogeneity: $Chi^2 = 5$	5.11, df =	3 (P =	0.16); I <sup>2</sup>	= 41%			0.01 0.1 1 10 100
Test for overall effect: 2	Z = 0.51	(P=0.6)	51)				0.01 0.1 1 10 100 Favours pregabalin Favours placebo

	Pregab	alin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Arezzo 2008	15	82	3	85	13.5%	5.18 [1.56, 17.24]	· · · · · · · · · · · · · · · · · · ·
Baba 2020	2	85	0	88	2.2%	5.17 [0.25, 106.23]	
Freynhagen 2005 (Fixed)	18	132	1	32	7.4%	4.36 [0.60, 31.49]	
Freynhagen 2005 (Flexed)	17	141	1	33	7.4%	3.98 [0.55, 28.84]	
Guan 2011	5	206	1	102	6.1%	2.48 [0.29, 20.91]	
Huffman 2015	5	198	1	186	4.7%	4.70 [0.55, 39.83]	
AcDonnell 2018	2	46	0	45	2.3%	4.89 [0.24, 99.18]	
NCT00394901 2006 (150 mg)	1	87	0	32	3.3%	1.13 [0.05, 26.93]	
NCT00394901 2006 (300 mg)	17	89	0	33	3.3%	13.22 [0.82, 213.83]	
NCT00394901 2006 (600 mg)	14	97	0	33	3.4%	10.06 [0.62, 164.15]	· · · · ·
Rauck 2012 (300 mg)	5	66	1	30	6.3%	2.27 [0.28, 18.62]	
Richter 2005 (150 mg)	1	79	0	42	3.0%	1.61 [0.07, 38.74]	
Richter 2005 (600 mg)	8	82	0	43	3.0%	9.01 [0.53, 152.51]	· · · · · ·
Satoh 2011 (300 mg)	15	134	1	67	6.1%	7.50 [1.01, 55.58]	· · · · · · · · · · · · · · · · · · ·
Satoh 2011 (600 mg)	5	45	2	68	7.3%	3.78 [0.77, 18.64]	
Stacey 2008 (Fixed)	4	88	0	45	3.0%	4.65 [0.26, 84.54]	
Stacey 2008 (Flexed)	8	91	0	45	3.1%	8.50 [0.50, 144.05]	
Van–Seventer 2006 (150 mg)	3	87	0	31	3.4%	2.55 [0.14, 47.93]	
Van-Seventer 2006 (300 mg)	8	98	0	31	3.5%	5.49 [0.33, 92.57]	· · · · ·
Van-Seventer 2006 (600 mg)	8	90	0	31	3.4%	5.98 [0.36, 100.65]	
Vinik 2014	0	50	1	108	4.4%	0.71 [0.03, 17.19]	
Total (95% CI)		2073		1210	100.0%	4.84 [2.94, 7.95]	•
Total events	161		12				
Heterogeneity: Chi <sup>2</sup> = 5.19, df =	= 20 (P =	1.00); I	$^{2} = 0\%$				0.01 0.1 1 10 10
Test for overall effect: $Z = 6.22$	(P < 0.00	001)					0.01 0.1 1 10 10 Favours pregabalin Favours placebo

# Figure 14.42 Pregabalin versus control; Adverse Event: Weight Gain

# Anticonvulsants (Topiramate)

# Figure 15.1 Topiramate versus control; Withdrawals due to Adverse Events

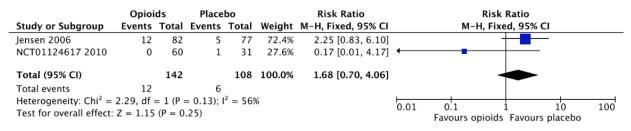
	Topirar	mate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Raskin 2004	52	214	9	109	100.0%	2.94 [1.51, 5.75]	
Total (95% CI)		214		109	100.0%	2.94 [1.51, 5.75]	◆
Total events	52		9				
Heterogeneity: Not ap	oplicable						0.01 0.1 1 10 100
Test for overall effect	:: Z = 3.16	5 (P = 0)	.002)				0.01 0.1 1 10 100 Favours topiramate Favours placebo

## Opioids

#### Figure 16.1 Opioids versus control; Withdrawals due to Adverse Events

	Opioi	ids	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Freeman 2007	13	160	10	153	31.5%	1.24 [0.56, 2.75]	
Hanna 2008	27	169	9	169	27.7%	3.00 [1.45, 6.19]	<b></b>
Jensen 2006	7	82	4	77	12.7%	1.64 [0.50, 5.39]	
NCT01124617 2010	5	60	2	31	8.1%	1.29 [0.27, 6.28]	
Simpson 2016	28	93	6	93	18.5%	4.67 [2.03, 10.74]	
Zin 2010	4	29	0	33	1.4%	10.20 [0.57, 181.74]	
Total (95% CI)		593		556	100.0%	2.55 [1.73, 3.76]	•
Total events	84		31				
Heterogeneity: Chi <sup>2</sup> =	7.48, df	= 5 (P =	= 0.19);	$ ^2 = 339$	%		0.01 0.1 1 10 100
Test for overall effect:	Z = 4.71	. (P < 0	.00001)				Favours opioids Favours placebo

#### Figure 16.2 Opioids versus control; Adverse Event: Asthenia



#### Figure 16.3 Opioids versus control; Adverse Event: Constipation

	Opioi	ds	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Freeman 2007	8	160	2	153	6.5%	3.83 [0.83, 17.73]	
Hanna 2008	45	169	10	169	31.7%	4.50 [2.35, 8.63]	
Jensen 2006	35	82	11	77	36.0%	2.99 [1.64, 5.45]	_ <b>_</b>
NCT01124617 2010	16	60	0	31	2.1%	17.31 [1.07, 279.26]	<b>_</b>
Zin 2010	18	29	8	33	23.7%	2.56 [1.31, 4.99]	<b>—</b>
Total (95% CI)		500		463	100.0%	3.72 [2.58, 5.35]	•
Total events	122		31				
Heterogeneity: Chi <sup>2</sup> =	3.22, df	= 4 (P =	= 0.52);	$^{2} = 0\%$			0.01 0.1 1 10 100
Test for overall effect:	Z = 7.08	(P < 0	.00001)				0.01 0.1 1 10 100 Favours opioids Favours placebo

#### Figure 16.4 Opioids versus control; Adverse Event: Diarrhea

	Opioi	ids	Place	bo		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Freeman 2007	8	160	3	153	36.0%	2.55 [0.69, 9.43]	
NCT01124617 2010	4	60	2	31	31.0%	1.03 [0.20, 5.33]	<b>+</b>
Zin 2010	1	29	3	33	33.0%	0.38 [0.04, 3.45]	
Total (95% CI)		249		217	100.0%	1.36 [0.57, 3.26]	-
Total events	13		8				
Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	,	-		$1^2 = 129$	%		0.01 0.1 1 10 100 Favours opioids Favours placebo

## Figure 16.5 Opioids versus control; Adverse Event: Dizziness

	Opioi	ds	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Freeman 2007	10	160	2	153	5.9%	4.78 [1.06, 21.47]	
Hanna 2008	25	169	6	169	17.2%	4.17 [1.75, 9.90]	
Jensen 2006	26	82	8	77	23.7%	3.05 [1.47, 6.33]	<b>_</b> _
NCT01124617 2010	5	60	2	31	7.6%	1.29 [0.27, 6.28]	
Zin 2010	22	29	17	33	45.7%	1.47 [1.00, 2.17]	-
Total (95% CI)		500		463	100.0%	2.49 [1.78, 3.50]	•
Total events	88		35				
Heterogeneity: Chi <sup>2</sup> =	10.04, di	f = 4 (P	= 0.04);	$I^2 = 60$	0%		
Test for overall effect:	Z = 5.28	(P < 0	.00001)				0.01 0.1 1 10 100 Favours opioids Favours placebo

## Figure 16.6 Opioids versus control; Adverse Event: Dry Mouth

	Opioi	ds	Place	bo		<b>Risk Ratio</b>		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M–H, Fixed, 95% Cl	
Jensen 2006	13	82	2	77	75.9%	6.10 [1.42, 26.17]			
NCT01124617 2010	1	60	0	31	24.1%	1.57 [0.07, 37.54]			
Total (95% CI)		142		108	100.0%	5.01 [1.38, 18.25]			
Total events	14		2						
Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	,			<sup>2</sup> = 0%			0.01	0.1 1 10 Favours opioids Favours placebo	100

## Figure 16.7 Opioids versus control; Adverse Event: Generalized Pain

	Opioi	ds	Place	bo		Risk Ratio		R	isk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		М-Н,	Fixed, 95%	CI	
Freeman 2007	3	160	8	153	86.1%	0.36 [0.10, 1.33]					
NCT01124617 2010	1	60	1	31	13.9%	0.52 [0.03, 7.98]	-		•		
Total (95% CI)		220		184	100.0%	0.38 [0.12, 1.24]					
Total events	4		9								
Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	,	,		$ ^2 = 0\%$			0.01	0.1	1 1	10	100
		<b>(</b> -	,					Favours opio	bids Favou	rs placebo	

## Figure 16.8 Opioids versus control; Adverse Event: Headache

	Opioi	ds	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Freeman 2007	9	160	11	153	20.4%	0.78 [0.33, 1.84]	
Hanna 2008	17	169	17	169	30.9%	1.00 [0.53, 1.89]	_ <b>+</b> _
Jensen 2006	9	82	18	77	33.7%	0.47 [0.22, 0.98]	
NCT01124617 2010	4	60	2	31	4.8%	1.03 [0.20, 5.33]	
Zin 2010	6	29	6	33	10.2%	1.14 [0.41, 3.14]	
Total (95% CI)		500		463	100.0%	0.79 [0.55, 1.15]	•
Total events	45		54				
Heterogeneity: Chi <sup>2</sup> =	3.04, df	= 4 (P =	= 0.55); I	$^{2} = 0\%$			
Test for overall effect:	Z = 1.22	(P = 0	.22)				0.01 0.1 1 10 100 Favours opioids Favours placebo

	Opioi	ds	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Freeman 2007	19	160	5	153	13.7%	3.63 [1.39, 9.49]	
Hanna 2008	43	169	18	169	48.1%	2.39 [1.44, 3.97]	<b>-∎</b> -
Jensen 2006	30	82	6	77	16.5%	4.70 [2.07, 10.65]	<b>_</b> _
NCT01124617 2010	19	60	0	31	1.8%	20.46 [1.28, 327.91]	│ ———→
Zin 2010	13	29	8	33	20.0%	1.85 [0.89, 3.82]	+
Total (95% CI)		500		463	100.0%	3.15 [2.23, 4.45]	•
Total events	124		37				
Heterogeneity: Chi <sup>2</sup> =	5.95, df	= 4 (P =	= 0.20); I	$^{2} = 33$	%		0.01 0.1 1 10 100
Test for overall effect:	Z = 6.49	(P < 0	.00001)				0.01 0.1 1 10 100 Favours opioids Favours placebo

## Figure 16.10 Opioids versus control; Adverse Event: Pruritus

	Opioi	ds	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Jensen 2006	20	82	6	77	84.6%	3.13 [1.33, 7.38]	
NCT01124617 2010	2	60	0	31	9.0%	2.62 [0.13, 53.00]	
Zin 2010	5	29	0	33	6.4%	12.47 [0.72, 216.20]	
Total (95% CI)		171		141	100.0%	3.68 [1.68, 8.06]	-
Total events	27		6				
Heterogeneity: Chi <sup>2</sup> =	0.89, df	= 2 (P =	= 0.64);	$ ^2 = 0\%$			
Test for overall effect:	Z = 3.26	(P = 0	.001)				0.01 0.1 1 10 100 Favours opioids Favours placebo

## Figure 16.11 Opioids versus control; Adverse Event: Serious Adverse Events

	Opioi	ds	Place	bo		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Freeman 2007	5	160	4	153	15.5%	1.20 [0.33, 4.37]	
Jensen 2006	5	82	9	77	35.3%	0.52 [0.18, 1.49]	
NCT01124617 2010	4	60	3	31	15.0%	0.69 [0.16, 2.89]	
Simpson 2016	10	93	9	93	34.2%	1.11 [0.47, 2.61]	_ <b>_</b>
Total (95% CI)		395		354	100.0%	0.85 [0.50, 1.46]	•
Total events	24		25				
Heterogeneity: Chi <sup>2</sup> =	1.56, df =	= 3 (P =	= 0.67);	$1^2 = 0\%$			
Test for overall effect:	Z = 0.58	(P = 0	.56)				0.01 0.1 1 10 100 Favours opioids Favours placebo

## Figure 16.12 Opioids versus control; Adverse Event: Somnolence and Fatigue

	Opioi	ds	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Freeman 2007	10	160	2	153	5.5%	4.78 [1.06, 21.47]	
Hanna 2008	68	169	23	169	62.2%	2.96 [1.94, 4.51]	
Jensen 2006	33	82	1	77	2.8%	30.99 [4.34, 221.09]	<b>→</b>
NCT01124617 2010	17	60	4	31	14.3%	2.20 [0.81, 5.96]	
Zin 2010	9	29	6	33	15.2%	1.71 [0.69, 4.22]	
Total (95% CI)		500		463	100.0%	3.54 [2.52, 4.97]	•
Total events	137		36				
Heterogeneity: Chi <sup>2</sup> =	8.92, df	= 4 (P =	= 0.06);	$l^2 = 55\%$	%		
Test for overall effect:	Z = 7.31	(P < 0	.00001)				0.01 0.1 1 10 100 Favours opioids Favours placebo

# Figure 16.13 Opioids versus control; Adverse Event: Upper Respiratory Tract Infection

	Opioi		Place			Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M–H, Fixed, 95% Cl	
Freeman 2007	9	160	8	153	92.6%	1.08 [0.43, 2.72]			
NCT01124617 2010	1	60	0	31	7.4%	1.57 [0.07, 37.54]		<b>-</b>	
Total (95% CI)		220		184	100.0%	1.11 [0.46, 2.71]			
Total events	10		8						
Heterogeneity: Chi <sup>2</sup> =	0.05, df	= 1 (P =	= 0.82);	$1^2 = 0\%$			0.01	0.1 1 10	100
Test for overall effect:	Z = 0.24	(P=0)	.81)				0.01	Favours opioids Favours placebo	100

## Figure 16.14 Opioids versus control; Adverse Event: Vomiting

	Opioi	ds	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Hanna 2008	16	169	7	169	57.1%	2.29 [0.97, 5.41]	
Jensen 2006	17	82	2	77	16.8%	7.98 [1.91, 33.41]	
NCT01124617 2010	12	60	1	31	10.8%	6.20 [0.84, 45.51]	
Zin 2010	3	29	2	33	15.3%	1.71 [0.31, 9.52]	
Total (95% CI)		340		310	100.0%	3.58 [1.90, 6.72]	•
Total events	48		12				
Heterogeneity: Chi <sup>2</sup> =	3.25, df	= 3 (P =	= 0.35);	$I^2 = 8\%$			0.01 0.1 1 10 100
Test for overall effect:	Z = 3.96	(P < 0	.0001)				0.01 0.1 1 10 100 Favours opioids Favours placebo

## Rubefacients (Capsaicin)

## Figure 17.1 Rubefacients versus control; Withdrawals due to Adverse Events

	Rubefa	cient	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Irving 2011	3	212	3	204	33.5%	0.96 [0.20, 4.71]	<b>+</b>
Vinik 2015	8	157	1	77	14.7%	3.92 [0.50, 30.81]	
Vinik 2015a	7	156	2	78	29.2%	1.75 [0.37, 8.23]	
Watson 1993	18	74	2	69	22.7%	8.39 [2.02, 34.84]	
Total (95% CI)		599		428	100.0%	3.31 [1.56, 7.01]	-
Total events	36		8				
Heterogeneity: Chi <sup>2</sup> =	= 4.64, df	= 3 (P =	= 0.20); I	$^{2} = 35\%$	6		
Test for overall effect	z = 3.13	B (P = 0)	.002)				0.01 0.1 1 10 100 Favours rubefacients Favours control

## Figure 17.2 Rubefacients versus control; Adverse Event: Back Pain

	Rubefa	cient	Conti	rol		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M−H, Fixe	ed, 95% CI	
Backonja 2008	6	205	4	197	75.6%	1.44 [0.41, 5.03]			
Webster 2010	3	102	1	53	24.4%	1.56 [0.17, 14.62]		-	
Total (95% CI)		307		250	100.0%	1.47 [0.49, 4.38]			
Total events	9		5						
Heterogeneity: Chi <sup>2</sup> =				$^{2} = 0\%$			0.01 0.1	1 10	100
Test for overall effect	Z = 0.69	P(P=0)	.49)				Favours rubefacients	Favours control	

## Figure 17.3 Rubefacients versus control; Adverse Event: Coughing and/or Sneezing

	Rubefa	cient	Cont	rol		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Capsaicin Study Group 1992	16	138	2	139	54.1%	8.06 [1.89, 34.39]	
Watson 1993	7	74	1	69	28.1%	6.53 [0.82, 51.70]	
Webster 2010	3	102	0	53	17.8%	3.67 [0.19, 69.76]	
Total (95% CI)		314		261	100.0%	6.85 [2.29, 20.43]	
Total events	26		3				
Heterogeneity: Chi <sup>2</sup> = 0.22, dt	f = 2 (P =	0.89); 1	$^{2} = 0\%$				
Test for overall effect: $Z = 3.4$	5 (P = 0.0)	0006)					0.01 0.1 1 10 100 Favours rubefacients Favours control

## Figure 17.4 Rubefacients versus control; Adverse Event: Dizziness

	Rubefa	cient	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Backonja 2008	5	205	6	197	36.6%	0.80 [0.25, 2.58]	
Irving 2011	3	212	6	204	36.6%	0.48 [0.12, 1.90]	
Watson 1993	1	74	0	69	3.1%	2.80 [0.12, 67.60]	
Webster 2010	1	102	3	53	23.6%	0.17 [0.02, 1.62]	
Total (95% CI)		593		523	100.0%	0.60 [0.28, 1.28]	-
Total events	10		15				
Heterogeneity: Chi <sup>2</sup> =	2.42, df	= 3 (P =	= 0.49); I	$^{2} = 0\%$			0.01 0.1 1 10 100
Test for overall effect	: Z = 1.33	(P = 0)	18)				Favours rubefacients Favours control

## Figure 17.5 Rubefacients versus control; Adverse Event: Headache

	Rubefa	cient	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Backonja 2008	7	205	8	197	43.2%	0.84 [0.31, 2.28]	
Irving 2011	4	212	10	204	54.0%	0.38 [0.12, 1.21]	
Watson 1993	2	74	0	69	2.7%	4.67 [0.23, 95.52]	
Total (95% CI)		491		470	100.0%	0.70 [0.35, 1.40]	-
Total events	13		18				
Heterogeneity: Chi <sup>2</sup> =	= 2.70, df	= 2 (P =	= 0.26); I	$^{2} = 26\%$	6		0.01 0.1 1 10 100
Test for overall effect	Z = 1.01	(P = 0)	.31)				Favours rubefacients Favours control

## Figure 17.6 Rubefacients versus control; Adverse Event: Increased Blood Pressure

	Rubefacient Control			Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Backonja 2008	7	205	4	197	41.7%	1.68 [0.50, 5.66]	
Simpson 2017	16	186	5	183	51.6%	3.15 [1.18, 8.42]	
Webster 2010	3	102	0	53	6.7%	3.67 [0.19, 69.76]	
Total (95% CI)		493		433	100.0%	2.57 [1.23, 5.35]	-
Total events	26		9				
Heterogeneity: Chi <sup>2</sup> =	= 0.69, df	= 2 (P =	= 0.71); I	$^{2} = 0\%$			
Test for overall effect	t: $Z = 2.52$	P = 0	.01)				0.01 0.1 1 10 100 Favours rubefacients Favours control

# Figure 17.7 Rubefacients versus control; Adverse Event: Local Reaction (Burning, Stinging, and/or Erythema)

	Rubefa	cient	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Backonja 2008	193	205	128	197	39.6%	1.45 [1.30, 1.61]	
Bernstein 1989	5	16	2	16	0.6%	2.50 [0.57, 11.05]	
Capsaicin Study Group 1992	97	138	27	139	8.2%	3.62 [2.54, 5.16]	
Irving 2011	194	212	141	204	43.6%	1.32 [1.20, 1.46]	
Tandan 1992	6	11	2	11	0.6%	3.00 [0.77, 11.74]	+
Watson 1993	45	74	23	69	7.2%	1.82 [1.25, 2.67]	
Webster 2010	7	102	0	53	0.2%	7.86 [0.46, 135.10]	
Total (95% CI)		758		689	100.0%	1.63 [1.50, 1.76]	•
Total events	547		323				
Heterogeneity: $Chi^2 = 42.64$ ,	df = 6 (P ·	< 0.000	$(01); I^2 =$	86%			0.01 0.1 1 10 100
Test for overall effect: $Z = 12$ .	.01 (P < 0	.00001)	)				0.01 0.1 1 10 100 Favours rubefacients Favours control

## Figure 17.8 Rubefacients versus control; Adverse Event: Nasopharyngitis

	Rubefa	cient	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Backonja 2008	7	205	7	197	53.1%	0.96 [0.34, 2.69]	
Watson 1993	1	74	1	69	7.7%	0.93 [0.06, 14.62]	
Webster 2010	4	102	4	53	39.2%	0.52 [0.14, 2.00]	
Total (95% CI)		381		319	100.0%	0.79 [0.36, 1.71]	-
Total events	12		12				
Heterogeneity: Chi <sup>2</sup> =	0.52, df	= 2 (P =	= 0.77); I	$^{2} = 0\%$			0.01 0.1 1 10 100
Test for overall effect	Z = 0.61	I (P = 0)	54)				Favours rubefacients Favours control

## Figure 17.9 Rubefacients versus control; Adverse Event: Nausea

	Rubefacient Control y or Subgroup Events Total Events Tota		Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup			Total	tal Weight M-H, Fixed, 95% Cl		M–H, Fixed, 95% Cl	
Backonja 2008	8	205	2	197	22.7%	3.84 [0.83, 17.88]	
Irving 2011	11	212	5	204	56.8%	2.12 [0.75, 5.99]	
Watson 1993	2	74	0	69	5.8%	4.67 [0.23, 95.52]	
Webster 2010	5	102	1	53	14.7%	2.60 [0.31, 21.67]	
Total (95% CI)		593		523	100.0%	2.73 [1.27, 5.87]	-
Total events	26		8				
Heterogeneity: Chi <sup>2</sup> =	= 0.54, df	= 3 (P =	= 0.91); I	$^{2} = 0\%$			
Test for overall effect	z = 2.57	7 (P = 0)	.01)				0.01 0.1 1 10 100 Favours rubefacients Favours control

## Figure 17.10 Rubefacients versus control; Adverse Event: Pain at Application Site

	Rubefa	cient	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events Tota		l Events Total		Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Backonja 2008	114	205	43	197	36.7%	2.55 [1.90, 3.41]	
Capsaicin Study Group 1992	2	138	5	139	4.2%	0.40 [0.08, 2.04]	
Irving 2011	134	212	57	204	48.6%	2.26 [1.77, 2.88]	
Simpson 2017	35	186	10	183	8.4%	3.44 [1.76, 6.75]	<b>_</b>
Webster 2010	7	102	2	53	2.2%	1.82 [0.39, 8.45]	
Total (95% CI)		843		776	100.0%	2.38 [1.99, 2.84]	•
Total events	292		117				
Heterogeneity: $Chi^2 = 6.26$ , di	f = 4 (P =	0.18); I	$^{2} = 36\%$				
Test for overall effect: $Z = 9.5$	3 (P < 0.0	00001)					0.01 0.1 1 10 100 Favours rubefacients Favours control

## Figure 17.11 Rubefacients versus control; Adverse Event: Papules at Application Site

	Rubefa	cient	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Backonja 2008	20	205	6	197	44.2%	3.20 [1.31, 7.81]	<b></b>
Irving 2011	15	212	5	204	36.8%	2.89 [1.07, 7.80]	
Webster 2010	4	102	2	53	19.0%	1.04 [0.20, 5.49]	
Total (95% CI)		519		454	100.0%	2.68 [1.46, 4.91]	◆
Total events	39		13				
Heterogeneity: Chi <sup>2</sup> = Test for overall effect	,		.,	<sup>2</sup> = 0%			0.01 0.1 1 10 100 Favours rubefacients Favours control

## Figure 17.12 Rubefacients versus control; Adverse Event: Pruritus at Application Site

	Rubefa	cient	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	udy or Subgroup Events Total Eve		Events	Events Total		M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Backonja 2008	10	205	6	197	35.8%	1.60 [0.59, 4.32]	
Irving 2011	6	212	3	204	17.9%	1.92 [0.49, 7.59]	
Webster 2010	17	102	6	53	46.3%	1.47 [0.62, 3.51]	
Total (95% CI)		519		454	100.0%	1.60 [0.89, 2.89]	•
Total events	33		15				
Heterogeneity: Chi <sup>2</sup> =	= 0.10, df	= 2 (P =	= 0.95); I	$^{2} = 0\%$			0.01 0.1 1 10 100
Test for overall effect	z = 1.56	5 (P = 0)	.12)				0.01 0.1 1 10 100 Favours rubefacients Favours control

	Rubefa	cient	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events Total		Weight M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl
Backonja 2008	10	205	6	197	16.8%	1.60 [0.59, 4.32]	
Irving 2011	11	212	8	204	22.4%	1.32 [0.54, 3.22]	
Simpson 2017	4	186	8	183	22.2%	0.49 [0.15, 1.61]	
Vinik 2015	12	157	5	77	18.4%	1.18 [0.43, 3.22]	
Vinik 2015a	19	156	5	78	18.3%	1.90 [0.74, 4.90]	+
Webster 2010	7	102	0	53	1.8%	7.86 [0.46, 135.10]	
Total (95% CI)		1018		792	100.0%	1.38 [0.90, 2.11]	•
Total events	63		32				
Heterogeneity: Chi <sup>2</sup> =	= 4.99, df	= 5 (P =	= 0.42); I	$^{2} = 0\%$			0.01 0.1 1 10 100
Test for overall effect	:: Z = 1.49	$\Theta(P=0)$	.14)				Favours rubefacients Favours control

#### Figure 17.13 Rubefacients versus control; Adverse Event: Serious Adverse Events

## Figure 17.14 Rubefacients versus control; Adverse Event: Sinusitis

	Rubefa	cient	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Backonja 2008	6	205	1	197	50.0%	5.77 [0.70, 47.46]	
Irving 2011	6	212	1	204	50.0%	5.77 [0.70, 47.54]	
Total (95% CI)		417		401	100.0%	5.77 [1.30, 25.62]	
Total events	12		2				
Heterogeneity: Chi <sup>2</sup> =	,			$^{2} = 0\%$			0.01 0.1 1 10 100
Test for overall effect	Z = 2.30	P = 0	.02)				Favours rubefacients Favours control

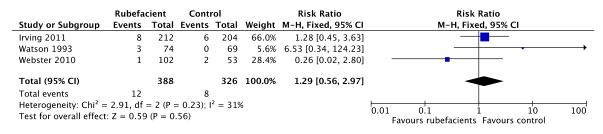
#### Figure 17.15 Rubefacients versus control; Adverse Event: Swelling at Application Site

	Rubefa	cient	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Backonja 2008	12	205	2	197	52.8%	5.77 [1.31, 25.43]	<b>_</b>
Irving 2011	13	212	0	204	13.2%	25.99 [1.55, 434.29]	· · · · · · · · · · · · · · · · · · ·
Webster 2010	10	102	1	53	34.0%	5.20 [0.68, 39.51]	
Total (95% CI)		519		454	100.0%	8.24 [2.80, 24.24]	
Total events	35		3				
Heterogeneity: Chi <sup>2</sup> =	1.06, df	= 2 (P =	= 0.59); I	$^{2} = 0\%$			0.01 0.1 1 10 100
Test for overall effect	: Z = 3.83	(P = 0)	.0001)				Favours rubefacients Favours control

#### Figure 17.16 Rubefacients versus control; Adverse Event: Unspecific Application Site Reaction

	Rubefa	cient	Cont	rol		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Simpson 2017	63	186	15	183	93.6%	4.13 [2.44, 6.98]	
Watson 1993	13	74	1	69	6.4%	12.12 [1.63, 90.23]	
Total (95% CI)		260		252	100.0%	4.64 [2.79, 7.72]	•
Total events	76		16				
Heterogeneity: Chi <sup>2</sup> =	= 1.07, df	= 1 (P =	= 0.30); I	$^{2} = 6\%$			0.01 0.1 1 10 100
Test for overall effect	z = 5.93	8 (P < 0	.00001)				Favours rubefacients Favours control

#### Figure 17.17 Rubefacients versus control; Adverse Event: Upper Respiratory Tract Infection



# Figure 17.18 Rubefacients versus control; Adverse Event: Vomiting

	Rubefacient Control			Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixe	d, 95% CI	
Backonja 2008	6	205	3	197	85.7%	1.92 [0.49, 7.58]		-	
Irving 2011	6	212	0	204	14.3%	12.51 [0.71, 220.68]	_		
Total (95% CI)		417		401	100.0%	3.43 [1.06, 11.14]			
Total events	12		3						
Heterogeneity: Chi <sup>2</sup> = Test for overall effect				<sup>2</sup> = 329	6		0.01 0.1 1 Favours rubefacients	10 Favours control	100

## SNRIs

## Figure 18.1 SNRIs versus control; Withdrawals due to Adverse Events

	I	Place	bo		Risk Ratio	Risk Ratio
Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
8	63	2	22	5.6%	1.40 [0.32, 6.08]	
7	87	1	22	3.0%	1.77 [0.23, 13.65]	
21	99	1	23	3.1%	4.88 [0.69, 34.43]	
21	69	1	23	2.9%	7.00 [1.00, 49.19]	
17	202	8	202	15.2%	2.13 [0.94, 4.81]	<b>⊢</b> ∎−−
5	115	2	38	5.7%	0.83 [0.17, 4.08]	
15	114	2	38	5.7%	2.50 [0.60, 10.44]	
22	113	2	39	5.7%	3.80 [0.94, 15.41]	
5	116	2	58	5.1%	1.25 [0.25, 6.25]	
14	116	1	58	2.5%	7.00 [0.94, 51.94]	
6	82	2	40	5.1%	1.46 [0.31, 6.93]	
8	82	1	41	2.5%	4.00 [0.52, 30.91]	
17	114	4	54	10.3%	2.01 [0.71, 5.70]	+
20	112	4	54	10.3%	2.41 [0.87, 6.71]	+
9	85	5	83	9.6%	1.76 [0.61, 5.03]	- <b>+</b>
12	86	4	84	7.7%	2.93 [0.98, 8.72]	
	1655		879	100.0%	2.48 [1.78, 3.45]	•
207		42				
7.58, df	= 15 (F	P = 0.94)	; $I^2 = 0$	%		0.01 0.1 1 10 100
Z = 5.38	B (P < 0	).00001)				0.01 0.1 1 10 100 Favours SNRIs Favours Placebo
	8 7 21 17 5 15 22 5 14 6 8 17 20 9 12 207 7.58, df	8         63           7         87           21         99           21         69           17         202           5         115           15         114           22         113           5         116           14         116           6         82           17         114           20         112           9         85           12         86           1655         207           7.58, df = 15 (free         15 (free	8       63       2         7       87       1         21       99       1         21       69       1         17       202       8         5       115       2         15       114       2         22       113       2         5       116       2         14       116       1         6       82       2         8       82       1         17       114       4         9       85       5         12       86       4         1655         207       42	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	8       63       2       22       5.6%       1.40 $[0.32, 6.08]$ 7       87       1       22       3.0%       1.77 $[0.23, 13.65]$ 21       99       1       23       3.1%       4.88 $[0.69, 34.43]$ 21       69       1       23       2.9%       7.00 $[1.00, 49.19]$ 17       202       8       202       15.2%       2.13 $[0.94, 4.81]$ 5       115       2       38       5.7%       0.83 $[0.17, 4.08]$ 15       114       2       38       5.7%       2.50 $[0.60, 10.44]$ 22       113       2       39       5.7%       3.80 $[0.94, 51.94]$ 6       82       2       40       5.1%       1.25 $[0.25, 6.25]$ 14       116       1       58       2.5%       7.00 $[0.94, 51.94]$ 6       82       2       40       5.1%       1.46 $[0.31, 6.93]$ 8       82       1       41       2.5%       4.00 $[0.52, 30.91]$ 17       114       4       54       10.3%

## Figure 18.2 SNRIs versus control; Adverse Event: Anorexia

	SNR	1	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	I M–H, Fixed, 95% Cl
Gao 2010	11	106	2	109	25.8%	5.66 [1.28, 24.91]	.]
Goldstein 2005	3	115	1	38	19.7%	0.99 [0.11, 9.25]	i]
Goldstein 2005a	3	114	0	38	9.8%	2.37 [0.13, 44.94]	.]
Goldstein 2005b	9	113	0	39	9.7%	6.67 [0.40, 111.95]	j]
Rowbotham 2005	6	82	1	40	17.6%	2.93 [0.36, 23.50]	)]
Rowbotham 2005a	4	82	1	41	17.5%	2.00 [0.23, 17.32]	2]
Total (95% CI)		612		305	100.0%	3.40 [1.47, 7.86]	
Total events	36		5				
Heterogeneity: Chi <sup>2</sup> =	2.15, df	= 5 (P	= 0.83);	$I^2 = 0\%$	6		
Test for overall effect	: Z = 2.8	5 (P = 0)	0.004)				0.01 0.1 1 10 100 Favours SNRIs Favours Placebo

## Figure 18.3 SNRIs versus control; Adverse Event: Asthenia

	SNR	1	Place	bo		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	I M–H, Fixed, 95% Cl	
Gao 2010	6	106	1	109	66.4%	6.17 [0.76, 50.39]	]	
Gao 2014	10	202	0	202	33.6%	21.00 [1.24, 355.98]	]	
Total (95% CI)		308		311	100.0%	11.16 [2.11, 59.13]		
Total events	16		1					
Heterogeneity: Chi <sup>2</sup> =	0.50, df	= 1 (P	= 0.48);	$I^2 = 0\%$	5			100
Test for overall effect:	Z = 2.84	4 (P = 0)	0.005)				0.01 0.1 1 10 Favours SNRIs Favours Placebo	100

Figure 18.4 SNRIs versus	control; Adverse	Event: Constipation

	SNR	I	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Allen 2014	3	63	0	22	2.2%	2.52 [0.14, 46.86]	
Allen 2014a	4	87	0	22	2.3%	2.35 [0.13, 42.13]	
Allen 2014b	6	99	0	23	2.4%	3.12 [0.18, 53.49]	
Allen 2014c	6	69	0	23	2.2%	4.46 [0.26, 76.20]	
Gao 2010	11	106	9	109	26.3%	1.26 [0.54, 2.91]	
Gao 2014	10	202	4	202	11.9%	2.50 [0.80, 7.84]	
Goldstein 2005	6	115	2	39	8.9%	1.02 [0.21, 4.83]	
Goldstein 2005a	17	114	1	38	4.4%	5.67 [0.78, 41.17]	
Goldstein 2005b	12	113	1	38	4.4%	4.04 [0.54, 30.02]	
Wernicke 2006	8	114	1	54	4.0%	3.79 [0.49, 29.54]	
Wernicke 2006a	21	112	1	54	4.0%	10.13 [1.40, 73.31]	
Yasuda 2011	6	85	4	83	12.0%	1.46 [0.43, 5.00]	
Yasuda 2011a	5	86	5	84	15.0%	0.98 [0.29, 3.25]	
Total (95% CI)		1365		791	100.0%	2.31 [1.52, 3.52]	•
Total events	115		28				
Heterogeneity: Chi <sup>2</sup> =	9.30, df	= 12 (	P = 0.68)	$ I^2 = 0$	%		
Test for overall effect	: Z = 3.90	) (P < 0	).0001)				0.01 0.1 1 10 100 Favours SNRIs Favours Placebo

## Figure 18.5 SNRIs versus control; Adverse Event: Decreased Appetite

	SNR	RI	Place	bo		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl	
Allen 2014	2	63	1	22	10.0%	0.70 [0.07, 7.33]			
Allen 2014a	2	87	1	22	10.7%	0.51 [0.05, 5.33]	-		
Allen 2014b	5	99	0	23	5.4%	2.64 [0.15, 46.12]			
Allen 2014c	3	69	0	23	5.0%	2.40 [0.13, 44.80]			
Gao 2014	11	202	8	202	53.8%	1.38 [0.56, 3.35]			
Goldstein 2005	3	115	0	38	5.0%	2.35 [0.12, 44.56]			
Goldstein 2005a	3	114	0	38	5.0%	2.37 [0.13, 44.94]			
Goldstein 2005b	14	113	0	39	5.0%	10.18 [0.62, 166.68]			$\rightarrow$
Total (95% CI)		862		407	100.0%	1.87 [0.97, 3.60]		•	
Total events	43		10						
Heterogeneity: Chi <sup>2</sup> =	3.86, df	= 7 (P	= 0.80);	$I^2 = 0\%$	5				
Test for overall effect	:: Z = 1.8	8 (P = 0	).06)				0.01	0.1 1 10 1 Favours SNRIs Favours Placebo	100

## Figure 18.6 SNRIs versus control; Adverse Event: Diarrhea

	SNR	a l	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Gao 2010	10	106	6	109	40.3%	1.71 [0.65, 4.55]	
Wernicke 2006	13	114	1	54	9.2%	6.16 [0.83, 45.87]	
Wernicke 2006a	5	112	1	54	9.2%	2.41 [0.29, 20.13]	
Yasuda 2011	4	85	3	83	20.7%	1.30 [0.30, 5.64]	
Yasuda 2011a	7	86	3	84	20.7%	2.28 [0.61, 8.52]	
Total (95% CI)		503		384	100.0%	2.22 [1.19, 4.13]	•
Total events	39		14				
Heterogeneity: Chi <sup>2</sup> =	= 1.78, df	= 4 (P	= 0.78);	$I^2 = 0\%$	6		
Test for overall effect	z = 2.52	2 (P = 0)	0.01)				0.01 0.1 1 10 100 Favours SNRIs Favours Placebo

0			,				
	SNR	1	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Allen 2014	1	63	2	22	5.5%	0.17 [0.02, 1.83]	
Allen 2014a	7	87	2	22	5.9%	0.89 [0.20, 3.97]	
Allen 2014b	18	99	2	23	6.0%	2.09 [0.52, 8.38]	
Allen 2014c	18	69	1	23	2.8%	6.00 [0.85, 42.49]	+
Gao 2010	16	106	12	109	22.0%	1.37 [0.68, 2.76]	- <b>+</b>
Gao 2014	17	202	9	202	16.7%	1.89 [0.86, 4.14]	+
Goldstein 2005	7	115	2	39	5.5%	1.19 [0.26, 5.48]	
Goldstein 2005a	11	114	3	38	8.4%	1.22 [0.36, 4.15]	
Goldstein 2005b	26	113	3	38	8.3%	2.91 [0.93, 9.09]	
Wernicke 2006	18	114	3	54	7.6%	2.84 [0.87, 9.24]	
Wernicke 2006a	12	112	3	54	7.5%	1.93 [0.57, 6.55]	
Yasuda 2011	6	85	1	83	1.9%	5.86 [0.72, 47.62]	
Yasuda 2011a	4	86	1	84	1.9%	3.91 [0.45, 34.24]	
Total (95% CI)		1365		791	100.0%	1.93 [1.39, 2.68]	•
Total events	161		44				
Heterogeneity: Chi <sup>2</sup> =	10.59, d	f = 12					
Test for overall effect	: Z = 3.90	) (P < 0	).0001)				0.01 0.1 1 10 100 Favours SNRIs Favours Placebo
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## Figure 18.7 SNRIs versus control; Adverse Event: Dizziness

Figure 18.8 SNRIs versus control; Adverse Event: Dry Mouth

	SNR	a l	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Allen 2014	2	63	0	22	4.1%	1.80 [0.09, 36.05]	
Allen 2014a	4	87	0	22	4.4%	2.35 [0.13, 42.13]	
Allen 2014b	6	99	1	23	9.0%	1.39 [0.18, 11.02]	
Allen 2014c	9	69	1	23	8.3%	3.00 [0.40, 22.42]	
Gao 2010	6	106	3	109	16.4%	2.06 [0.53, 8.01]	
Goldstein 2005	6	115	2	38	16.6%	0.99 [0.21, 4.71]	<b>_</b>
Goldstein 2005a	8	114	2	38	16.6%	1.33 [0.30, 6.01]	
Goldstein 2005b	17	113	3	39	24.7%	1.96 [0.61, 6.32]	
Total (95% CI)		766		314	100.0%	1.76 [0.97, 3.17]	•
Total events	58		12				
Heterogeneity: Chi <sup>2</sup> =	= 1.09, df	= 7 (P	= 0.99);	$I^2 = 0\%$	5		
Test for overall effect	:: Z = 1.87	7 (P = 0	0.06)				0.01 0.1 1 10 100 Favours SNRIs Favours Placebo

## Figure 18.9 SNRIs versus control; Adverse Event: Fatigue

	SNR	a l	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Allen 2014	4	63	1	22	6.7%	1.40 [0.16, 11.84]	
Allen 2014a	6	87	1	22	7.2%	1.52 [0.19, 11.96]	
Allen 2014b	8	99	1	23	7.3%	1.86 [0.24, 14.13]	
Allen 2014c	8	69	1	23	6.8%	2.67 [0.35, 20.19]	
Gao 2010	8	106	8	109	35.6%	1.03 [0.40, 2.64]	<b>_</b>
Gao 2014	10	202	4	202	18.1%	2.50 [0.80, 7.84]	+
Wernicke 2006	14	114	2	54	12.3%	3.32 [0.78, 14.08]	
Wernicke 2006a	14	112	1	54	6.1%	6.75 [0.91, 50.01]	
Total (95% CI)		852		509	100.0%	2.15 [1.28, 3.62]	•
Total events	72		19				
Heterogeneity: Chi <sup>2</sup> =	4.35, df	= 7 (P	= 0.74);	$I^2 = 0\%$	,		
Test for overall effect	:: Z = 2.90	O(P = 0)	0.004)				0.01 0.1 i 10 100 Favours SNRIs Favours Placebo

## Figure 18.10 SNRIs versus control; Adverse Event: Headache

	SNR	a l	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Gao 2010	6	106	6	109	38.4%	1.03 [0.34, 3.09]	
Wernicke 2006	12	114	4	54	35.3%	1.42 [0.48, 4.20]	
Wernicke 2006a	15	112	3	54	26.3%	2.41 [0.73, 7.97]	
Total (95% CI)		332		217	100.0%	1.53 [0.81, 2.91]	•
Total events	33		13				
Heterogeneity: Chi <sup>2</sup> =	= 1.07, df	= 2 (P	= 0.58);	$I^2 = 0\%$	6		0.01 0.1 1 10 100
Test for overall effect	z = 1.30	O(P = 0)	).19)				0.01 0.1 1 10 100 Favours SNRIs Favours Placebo

## Figure 18.11 SNRIs versus control; Adverse Event: Increased Sweating

	SNR	3	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
Gao 2010	9	106	3	109	21.9%	3.08 [0.86, 11.08]	
Goldstein 2005	7	115	1	38	11.1%	2.31 [0.29, 18.20]	
Goldstein 2005a	4	114	1	38	11.1%	1.33 [0.15, 11.57]	
Goldstein 2005b	10	113	1	39	11.0%	3.45 [0.46, 26.10]	
Rowbotham 2005	4	82	2	40	19.9%	0.98 [0.19, 5.10]	<b>_</b>
Rowbotham 2005a	8	82	1	41	9.9%	4.00 [0.52, 30.91]	
Wernicke 2006	10	114	1	54	10.1%	4.74 [0.62, 36.07]	
Wernicke 2006a	8	112	0	54	5.0%	8.27 [0.49, 140.76]	
Total (95% CI)		838		413	100.0%	2.94 [1.53, 5.63]	•
Total events	60		10				
Heterogeneity: Chi <sup>2</sup> =	3.11, df	= 7 (P	= 0.87);	$I^2 = 0\%$	6		
Test for overall effect:	Z = 3.25	5 (P = 0)	).001)				0.01 0.1 1 10 100 Favours SNRIs Favours Placebo

## Figure 18.12 SNRIs versus control; Adverse Event: Insomnia

-								
	SNR	I	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl
Allen 2014	3	63	0	22	7.0%	2.52 [0.14, 46.86]		
Allen 2014a	1	87	0	22	7.5%	0.78 [0.03, 18.62]	-	
Allen 2014b	4	99	0	23	7.6%	2.16 [0.12, 38.77]		
Allen 2014c	5	69	1	23	14.2%	1.67 [0.21, 13.54]		
Rowbotham 2005	4	82	1	40	12.7%	1.95 [0.23, 16.89]		
Rowbotham 2005a	8	82	2	41	25.3%	2.00 [0.44, 8.99]		
Wernicke 2006	6	114	1	54	12.9%	2.84 [0.35, 23.03]		
Wernicke 2006a	11	112	1	54	12.8%	5.30 [0.70, 40.03]		
Total (95% CI)		708		279	100.0%	2.43 [1.14, 5.19]		-
Total events	42		6					
Heterogeneity: Chi <sup>2</sup> =	= 1.32, df	= 7 (P	= 0.99);	$I^2 = 0\%$	6			
Test for overall effect	z = 2.30	P = 0	0.02)				0.01	0.1 1 10 100 Favours SNRIs Favours Placebo

## Figure 18.13 SNRIs versus control; Adverse Event: Lethargy

	SNR	I.	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Allen 2014	1	63	0	22	10.5%	1.08 [0.05, 25.54]	]
Allen 2014a	2	87	0	22	11.3%	1.31 [0.06, 26.29]	]
Allen 2014b	5	99	0	23	11.5%	2.64 [0.15, 46.12]	]
Allen 2014c	2	69	0	23	10.6%	1.71 [0.09, 34.46]	]
Gao 2010	11	106	4	109	56.2%	2.83 [0.93, 8.60]	1
Total (95% CI)		424		199	100.0%	2.33 [0.96, 5.66]	
Total events	21		4				
Heterogeneity: Chi <sup>2</sup> =	0.53, df	= 4 (P	= 0.97);	$I^2 = 0\%$	5		0.01 0.1 1 10 100
Test for overall effect	Z = 1.87	7 (P = 0)	0.06)				0.01 0.1 1 10 100 Favours SNRIs Favours Placebo

	SNR	1	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Allen 2014	2	63	0	22	2.1%	1.80 [0.09, 36.05]	
Allen 2014a	6	87	0	22	2.3%	3.40 [0.20, 58.13]	
Allen 2014b	5	99	1	23	4.6%	1.16 [0.14, 9.47]	
Allen 2014c	3	69	0	23	2.1%	2.40 [0.13, 44.80]	
Wernicke 2006	8	114	3	54	11.6%	1.26 [0.35, 4.57]	
Wernicke 2006a	7	112	2	54	7.7%	1.69 [0.36, 7.85]	
Yasuda 2011	10	85	12	83	34.7%	0.81 [0.37, 1.78]	<b>_</b>
Yasuda 2011a	14	86	12	84	34.7%	1.14 [0.56, 2.32]	
Total (95% CI)		715		365	100.0%	1.18 [0.76, 1.82]	•
Total events	55		30				
Heterogeneity: Chi <sup>2</sup> =	= 1.92, df	= 7 (P					
Test for overall effect	z = 0.73	B (P = 0)	).47)				0.01 0.1 1 10 100 Favours SNRIs Favours Placebo

# Figure 18.14 SNRIs versus control; Adverse Event: Nasopharyngitis

# Figure 18.15 SNRIs versus control; Adverse Event: Nausea

	SNR	RI	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Allen 2014	9	63	0	22	1.3%	6.83 [0.41, 112.69]	
Allen 2014a	11	87	0	22	1.3%	6.01 [0.37, 98.26]	
Allen 2014b	27	99	1	23	2.8%	6.27 [0.90, 43.81]	
Allen 2014c	12	69	1	23	2.6%	4.00 [0.55, 29.11]	
Gao 2010	32	106	13	109	21.8%	2.53 [1.41, 4.55]	<b>-</b>
Gao 2014	21	202	7	202	11.9%	3.00 [1.30, 6.90]	
Goldstein 2005	16	115	4	38	10.2%	1.32 [0.47, 3.71]	<b>-</b>
Goldstein 2005a	19	114	4	38	10.2%	1.58 [0.57, 4.36]	- <b>+-</b>
Goldstein 2005b	31	113	3	39	7.6%	3.57 [1.15, 11.02]	
Rowbotham 2005	18	82	2	40	4.6%	4.39 [1.07, 18.00]	
Rowbotham 2005a	8	82	2	41	4.5%	2.00 [0.44, 8.99]	
Wernicke 2006	32	114	4	54	9.2%	3.79 [1.41, 10.18]	
Wernicke 2006a	36	112	3	54	6.9%	5.79 [1.86, 17.95]	
Yasuda 2011	10	85	2	83	3.4%	4.88 [1.10, 21.61]	
Yasuda 2011a	14	86	1	84	1.7%	13.67 [1.84, 101.68]	│
Total (95% CI)		1529		872	100.0%	3.36 [2.50, 4.52]	•
Total events	296		47				
Heterogeneity: Chi <sup>2</sup> =	= 10.73, d	f = 14	(P = 0.7)	1); $I^2 =$	0%		
Test for overall effect	:: Z = 7.99	9 (P < 0	).00001)				0.01 0.1 1 10 100 Favours SNRIs Favours Placebo

	SNR	1	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Allen 2014	1	63	1	22	3.2%	0.35 [0.02, 5.35]	
Allen 2014a	1	87	1	22	3.4%	0.25 [0.02, 3.89]	
Allen 2014b	1	99	2	23	7.0%	0.12 [0.01, 1.23]	
Allen 2014c	3	69	2	23	6.4%	0.50 [0.09, 2.81]	
Gao 2010	2	106	2	109	4.2%	1.03 [0.15, 7.17]	
Gao 2014	3	202	2	202	4.3%	1.50 [0.25, 8.88]	
Goldstein 2005	2	115	0	38	1.6%	1.68 [0.08, 34.26]	
Goldstein 2005a	0	114	1	38	4.8%	0.11 [0.00, 2.72]	· · · · · · · · · · · · · · · · · · ·
Goldstein 2005b	2	113	1	39	3.2%	0.69 [0.06, 7.40]	
Raskin 2005	4	116	2	58	5.7%	1.00 [0.19, 5.30]	
Raskin 2005a	2	116	2	58	5.7%	0.50 [0.07, 3.46]	
Rowbotham 2005	7	82	4	40	11.5%	0.85 [0.27, 2.75]	
Rowbotham 2005a	10	82	4	41	11.4%	1.25 [0.42, 3.74]	
Wernicke 2006	5	114	3	54	8.7%	0.79 [0.20, 3.18]	
Wernicke 2006a	2	112	2	54	5.8%	0.48 [0.07, 3.33]	
Yasuda 2011	3	85	3	83	6.5%	0.98 [0.20, 4.70]	
Yasuda 2011a	2	86	3	84	6.5%	0.65 [0.11, 3.80]	
Total (95% CI)		1761		988	100.0%	0.75 [0.50, 1.13]	•
Total events	50		35				
Heterogeneity: Chi <sup>2</sup> =	7.35, df	= 16 (	P = 0.97	; $I^2 = 0$	%		
Test for overall effect	: Z = 1.36	5 (P = 0	).17)				0.01 0.1 1 10 10 Favours SNRIs Favours Placebo

## Figure 18.16 SNRIs versus control; Adverse Event: Serious Adverse Events

## Figure 18.17 SNRIs versus control; Adverse Event: Somnolence and Fatigue

	SNR	a	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Allen 2014	5	63	1	22	2.4%	1.75 [0.22, 14.14]	
Allen 2014a	12	87	1	22	2.6%	3.03 [0.42, 22.10]	
Allen 2014b	12	99	2	23	5.3%	1.39 [0.33, 5.80]	
Allen 2014c	13	69	1	23	2.4%	4.33 [0.60, 31.34]	
Gao 2010	25	106	14	109	22.4%	1.84 [1.01, 3.34]	- <b>-</b> -
Gao 2014	27	202	5	202	8.1%	5.40 [2.12, 13.74]	
Goldstein 2005	9	115	3	38	7.3%	0.99 [0.28, 3.47]	
Goldstein 2005a	23	114	3	38	7.3%	2.56 [0.81, 8.04]	+
Goldstein 2005b	32	113	3	39	7.2%	3.68 [1.19, 11.35]	
Rowbotham 2005	11	82	1	40	2.2%	5.37 [0.72, 40.12]	
Rowbotham 2005a	12	82	0	41	1.1%	12.65 [0.77, 208.50]	· · · · · · · · · · · · · · · · · · ·
Wernicke 2006	23	114	2	54	4.4%	5.45 [1.33, 22.27]	· · · · · · · · · · · · · · · · · · ·
Wernicke 2006a	31	112	2	54	4.4%	7.47 [1.86, 30.08]	
Yasuda 2011	16	85	7	83	11.5%	2.23 [0.97, 5.14]	
Yasuda 2011a	21	86	7	84	11.5%	2.93 [1.32, 6.53]	
Total (95% CI)		1529		872	100.0%	3.09 [2.31, 4.13]	•
Total events	272		52				
Heterogeneity: Chi <sup>2</sup> =	13.25, d	f = 14	(P = 0.5)	1); $I^2 =$	0%		0.01 0.1 1 10 100
Test for overall effect	: Z = 7.60	) (P < 0	).00001)				0.01 0.1 1 10 100 Favours SNRIs Favours Placebo
							Tavours Sinkis Favours Flacebo

## Figure 18.18 SNRIs versus control; Adverse Event: Sustained Hypertension

	SNR	RI	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	I M–H, Fixed, 95% Cl
Goldstein 2005	6	115	1	38	10.9%	1.98 [0.25, 15.95]	]
Goldstein 2005a	9	114	1	38	10.9%	3.00 [0.39, 22.91]	]
Goldstein 2005b	1	113	1	39	10.8%	0.35 [0.02, 5.39]	]
Raskin 2005	4	116	4	58	38.6%	0.50 [0.13, 1.93]	]
Raskin 2005a	6	116	3	58	28.9%	1.00 [0.26, 3.86]	]
Total (95% CI)		574		231	100.0%	1.06 [0.51, 2.20]	1 +
Total events	26		10				
Heterogeneity: Chi <sup>2</sup> =	3.19, df	= 4 (P	= 0.53);	$I^2 = 0\%$	5		0.01 0.1 1 10 100
Test for overall effect:	Z = 0.10	6 (P = 0	).87)				Favours SNRIs Favours Placebo

Figure 18.19 SNRIs versus control; Adverse Eve	nt: Vomiting
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	SNR	I	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Allen 2014	3	63	0	22	5.7%	2.52 [0.14, 46.86]	1
Allen 2014a	3	87	0	22	6.1%	1.83 [0.10, 34.17]	1
Allen 2014b	10	99	1	23	12.5%	2.32 [0.31, 17.25]	]
Allen 2014c	2	69	1	23	11.6%	0.67 [0.06, 7.02]	]
Gao 2010	6	106	5	109	38.1%	1.23 [0.39, 3.92]	]
Rowbotham 2005	5	82	0	40	5.2%	5.43 [0.31, 95.91]	]
Rowbotham 2005a	4	82	0	41	5.1%	4.55 [0.25, 82.61]	1
Yasuda 2011	4	85	1	83	7.8%	3.91 [0.45, 34.22]	]
Yasuda 2011a	5	86	1	84	7.8%	4.88 [0.58, 40.93]	]
Total (95% CI)		759		447	100.0%	2.30 [1.17, 4.49]	
Total events	42		9				
Heterogeneity: Chi <sup>2</sup> =	3.47, df	= 8 (P	= 0.90);	$I^2 = 0\%$	5		
Test for overall effect	Z = 2.43	B (P = 0)	0.02)				0.01 0.1 1 10 100 Favours SNRIs Favours Placebo

## **Funnel Plots**

Funnel plots were generated via RevMan for interventions with  $\geq 8$  studies. This information was used in the GRADE process to assess potential publication bias.



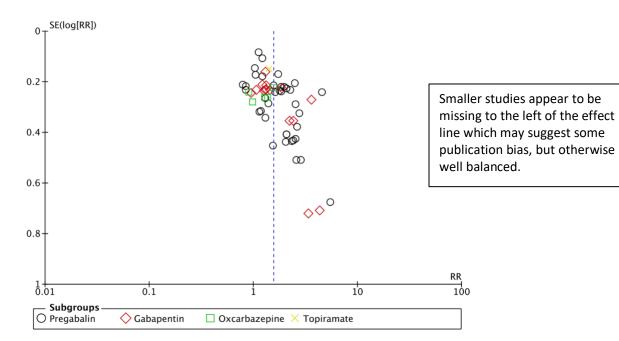
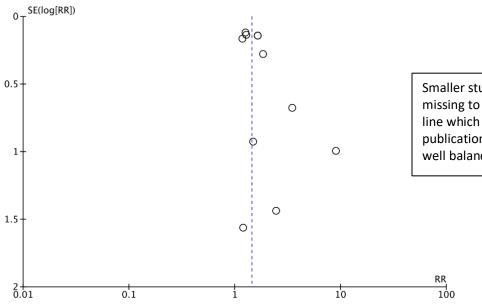
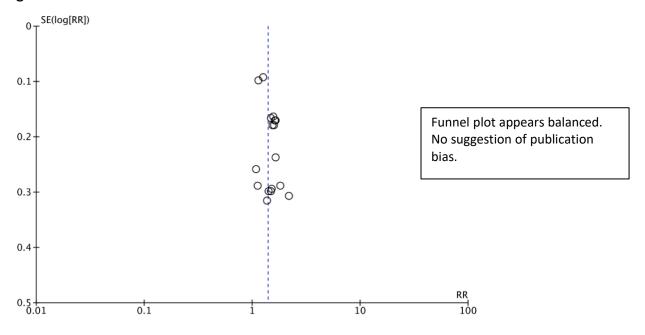


Figure 19.2 Rubefacients



Smaller studies appear to be missing to the left of the effect line which may suggest some publication bias, but otherwise well balanced.

## Figure 19.3 SNRIs



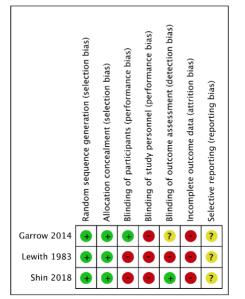
### **Quality Assessment**

### **Cochrane Risk of Bias Tables**

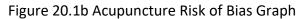
The Cochrane Risk of Bias is an assessment tool that addresses seven specific domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other bias. Due to the subjective nature of the outcomes, we chose to split the 'blinding of participants and personnel' domain and use the 'other bias' domain specifically for blinding of personnel. Each domain was assigned a judgement related to the risk of bias, specifically 'low', 'high' or 'unclear' risk of bias.

### **Determining Risk of Bias Median**

To generate the meta-analyses that utilized a risk of bias median we assigned a quality score to each risk domain highlighted in the Cochrane Risk of Bias tool. Assignment is outlined as follows: (Low Risk = 0, Unclear Risk = 1, High Risk = 2). We found the sum for each study, determined the median score, and divided studies into two subgroups: 1) less than the median and 2) equal to or greater than the median.



#### Figure 20.1a Acupuncture Risk of Bias Summary



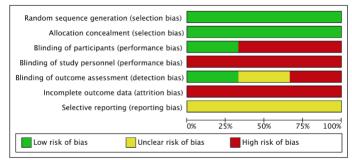
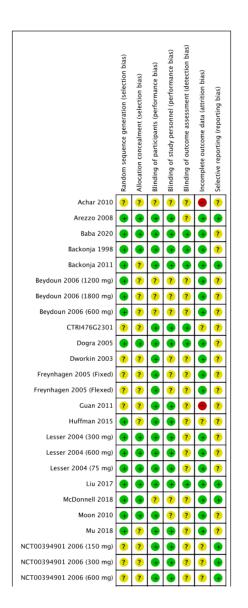
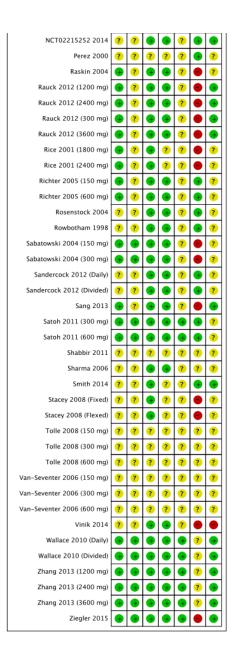
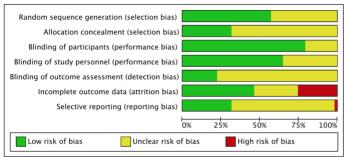


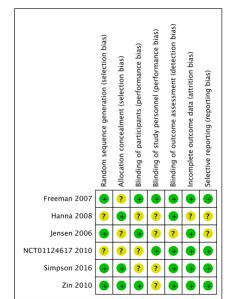
Figure 20.2a Anticonvulsants Risk of Bias Summary





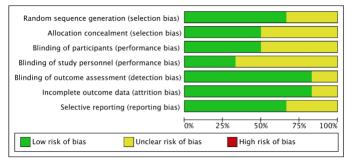
### Figure 20.2b Anticonvulsants Risk of Bias Graph

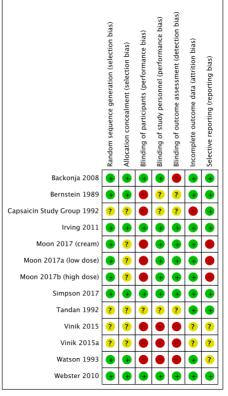




#### Figure 20.3a Opioids Risk of Bias Summary

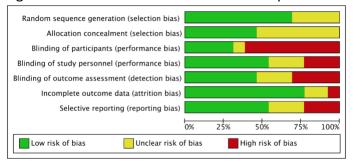
Figure 20.3b Opioids Risk of Bias Graph

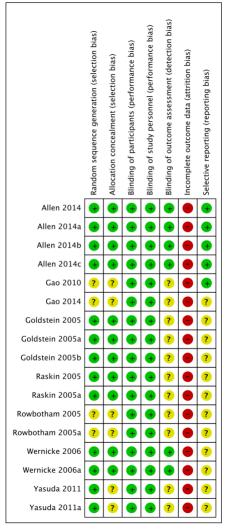




#### Figure 20.4a Rubefacients Risk of Bias Summary

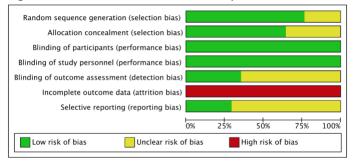
### Figure 20.4b Rubefacients Risk of Bias Graph



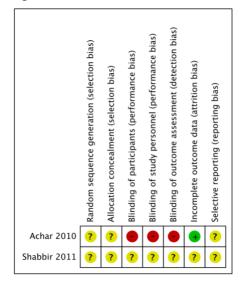


#### Figure 20.5a SNRIs Risk of Bias Summary

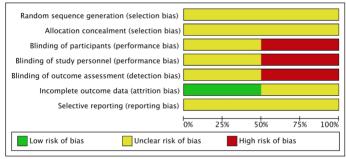
#### Figure 20.5b SNRIs Risk of Bias Graph



#### Figure 20.6a TCAs Risk of Bias Summary



## Figure 20.6b TCAs Risk of Bias Graph



### Table 15: GRADE Evaluation of Evidence Quality

Interventions ordered alphabetically.

Intervention	Number of RCTs	Risk Ratio	Reasons for Downgrading	Certainty in Evidence
Acupuncture	3	RR 1.81 (95% CI 0.55, 5.98)	Risk of Bias (-1) Inconsistency (-1) Imprecision (-1) Publication Bias (-1)	Very Low
Anticonvulsants	40	RR 1.54 (95% Cl 1.45, 1.63)	Publication Bias (-1)	Moderate
Opioids	6	RR 1.37 (95% Cl 1.19, 1.57)	Indirect (-1) Publication Bias (-1)	Low
Rubefacients	10	RR 1.40 (95% Cl 1.26, 1.55)	Risk of Bias (-1) Publication Bias (-1)	Low
SNRIs	8	RR 1.45 (95% Cl 1.33, 1.59)	Publication Bias (-1)	Moderate
TCAs	2	RR 3.00 (95% Cl 2.05, 4.38)	Risk of Bias (-1) Inconsistency (-1) Indirectness (-1) Imprecision (-1) Publication Bias (-1)	Very Low

Cl: Confidence Interval; RCTs: Randomized Controlled Trials; RR: Risk Ratio; SNRIs: Serotonin Norepinephrine Reuptake Inhibitor; TCAs: Tricyclic Antidepressants

### **GRADE Criteria for Quality Assessment Sections**

	Consider allocation concealment, blinding, large losses to follow-up, ITT analysis, stopping early for
Risk of Bias	benefit, etc.
	Failure to report outcomes/selective reporting of outcomes
Inconsistency Do the estimates of the treatment effect vary widely across studies?	
inconsistency	Statistical heterogeneity, variability in results
	Unexplained inconsistency/heterogeneity $ ightarrow$ decreased quality
	Differences in population (i.e. patients or animal studies)
Indirectness	Differences in intervention (i.e. method or timing of delivery)
	Differences in outcome measures (i.e. surrogates or length of time)
	Indirect comparison (i.e. network meta-analyses)
Imprecision	Does confidence interval cross threshold for clinical decision making?
	Wide confidence intervals (few patients, few events)
Publication	Small number of trials
bias	Only industry funded trials included
	Funnel plot
Magnitude	Large and consistent estimates of the magnitude of a treatment effect
of effect	Large effect: RR >2 or <0.5; very large effect: RR >5 or <0.2
Dose	
response	Presence of this gradient increases the confidence.
gradient	
Plausible	If residual confounding would be expected to bias the treatment effect in the opposite direction as
confounding	observed - increases confidence in results.
	emann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of s. Updated October 20 The GRADE Working Group, 20 Available from <u>guidelinedevelopment.org/handbook</u> .

### Peer Review Comments/Feedback

#### **Peer Reviewer Information**

7 reviewers

- 5 family physicians
- 2 pharmacists

\*NO competing conflicts of interest declared (5 reviewers also provided comments on KT tool)

#### Familiarity with treating neuropathic pain

All responded that they routinely care for patients with neuropathic pain (estimate 1-2 times per week).

#### Strengths of the Systematic Review

Looking at all the different categories of good quality evidence for neuropathic pain treatment. Eliminating poor quality studies to create the recommendation.

Attempted to compare a variety of drug and non-drug treatment options in addition to drugs within the same class. Wide selection of interventions were addressed. Tools and methods used (ex. Cochrane) makes the review credible, high quality and objective. Decision aid visual is helpful and practical. Overall, I found it helpful and detailed.

Neuropathic pain is a difficult problem to manage, especially in the elderly. There is not a lot of large, good quality studies to direct the best management. Therefore, this is an important topic to address, and this review is very valuable to help guide clinicians in practice. The methods were well-described, and it appeared to be free from bias.

Thank you for the opportunity to review this manuscript. I like that it addresses a common condition seen in primary care, with common interventions used in this setting. The use of NNT/NNH in summary tables is helpful from a clinical perspective.

This was reviewed by me along with 10 family medicine residents. The methods used in this review are well justified and thorough. It is clear there has been an attempt to make this review more relevant and specific to primary care practice than previous NP reviews. Writing is clear.

Weaknesses of the Systematic Review	Authors' response
Although it is inevitable, by combining all anticonvulsants into the same category even though pregabalin and gabapentin are the most commonly used ones decreases the power of the recommendations in that category.	Test for subgroup differences was not statistically significant.
Did not address data (or perhaps lack thereof) for other non- drug interventions such as physiotherapy/massage (unless it was considered "exercise?"), compounded topicals (especially those containing gabapentin). Likely very limited information out there but would be helpful to know.	The number of included interventions was limited to those most commonly used in primary care settings. Topical lidocaine/exercise (including physiotherapy) were included, however no RCTs with responder analyses were identified.

	These potential topics will be forwarded to our chronic pain guideline committee.
I did not find any concerning areas of weakness other than the limitations identified by the authors.	
Para 1: as a reader I felt several phrases were unclear including "symptom-based prevalence" and "both persistent and intermittent".	Manuscript revised.
Line 8, page 1: Please define "neuropathic pain conditions", this was not defined in the prior paragraph?	Manuscript revised.
Line 23, page 1: "These three conditions were chosen as they are commonly seen and treated in primary care" please provide a reference.	Manuscript revised.
Overall, I would suggest more background about why you combined different interventions into one category. This is addressed as a limitation further on in the manuscript but is inadequately justified initially.	We initially chose to report medications as a class, however tested for subgroup differences to determine if individual agents provided improved efficacy compared to others. We tested for differences for both anticonvulsants and SNRIs, however found no difference between agents. We added the most commonly studied agents (pregabalin/gabapentin and duloxetine) for further clarity.
Furthermore, it is unclear how this manuscript builds on existing literature in the 'introduction', please expand on this.	To our knowledge, this is the first systematic review in multiple interventions for neuropathic pain, that focuses solely on responder outcomes. One reason we chose to focus on responders was to inform our clinical decision aid.
Methods, page 1: Please describe specific exclusion criteria in addition to inclusion criteria.	Manuscript revised.
Line 40: please provide a reference for selection of primary outcome. It is unclear why "30% reduction" was chosen. If this was not identified from a reference but from team consensus about what would be a clinically important outcome, please state this.	Added IMMPACT reference, referring to the clinical importance of treatment outcomes in chronic pain clinical trials.
Line 65: I am surprised by the use of fixed effects models throughout, in this situation where interventions and populations are different between studies. There may be a very appropriate reason for this, that is to me not clearly described in	We have added a reference to the Cochrane handbook that refers to our choice for fixed/random effects. Secondly, for TCAs, we have presented both fixed and random effects to

the manuscript. I would suggest reviewing this decision and its description with a statistician, if you have not already done so.	highlight the uncertainty of the data. Added reference to Cochrane handbook (line 68).
"Efficacy" and "effectiveness" are used interchangeably throughout the manuscript; please revise.	Manuscript revised.
I think it is worth saying more about heterogeneity, both statistically and clinically. One of the core 'critiques' that could be applied to this manuscript is that the population, intervention, comparators are all are heterogenous. Therefore, this should be a central aspect of the discussion.	We did address heterogeneity throughout the results, quality assessment and discussion. With the exception of TCAs and acupuncture, the other interventions had fairly homogenous results.
Comments, considerations or changes	
As stated above, would be nice to see inclusion of more non- systemic options such as other topicals (ex. compounded topicals containing gabapentin) and more non-drug modalities such as stress reduction, massage/physiotherapy which would be helpful in geriatrics and other patient populations who cannot take oral meds. Clarification for what was classified as "exercise"ex. what type of exercise was includedall types?	Addressed. See above.
Overall solid paper. A few suggestions:	
Introduction	
<ul> <li>1st paragraph could be simplified – line 2: by removing "symptom based"; line 3 by removing "is typically both persistent and paroxysmal in nature"</li> </ul>	Addressed. See above.
Objectives with PICOs well explained	
Methods – sensitivity vs subgroup analysis	
• Line 23 – remove "most" or provide a reference to "most commonly seen in primary care"	Addressed. See above.
• Line 24 – what was the rational for choosing these	Addressed. See above.
<ul> <li>interventions?</li> <li>Search strategy – specify whether only publications in English were considered and provide the clinical trial registries that were used</li> </ul>	Added that only English publications were included. References 12 and 13 refer to the two clinical trial registries that were searched.
• Line 43 – Appendix XX needs to be specified	Manuscript revised.
• Line 43 – Appendix At needs to be specified • Line 69 – Please add something like "If RCTs reported outcomes at multiple time-points, we chose the data that came from"	See line 79
• Random vs fixed effect analyses –whether to choose one or the other was quite arbitrary. For the next review, picking one or	Addressed. See above.

the other with more objective criteria might be better. Given that studies on neuropathic pain tend to have different protocols / study populations etc, random effect analysis might be the most appropriate to report all results. (see later comment on that same topic)	
• Line 75 – consider removing "to explore potential sources of heterogeneity" as I2 is not what is being discussed in that paragraph. I would just leave at "we determined a priori to analyze a series of subgroups. These were"	We felt it was important to specify that we were exploring, through subgroup analyses, only some potential sources of heterogeneity. This list was not exhaustive as we do not know all causes of heterogeneity. This relates to I <sup>2</sup> , as it is the statistical test that quantifies the amount of heterogeneity present, not due to chance.
Results	
• Results are well reported; however, the paper would benefit from more consistency between sections	Manuscript revised.
o For example, only the TCA and acupuncture sections comment on study quality and heterogeneity. These should be reported for all studied interventions.	We did report on quality throughout all interventions, when we were referring to our subgroup analyses. Overall quality and heterogeneity are discussed in the Quality Assessment section of results.
o I would suggests that all sections report on % studies with high risk of bias and I2	We are unable to report on the proportion of studies at high risk of bias, as we reported only a median split of the risk of bias (those falling below or above the median). We have added the specific I <sup>2</sup> for each intervention in the Quality Assessment section.
• Line 118-122: was the benefit still there in larger trials / trials with less risk of bias? (if anything, I am more interested to know that instead of knowing the benefit of herpetic neuropathy vs diabetic neuropathy)	Manuscript revised.
• Line 106-108: instead of saying "the majority", a "small proportion", give the actual numbers	Manuscript revised.
• Line 187: what do "small" studies refer to (no definition)?	This is addressed on line 77.
• TCA section o A fixed effect model should be used for consistency. It was used for the rest of the paper with no clear justification to use a random effects model.	See line 65-69 for rationale of when to use fixed or random effects. We will present both models, however, for TCAs, because of the inconsistencies with the data.

o If the data from the trial is of too low quality to be believable (it seems like it), another option would be not to do a meta- analysis for this section	Manuscript revised to include both fixed and random effects models.
Quality assessment • Would it be possible to add 1-2 sentences in the main text to justify the quality assessments? Text such as lines 187-190 and 197 might be better suited for this section (the results section should still report on % studies at high risk of bias and heterogeneity in a more standardized fashion)	Addressed in methods section of manuscript.
Discussion <ul> <li>Lines 228-229. Consider removing topiramate and oxcarbazepine are typically not prescribed for neuropathic pain (especially not in primary care)</li> </ul>	We decided to include topiramate and oxcarbazepine as they are still list as treatment options for neuropathic pain. Manuscript revised to highlight the absence of carbamazepine responder data in the literature.
<ul> <li>Consider including the typical placebo response and general NNT (5-10)</li> <li>Consider simplifying paragraph on TCA (lines 237-248). Somewhat convoluted. The end point is that there is no good data to know with certainty whether TCAs are useful – this could be told in more simple terms</li> </ul>	Refer to PEER Simplified Decision Aid for Neuropathic Pain Manuscript revised.
<ul> <li>The general consensus is that opioids are not particularly effective in chronic pain. Why is it that they seem to work (with some limitations) for neuropathic pain?</li> <li>It would also be interesting to know whether tramadol is any</li> </ul>	Requires further study to answer. Manuscript revised.
different than the other opioids as it is currently being marketed as the opioid to use for neuropathic pain Strengths and limitations	
Lines 273-274. First part of the sentence is a repeat of the previous sentence	Manuscript revised.
I find it interesting that there appears to be a delay to the efficacy of the different treatments (often 4-12 weeks into treatment). Given the NNH for some of the treatments and the side effects reported, it would seem to me that these ADR's would often be an issue PRIOR to the onset of benefit. It would be interesting to comment on this and how it might determine how long a patient should try one of these interventions before considering it a failure or non-response. I also find the high placebo rate in all the studies to be very interesting and might be worth commenting on as well. I think this is very well-done and provides valuable information to help make decisions with the patient to manage neuropathic pain	SNRIs – no studies <4 weeks Not necessarily a delay – no data to confirm. (most in 4-12-week range) We have added further detail on this in the discussion section.

There appears to be significant emphasis on responder analysis and its advantages over other types of outcome analysis. Yet the meaning of "30% reduction in pain", especially when various measures of pain are included, is not well described and it is not entirely convincing that this is much more meaningful than other types of outcome measures. It is also not clear how much literature has been lost by restricting the analysis to this outcome. It would be good to have this discussed possibly in limitations. It is remarkable that TCA's in this analysis have lost their top rank in the hierarchy where they were located in some previous reviews and appreciate your discussion about this. In the end then, since this is meant to be more relevant to primary care than other reviews, is it not important to mention that none of these trials are addressing most of the patients we are managing, who have been on their treatments or had their pain for much longer than 3 months? Is it not semantics that we are looking for the most trustworthy evidence to address a problem that we are most often not treating (ie people who have been on less than 3 months of treatment?) It would be good to hear this mentioned at least. Also, it may be worth a comment about how consistent these findings are with other reviews that use different outcomes, for which my impression is that the differences in NNT within your review and compared to other reviews are really pretty small, and the hierarchy does not have large spread. Finally, the absence of cannabinoids is understood but awkward, especially since they have made it high onto some guidelines. This will make the upcoming guidelines form this review all the more anticipated, which we assume will include the work you have done on cannabinoids.	Added a reference on choice of outcome for patients with chronic pain. Added in limitations, that a proportion of studies were missed that do not have responder data. TCAs- other high quality systematic reviews have addressed the limitations of the body of evidence around TCAs Cannabinoids- forwarded to guideline committee.
I would like to congratulate the authors on such a wonderful work on preparing this manuscript. I read it with great interest and have a few small comments as below:	
Line 10,11 what is the purpose of mentioning these previous systematic reviews? It would be nice to review any existing systematic review on the topic and why the current systematic review is different?	See above.
Line 36 grey literature usually addresses other websites not Cochrane library or clinical trial registry.	While we agree that a grey literature search can include a variety of websites, we felt that searching Cochrane and clinical trial registries were adequate to address our questions.
Line 42-43 "When multiple responder outcome data was reported, we utilized a hierarchy to prioritize outcomes" this sentence is confusing. Does this mean the time interval that was different for each drug was prioritized?	This refers to studies that report multiple responder outcomes. For example, if both 30% and 50% reductions in pain were reported, we chose to prioritize a 30% reduction.

Line 67-68—"If both the effect estimates and confidence	Addressed above (added a reference to
	Addressed above (added a reference to
intervals were reasonably similar between fixed and random	the Cochrane handbook).
effect analyses, we concluded that it was unlikely that <i>small</i>	
studies were disproportionately influencing the result and chose	
fixed effects for the primary analysis". ???	
This sentence does not make sense. The size of the study is not	Added a reference to the Cochrane
the only factor affecting the fixed or random effect model.	handbook.
Perhaps delete it or provide more explanation	
Line 167 what type of opioids? Please provide some example	Manuscript revised.
Line 201 should this be exercise or lidocaine at the tile?	Correct the way it is.
Line 211-214 "Heterogeneity may be due in part to the lower	Heterogeneity may also be due to
quality of trials, the inclusion of a number of neuropathic pain	other things, not only those that were
types or different patient populations, and variance in the	examined in subgroup analyses.
delivery of the intervention (e.g., acupuncture,	
electroacupuncture and auricular acupuncture)"	
The subgroup analysis explains the heterogeneity. It is better	
here to use those subgroup analyses to explain the	
heterogeneity rather hypothesizing it.	
Additional comments:	
Are any of these studies conducted in primary care setting? As	A very small percentage (1%) of studies
the systematic review claims that these results are appropriate	were clearly conducted in primary
for primary care providers, it is worth mentioning if they have	care, however 66% of trials did not
been done in the primacy care setting.	clearly state the setting where the
	study was conducted.
Defining outcomes of interest"While only a proportion of RCTs	We did report the limitations of only
report a responder analysis, focusing on dichotomous outcomes	reporting responder analyses within
allowed us to combine trials utilizing different pain measures, by	the discussion section.
using counts of responders, without losing clinical meaning.	
Changes on a pain scale, or their combination into Standard	
Mean Differences (SMD), are challenging to interpret and do not	
translate easily in a patient conversation"	
I worry taking this approach introduce "selective outcome	
reporting bias". One approach was to use the SMD and translate	
back the Estimate effect for clinician.	

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