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

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Table of Contents

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:
        i. ≥2 change on VAS/NRS out of 10-11 or change of ≥20 on VAS/NRS out of 100.
        ii. ≥3 change on VAS/NRS out of 10-11 or change of ≥30 on VAS/NRS out of 100.
        iii. ≥1 change on VAS / NRS out of 10-11 or change of ≥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.
4. 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:
        i. 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).
        ii. 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 ≤1 on VAS / NRS scale (out of 11 or 10); Or score of ≤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 Type	Author, Year	Sample Size	Duration of Neuropathic Pain (weeks)/Type of Neuropathic Pain	Mean Age	Outcome Measured At	Intervention(s)	Outcome used in 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	≥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	≥75% Improvement in Pain
Anticonvulsants	Arezzo 2008	167	242 weeks/ Diabetic Neuropathy	58	13 weeks	Pregabalin 300 mg twice daily Placebo	≥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	CTRI476G2301	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	≥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	NCT02215252 2014	91	Not Reported/ Diabetic Neuropathy	59	4 weeks	Pregabalin 300 mg daily Placebo	≥30% Reduction in Pain
Anticonvulsants	NCT00394901 2006	372	Not Reported/ Diabetic Neuropathy	70	13 weeks	Pregabalin 150 mg daily Pregabalin 300 mg daily Pregabalin 600 mg daily Placebo	≥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	≥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	NCT01124617 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 8% Capsaicin Patch (Applied for 30 minutes for 1-7 treatments with 8-week intervals between each treatment) + Standard of Care Standard of Care	≥30% Pain Improvement
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	≥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% CI)	NNT
Acupuncture	**3**	**Overall Efficacy**	**22% (27/121)**	**13% (16/126)**	**RR 1.81 (95% CI 0.55, 5.98)**	**NSS**
	-	Assessed at: ≤4 weeks	-	-	-	-
	3	Assessed at: >4 weeks to <12 weeks	22% (27/121)	13% (16/126)	RR 1.81 (95% CI 0.55, 5.98)	NSS
	-	Assessed at: ≥12 weeks	-	-	-	-
Anticonvulsants	**40**	**Overall Efficacy**	**46% (2698/5837)**	**30% (1120/3738)**	**RR 1.54 (95% CI 1.45, 1.63)**	**7**
	6	Assessed at: ≤4 weeks	49% (211/431)	21% (63/300)	RR 2.26 (95% CI 1.78, 2.87)	4
	20	Assessed at: >4 weeks to <12 weeks	45% (1202/2659)	29% (627/2128)	RR 1.56 (95% CI 1.44, 1.68)	7
	14	Assessed at: ≥12 weeks	47% (1285/2747)	33% (430/1310)	RR 1.42 (95% CI 1.30, 1.55)	8
Opioids	**6**	**Overall Efficacy**	**49% (289/593)**	**36% (198/556)**	**RR 1.37 (95% CI 1.19, 1.57)**	**8**
	1	Assessed at: ≤4 weeks	41% (12/29)	36% (12/33)	RR 1.14 (95% CI 0.61, 2.13)	NSS
	3	Assessed at: >4 weeks to <12 weeks	52% (142/271)	37% (96/263)	RR 1.45 (95% CI 1.19, 1.76)	7
	3	Assessed at: ≥12 weeks	46% (147/322)	35% (102/293)	RR 1.30 (95% CI 1.07, 1.58)	10
Rubefacients (Capsaicin)	**10**	**Overall Efficacy**	**49% (635/1303)**	**34% (350/1041)**	**RR 1.40 (95% CI 1.26, 1.55)**	**7**
	2	Assessed at: ≤4 weeks	30% (27/90)	19% (16/85)	RR 1.60 (95% CI 0.93, 2.75)	NSS
	8	Assessed at: >4 weeks to <12 weeks	41% (365/888)	30% (254/833)	RR 1.37 (95% CI 1.20, 1.56)	10

	5	Assessed at: ≥12 weeks	52% (529/1018)	36% (288/792)	RR 1.36 (95% CI 1.22, 1.52)	7
SNRIs	**8**	**Overall Efficacy**	**57% (995/1759)**	**41% (405/987)**	**RR 1.45 (95% CI 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% CI 0.97, 1.91)	NSS
	7	Assessed at: ≥12 weeks	58% (918/1595)	42% (377/906)	RR 1.46 (95% CI 1.34, 1.60)	7
TCAs	**2**	**Overall Efficacy**	**78% (66/85)**	**26% (22/85)**	**RR 3.00 (95% CI 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% CI 2.05, 4.38)	8
	-	Assessed at: ≥12 weeks	-	-	-	-

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

CI: 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

Table 5: Proportion of patients with clinically meaningful response based on funding source (clearly publicly or industry funding)

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

CI: 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.

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

Intervention Type	Number of RCTs	Subgroup	Intervention Event Rate	Control Event Rate	Risk Ratio (95% CI)	NNT	p-value†
Anticonvulsants	16	Less than the median risk of bias score	48% (995/2083)	33% (527/1574)	RR 1.41 (95% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 1.21, 1.52)	8	

CI: 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.

†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.

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

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

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.

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

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

CI: 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.

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

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

CI: 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% CI)	NNT	p-value*
Acupuncture	2	Non-Sham Comparator	15% (14/93)	13% (12/95)	RR 1.27 (95% CI 0.26, 6.29)	NSS	P=0.28
	1	Sham Comparator	46% (13/28)	13% (4/31)	RR 3.60 (95% CI 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

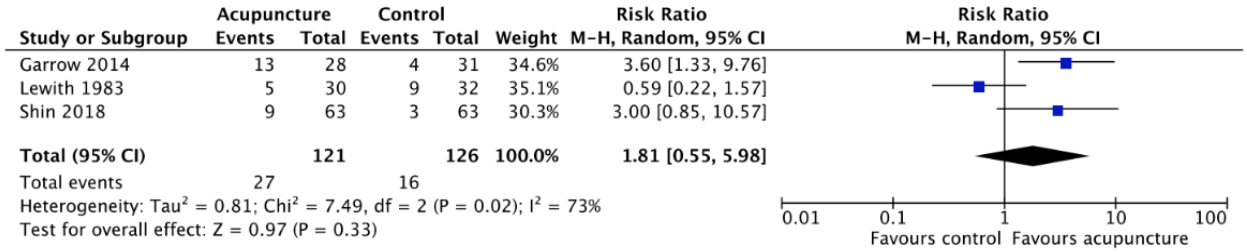


Figure 1.2: Acupuncture versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater

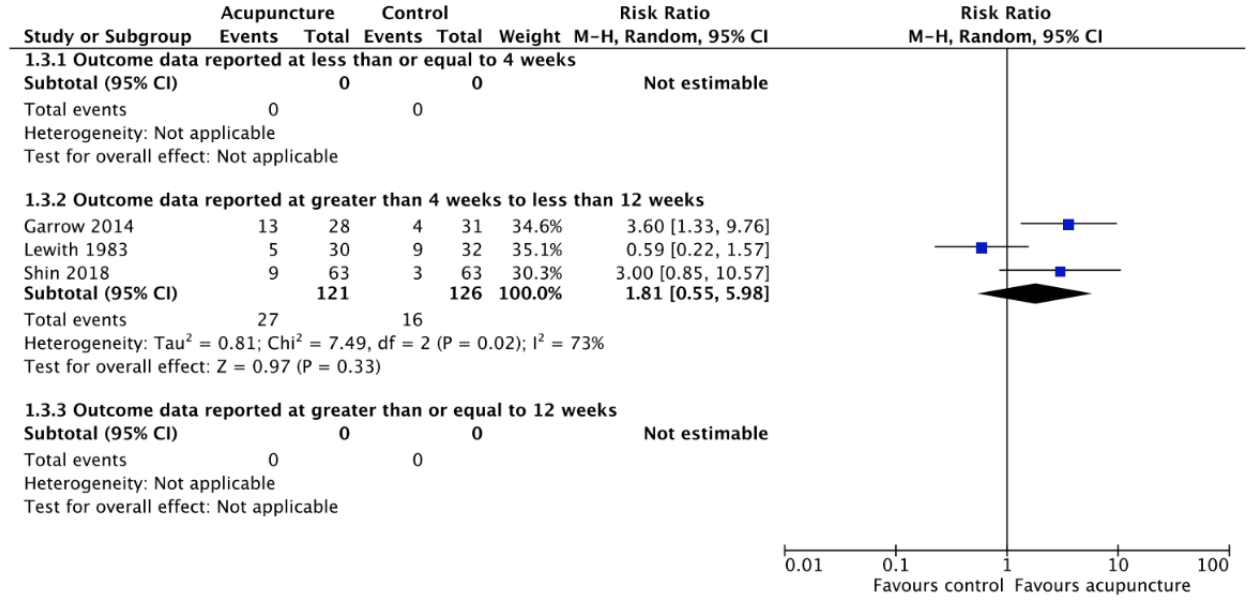


Figure 1.3: Acupuncture versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source

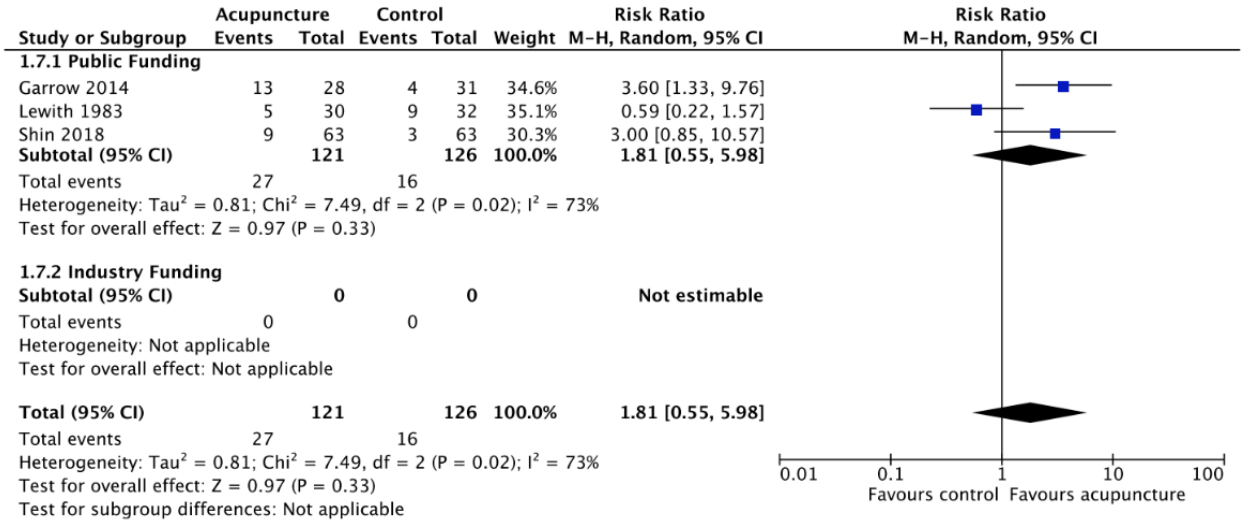


Figure 1.4: Acupuncture versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by neuropathic pain type

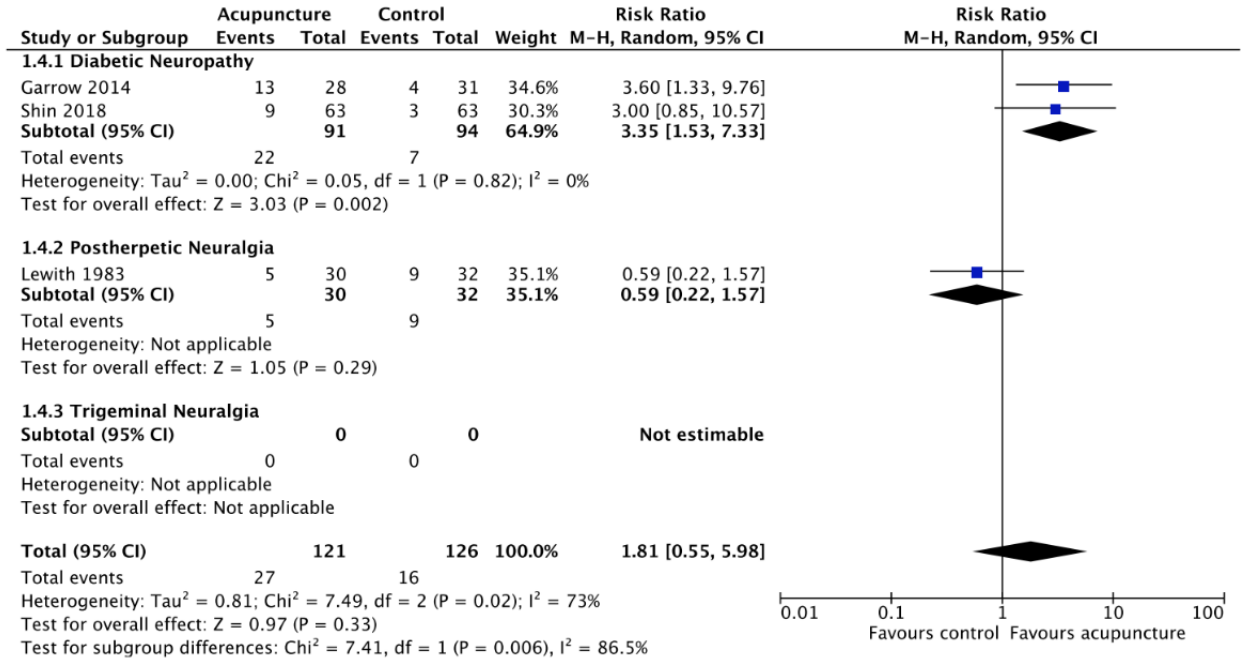


Figure 1.5: Acupuncture versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size

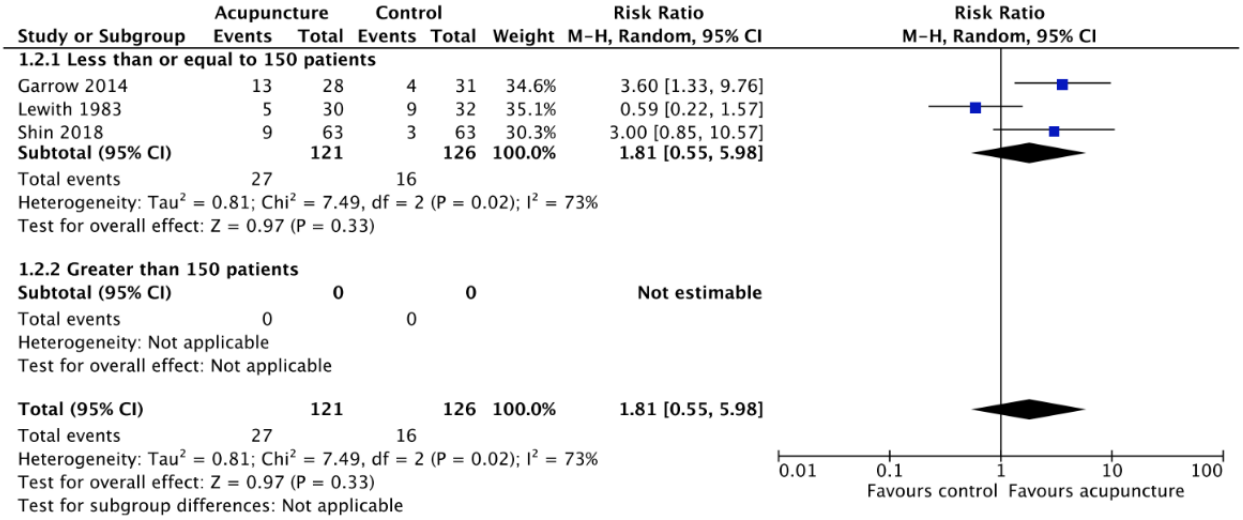
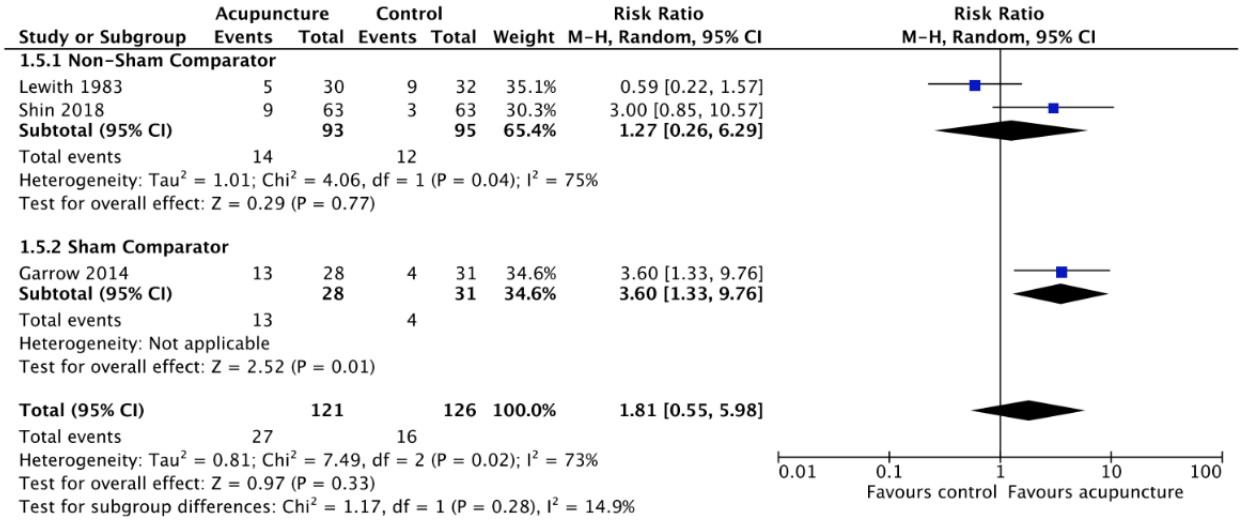


Figure 1.6: Acupuncture versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by control group characteristics



Anticonvulsants

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

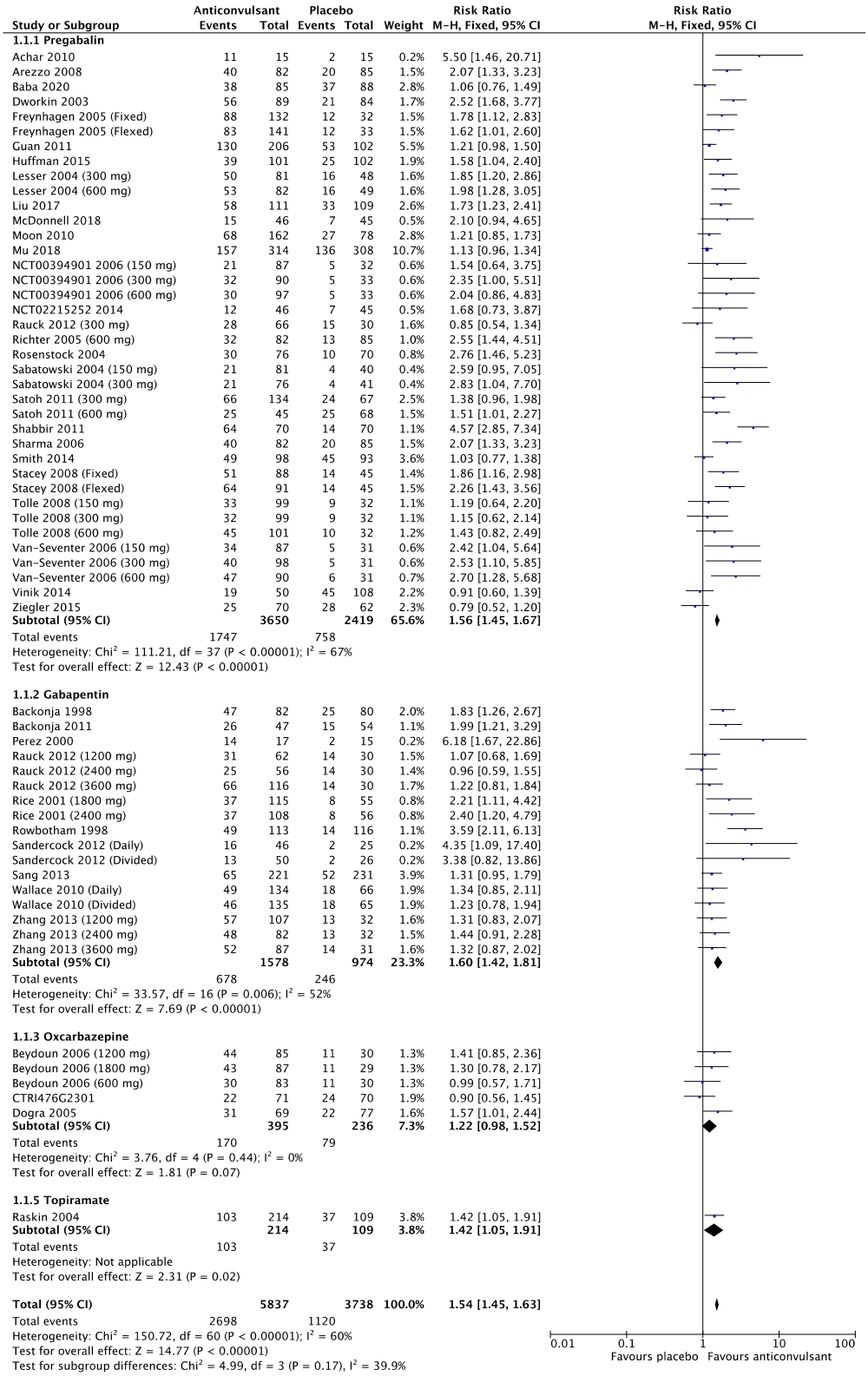


Figure 2.2: Anticonvulsants versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater

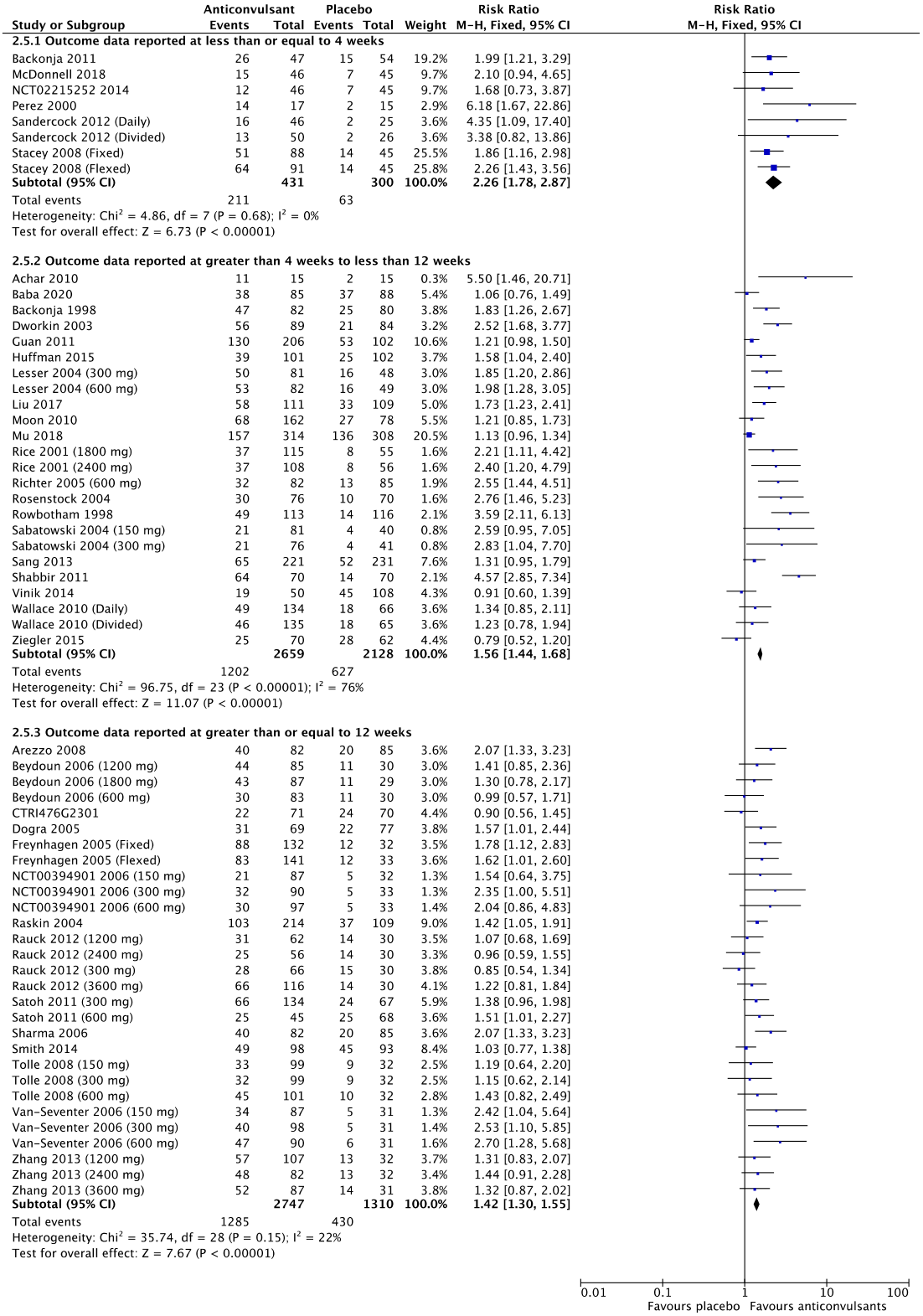


Figure 2.3: Anticonvulsants versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source

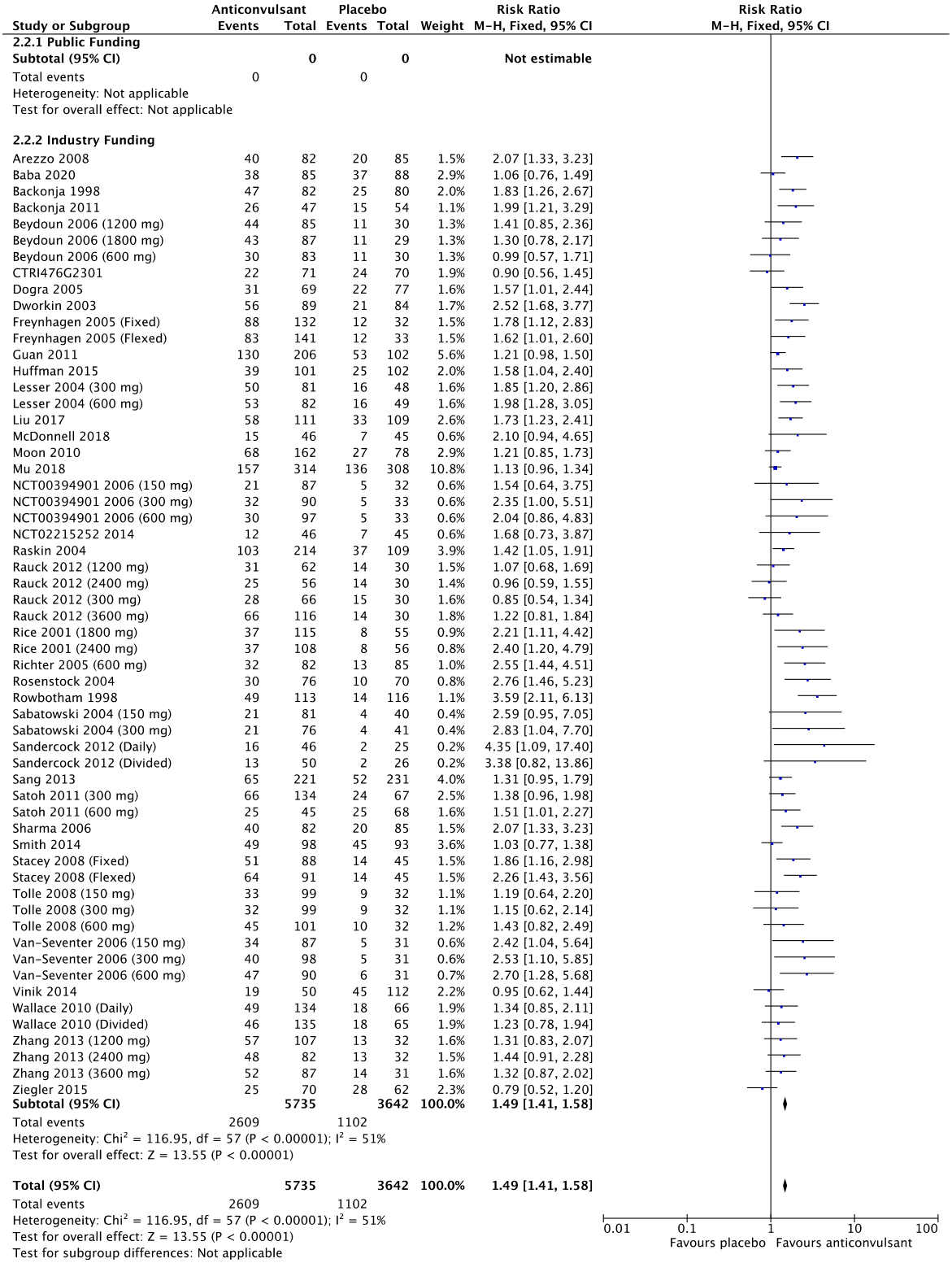
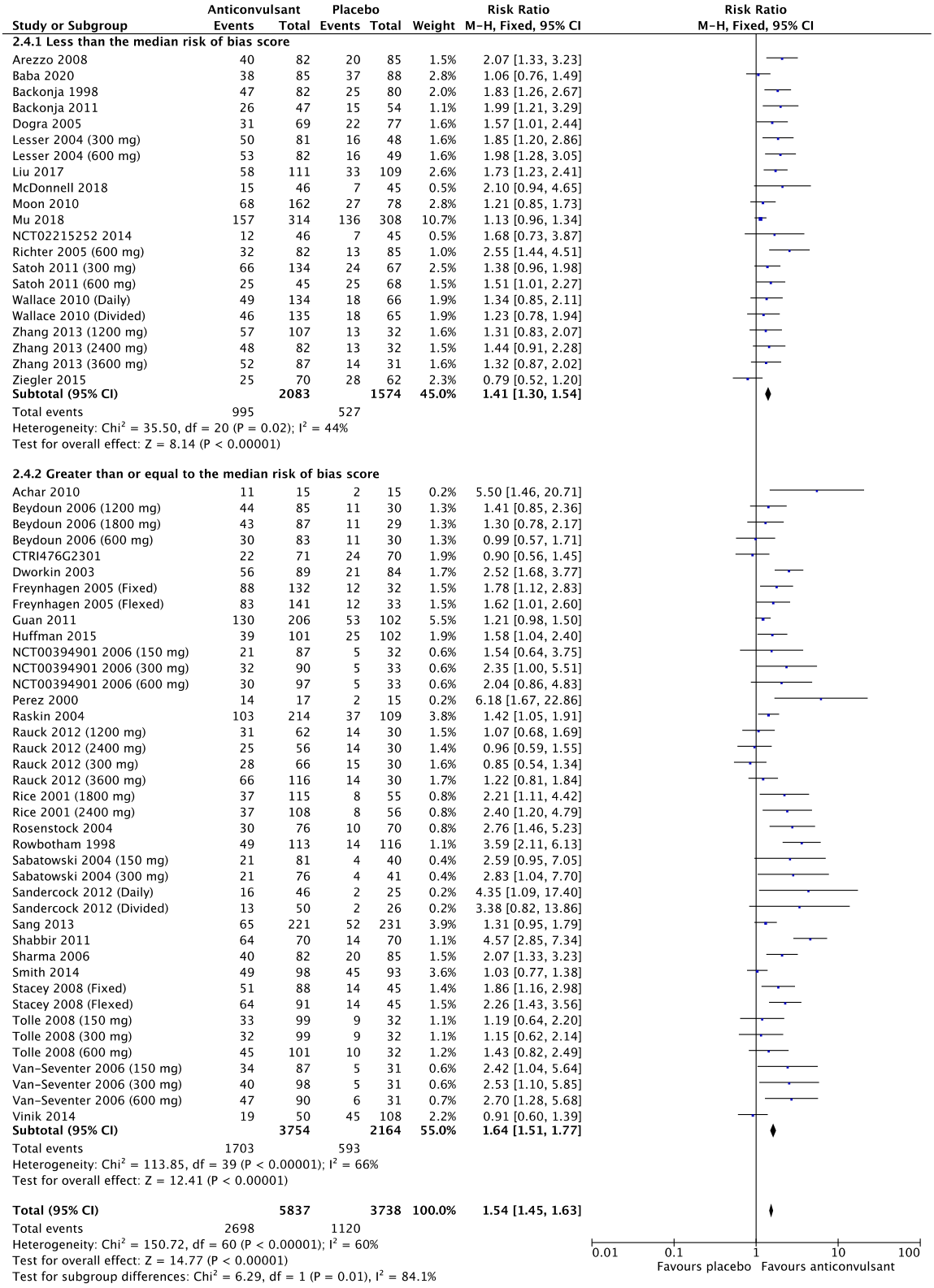


Figure 2.4: Anticonvulsants versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by median risk of bias



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

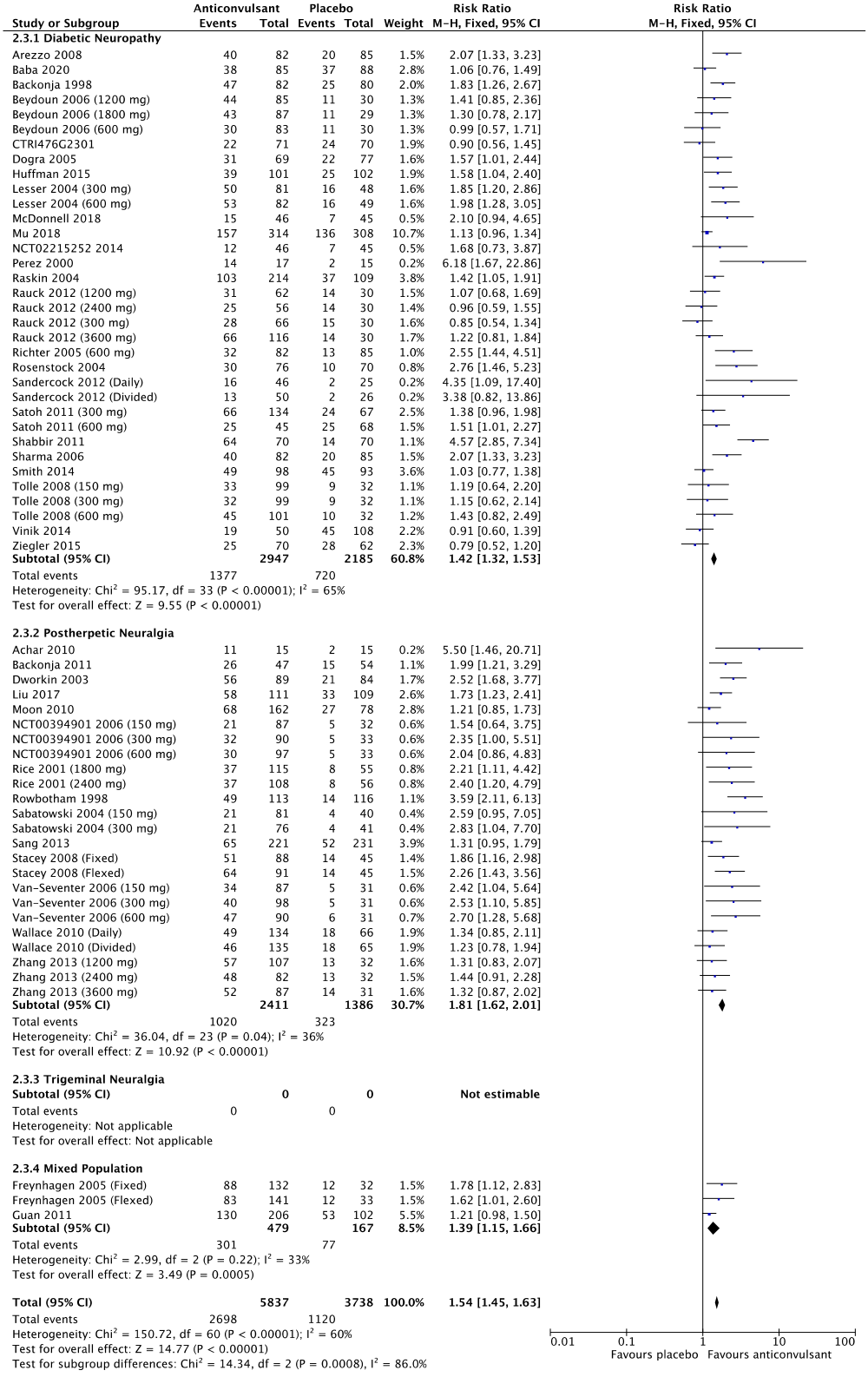
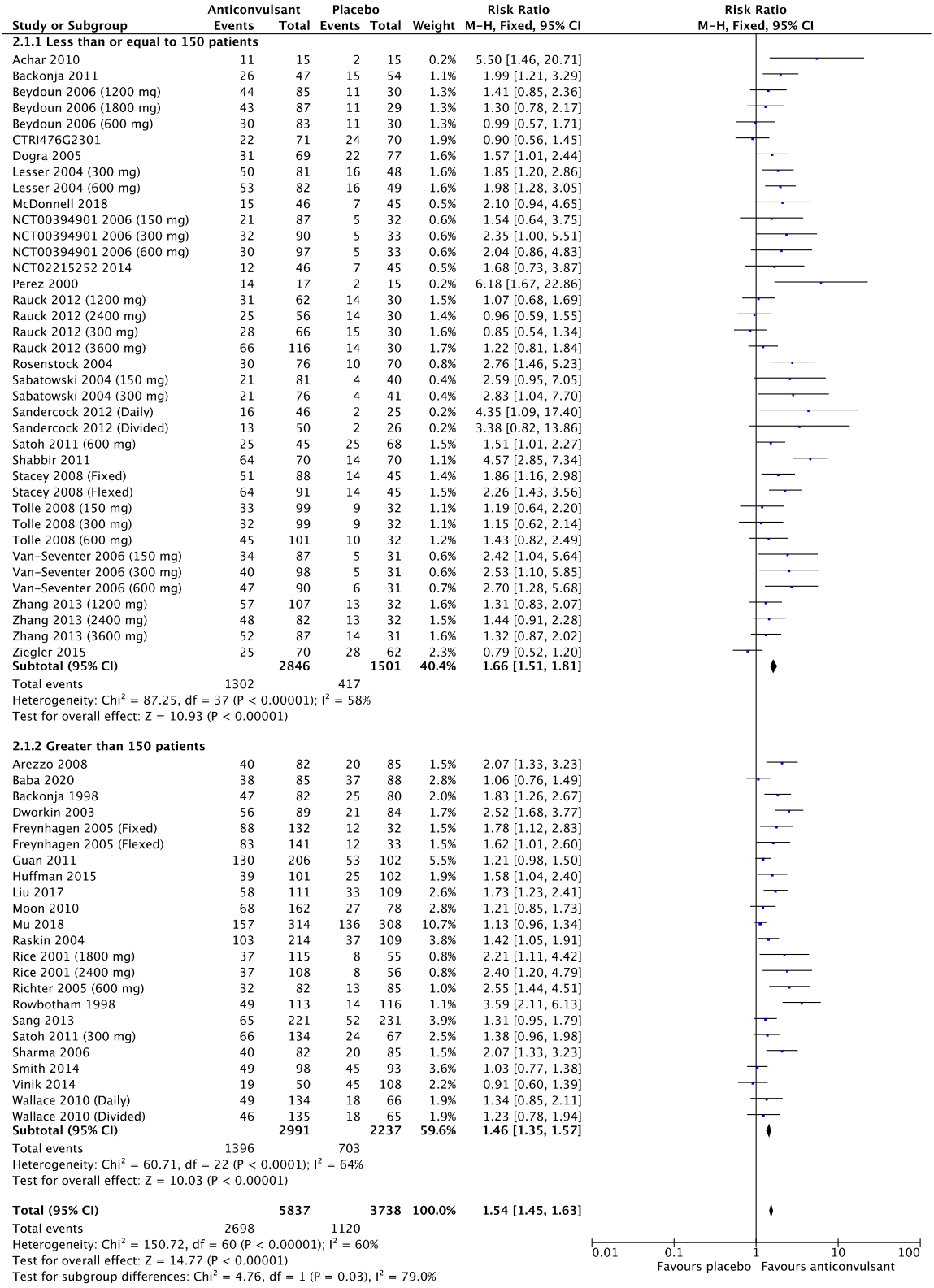


Figure 2.6: Anticonvulsants versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size



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

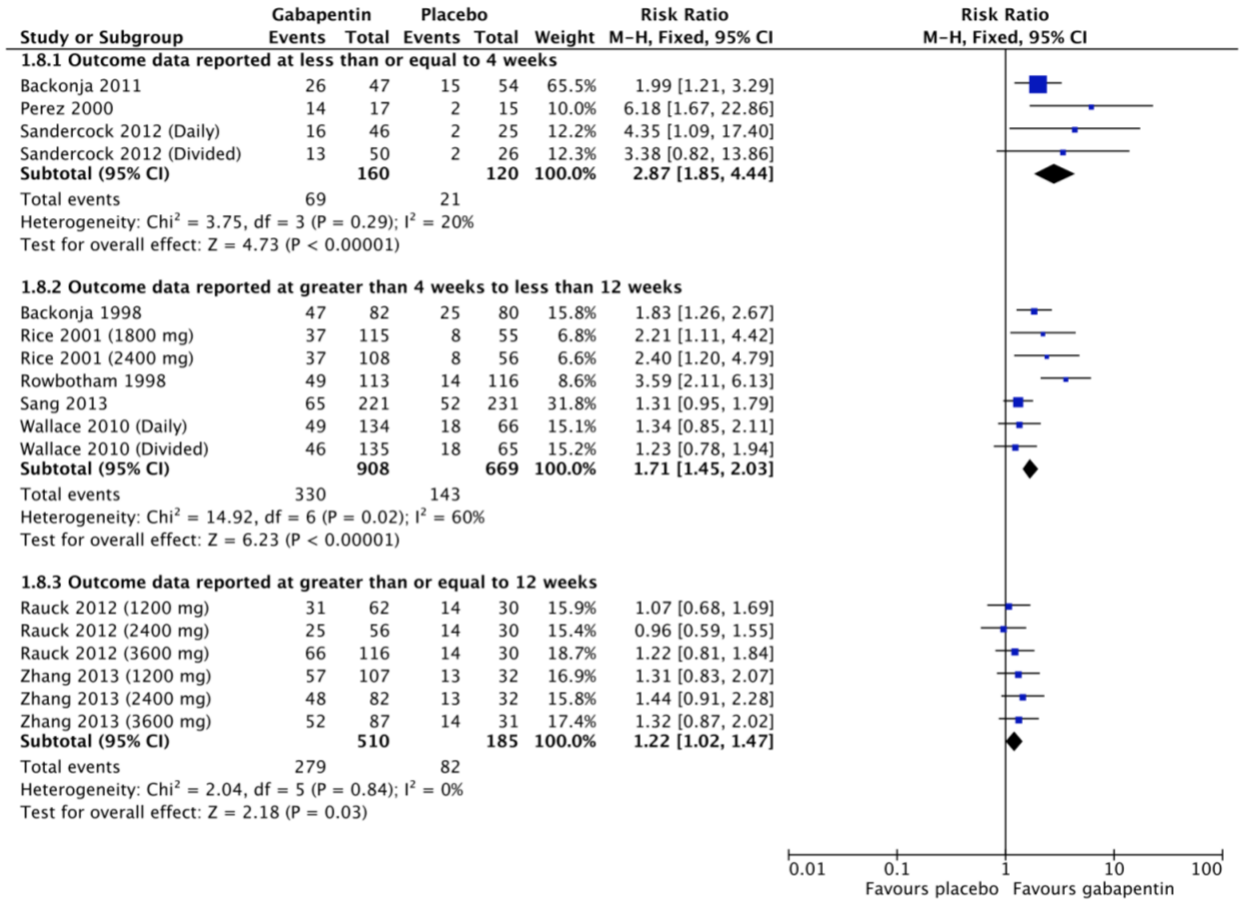


Figure 3.2: Gabapentin versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source

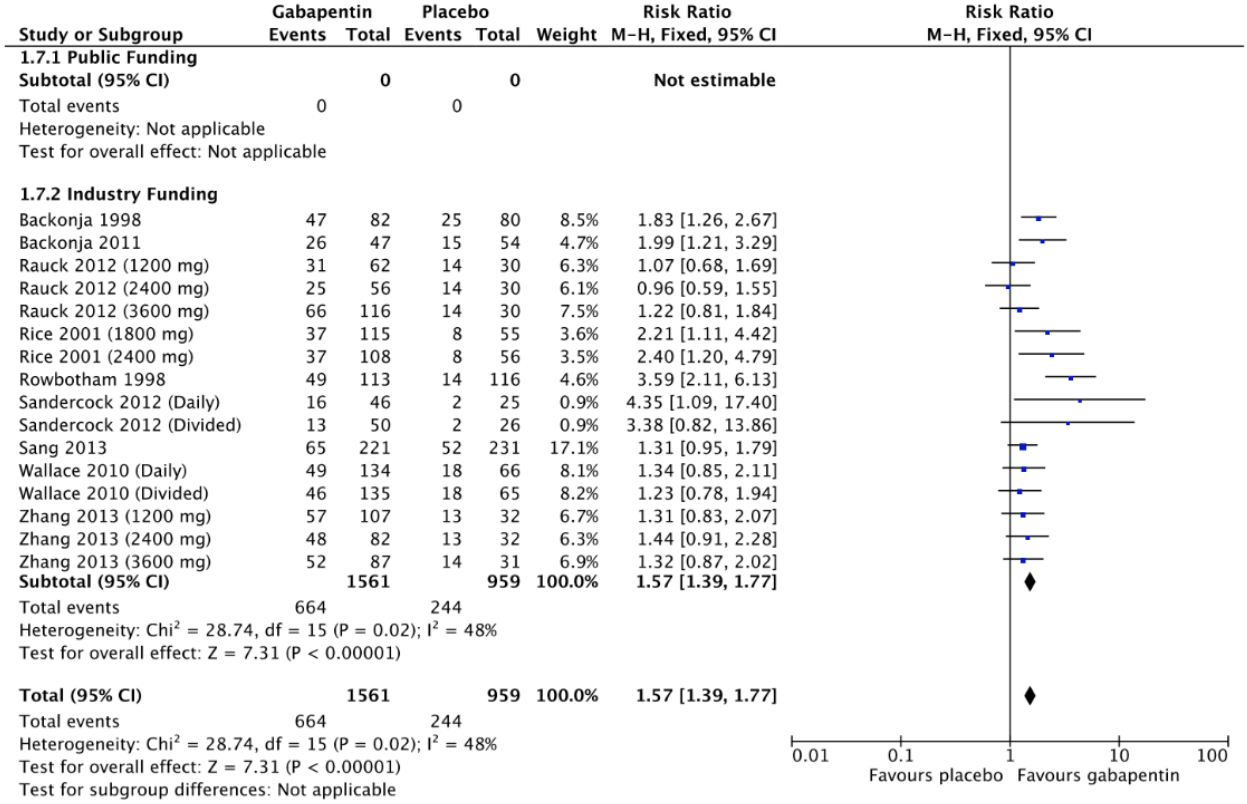


Figure 3.3: Gabapentin versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by neuropathic pain type

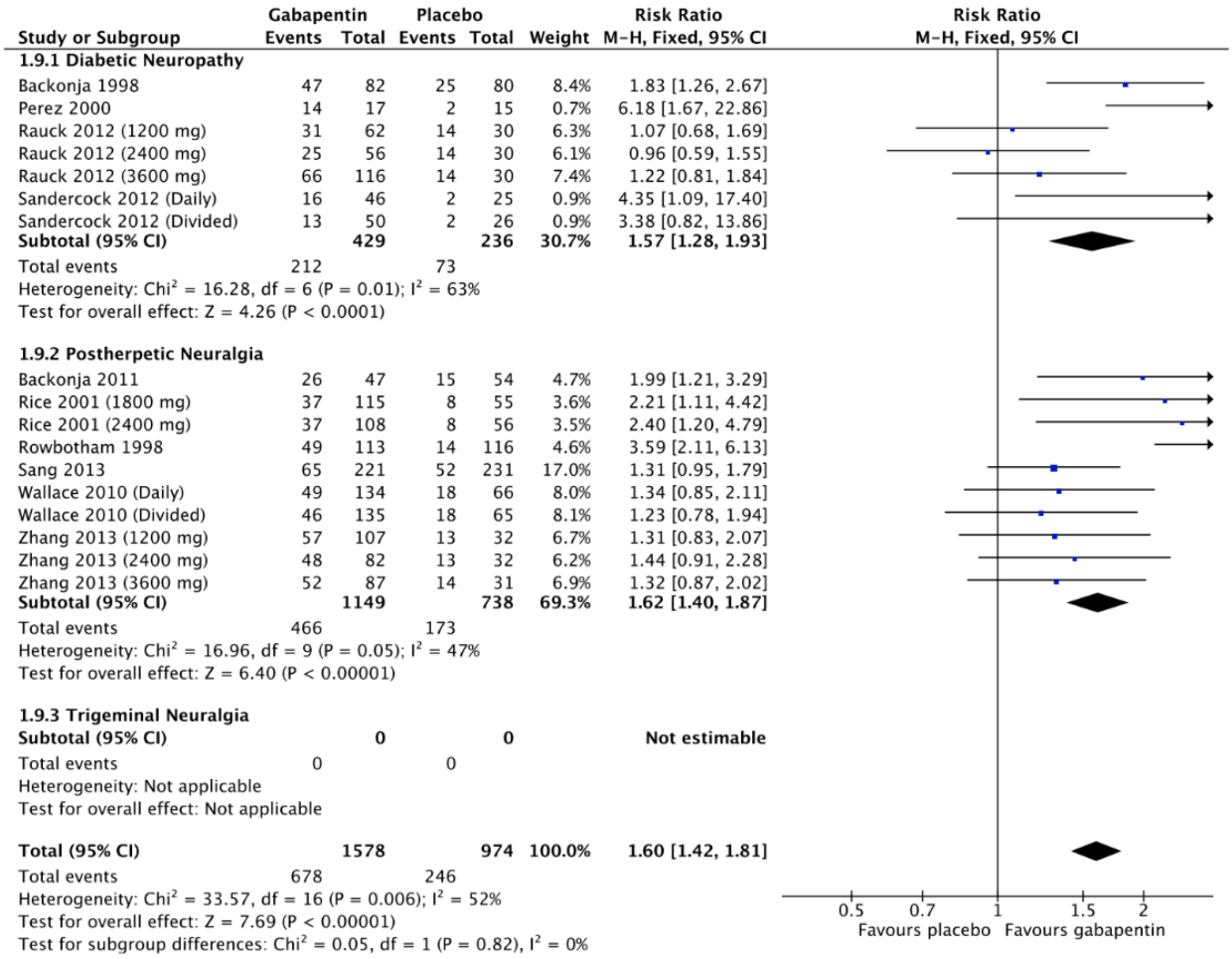
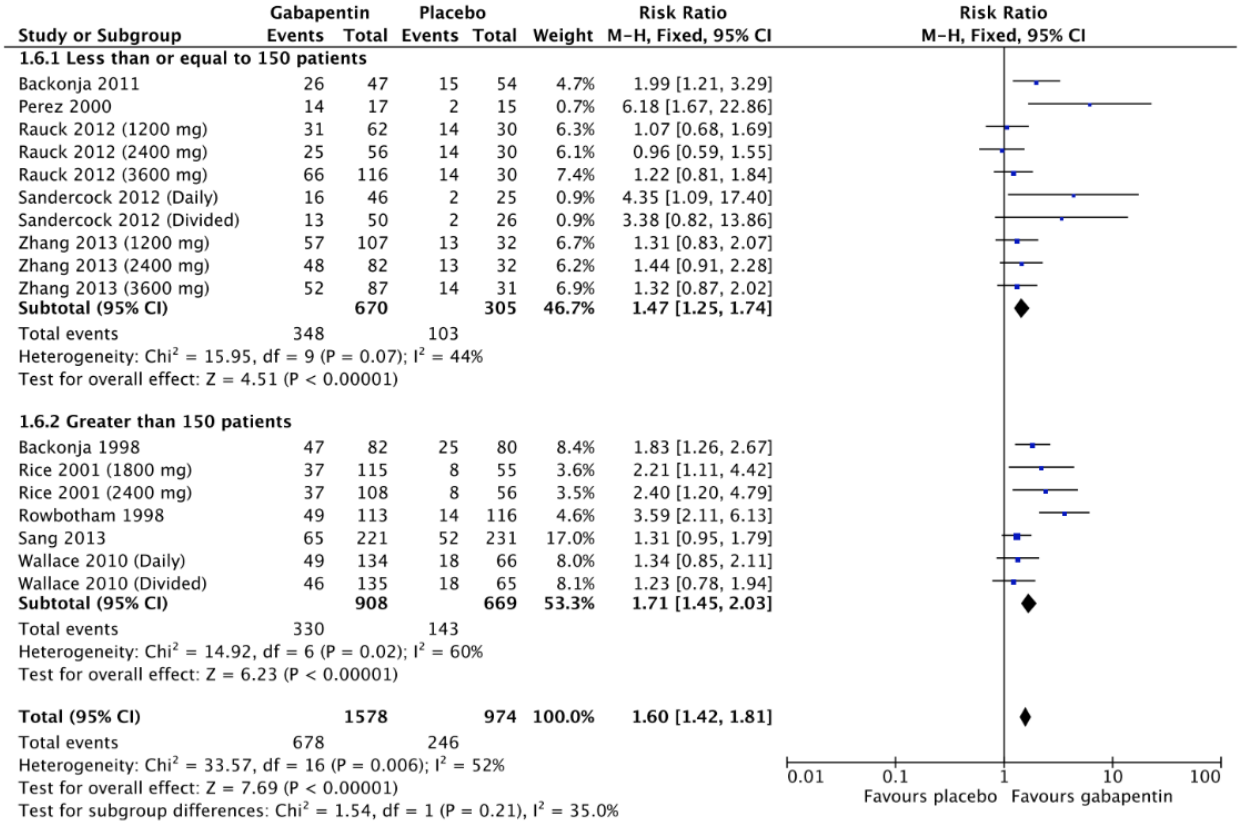


Figure 3.4: Gabapentin versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size



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

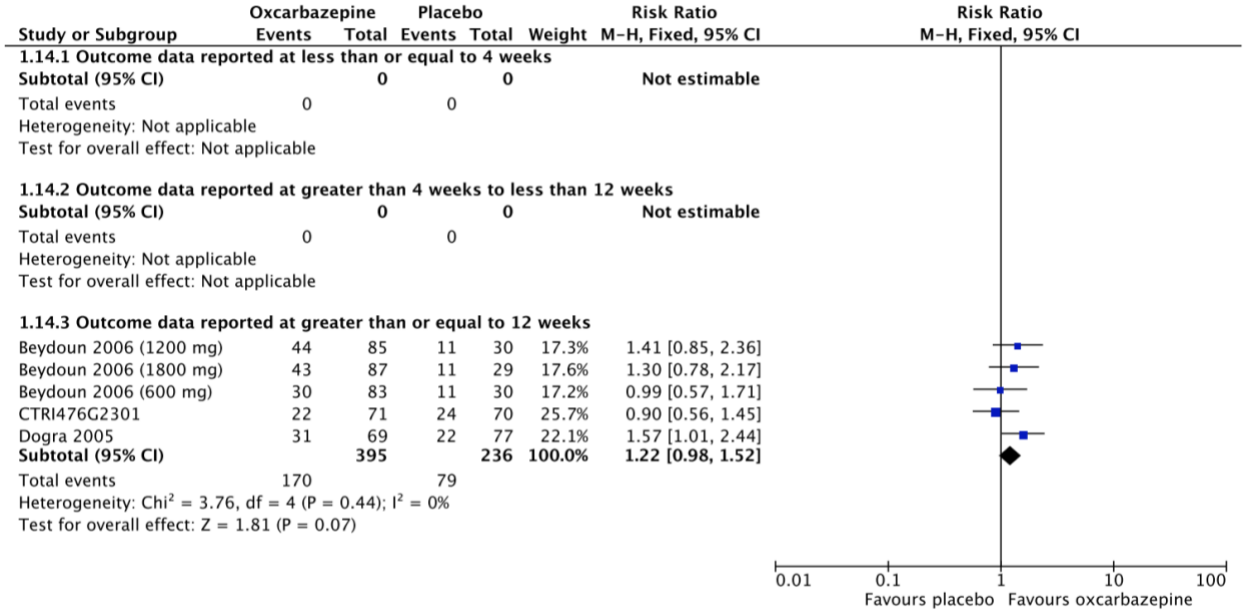


Figure 4.2: Oxcarbazepine versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source

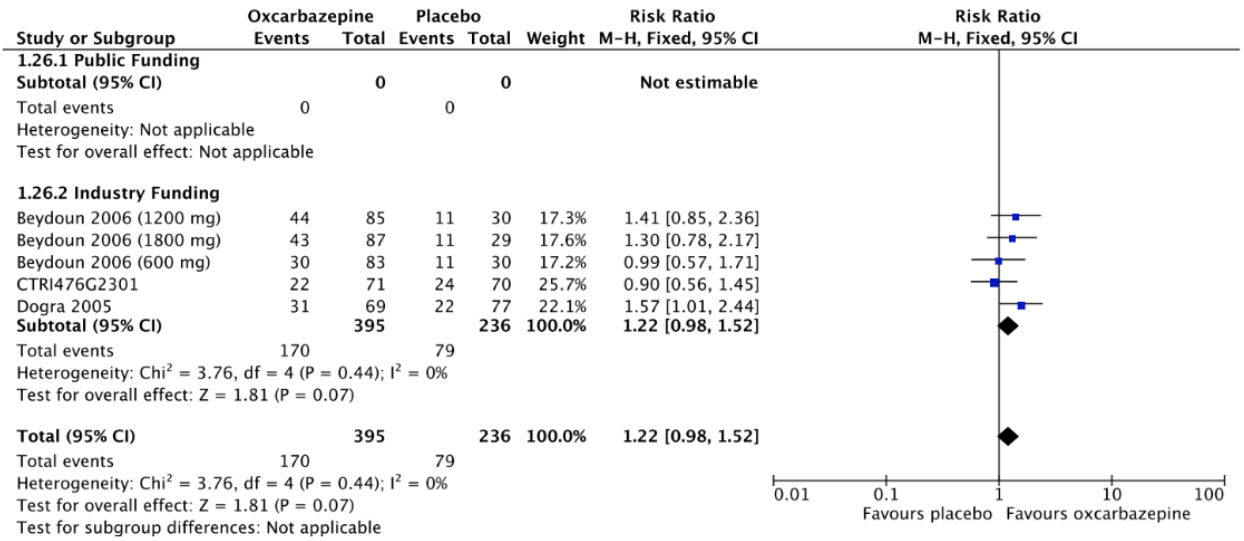


Figure 4.3: Oxcarbazepine versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by neuropathic pain type

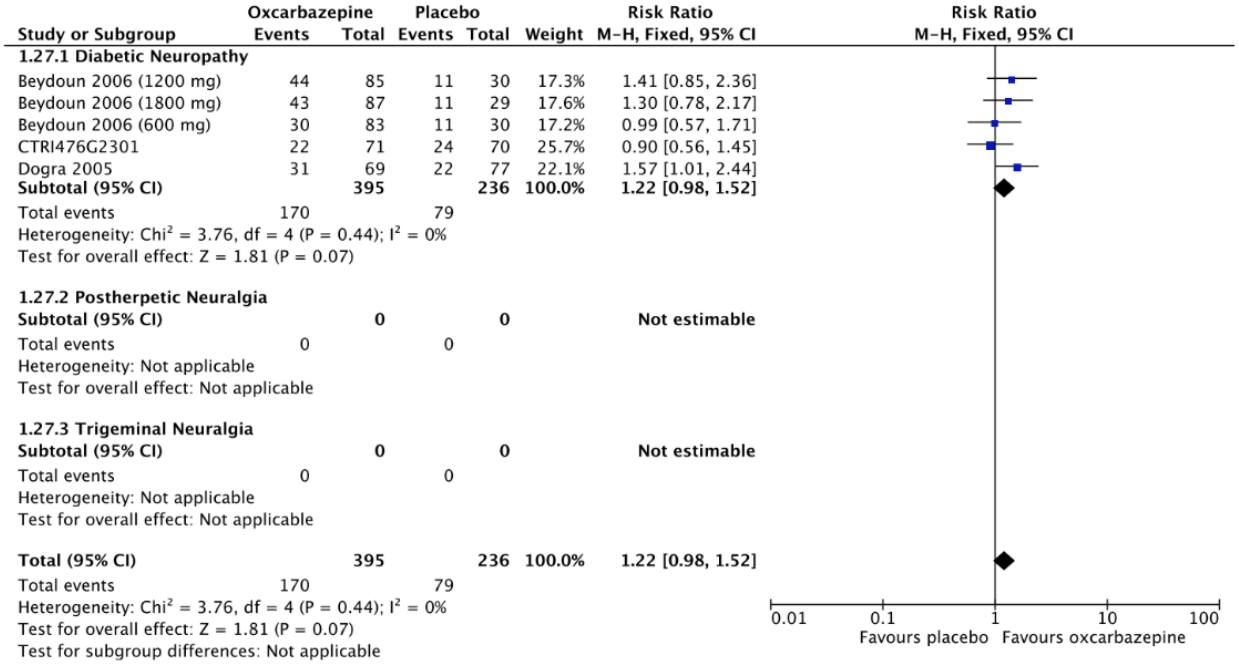
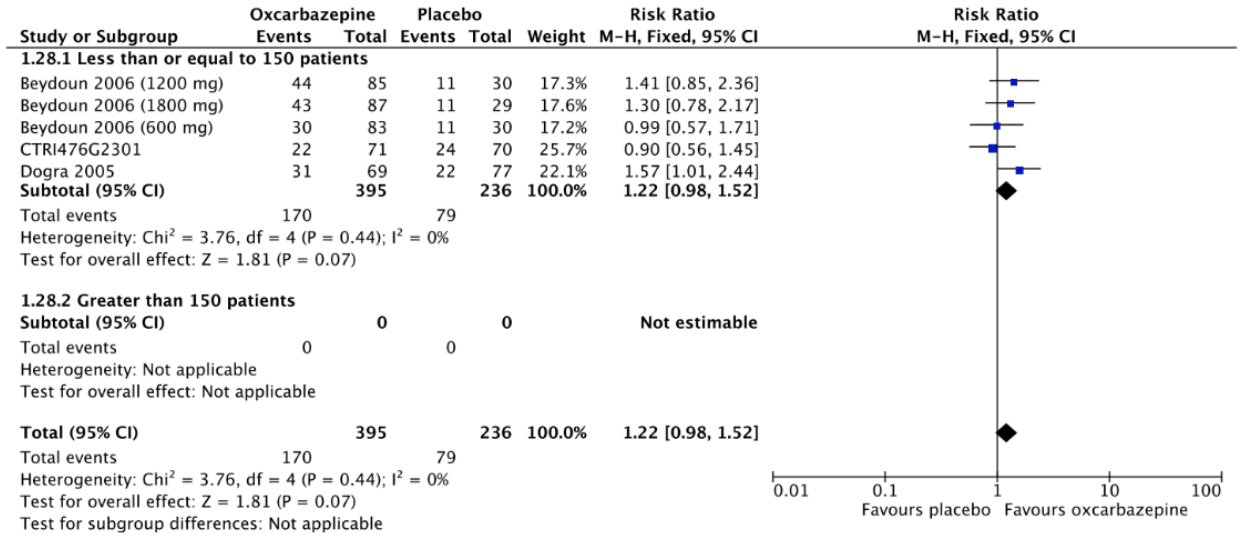


Figure 4.4: Oxcarbazepine versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size



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

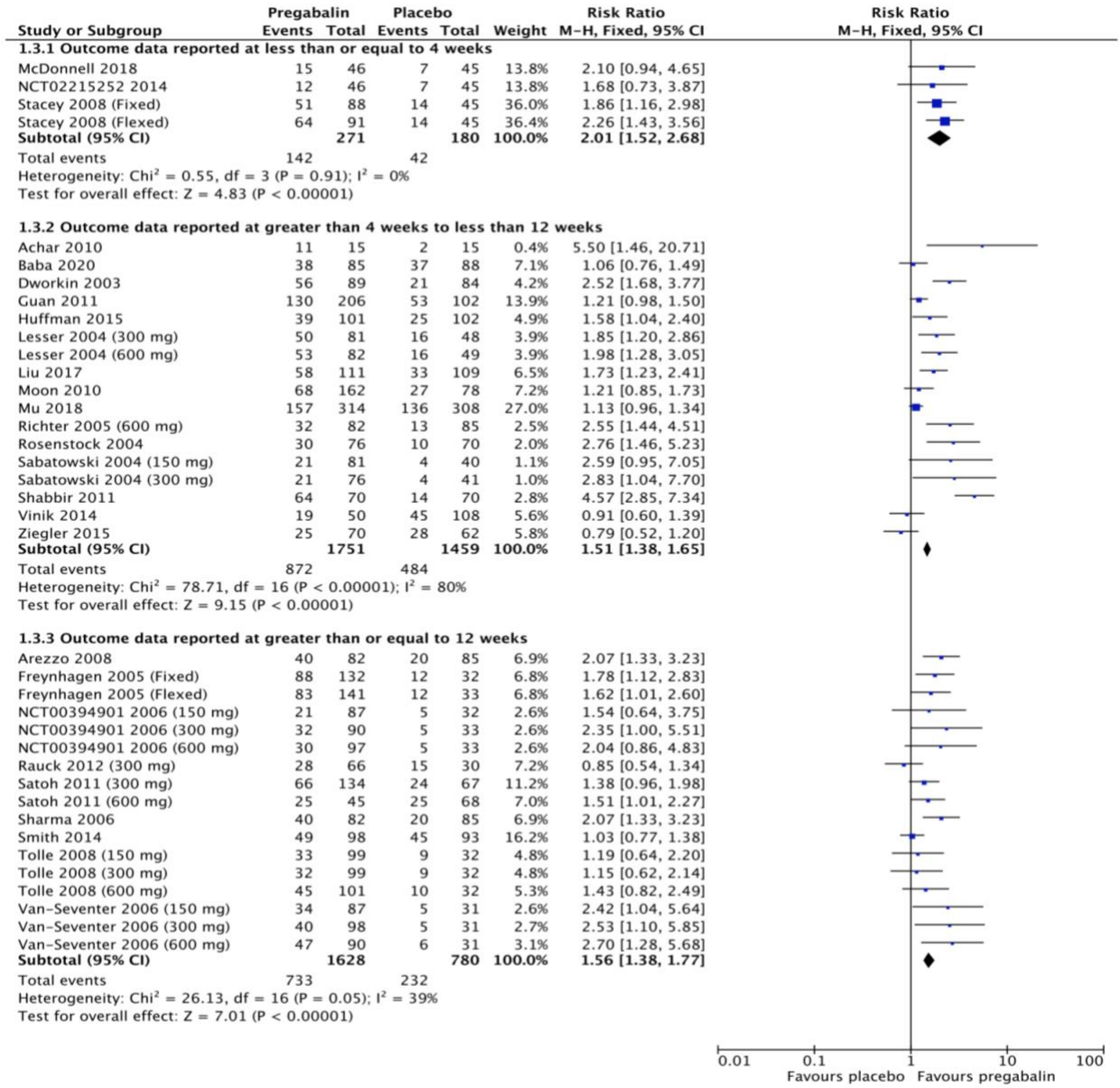


Figure 5.2: Pregabalin versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source

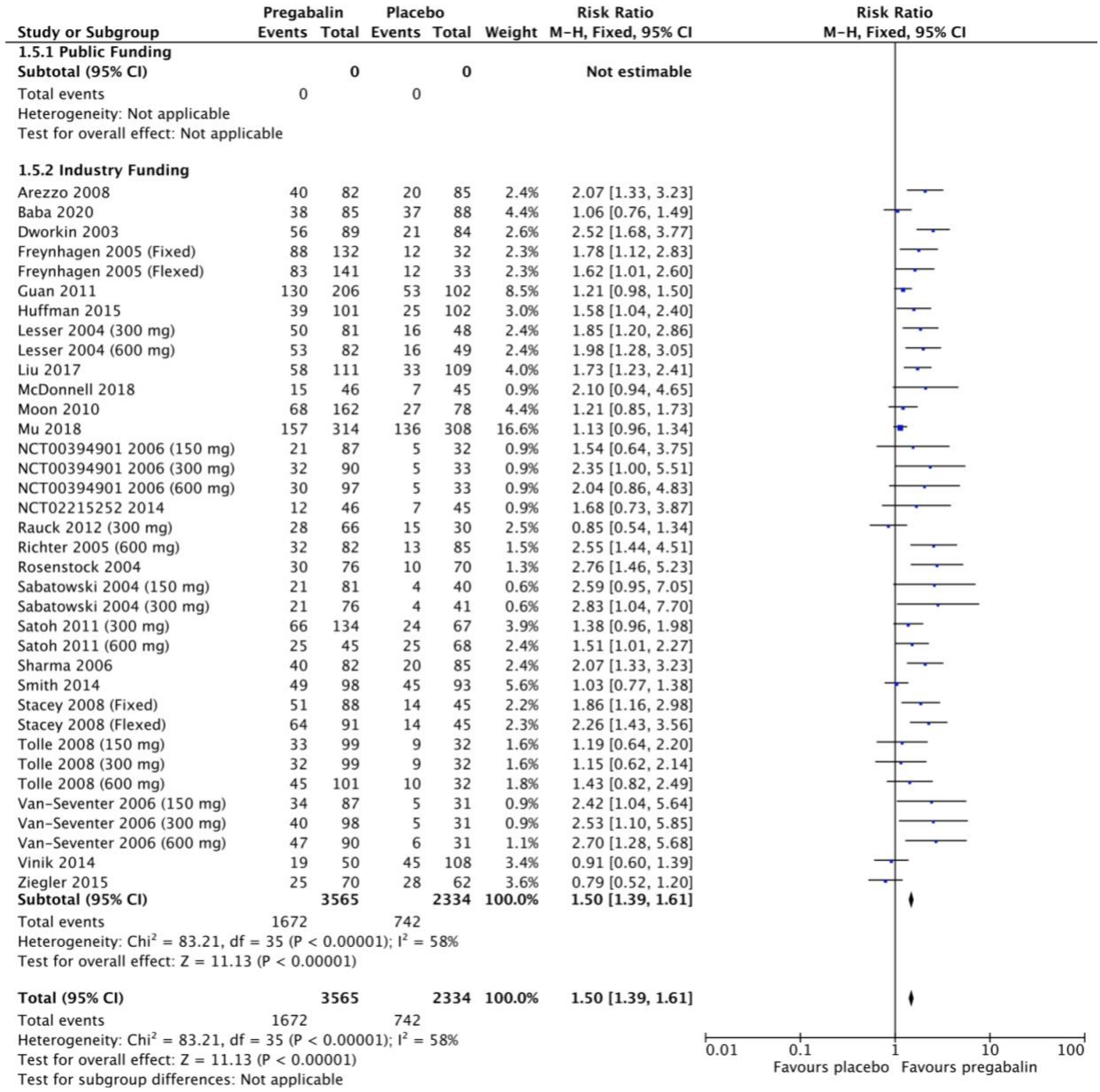


Figure 5.3: Pregabalin versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by neuropathic pain type

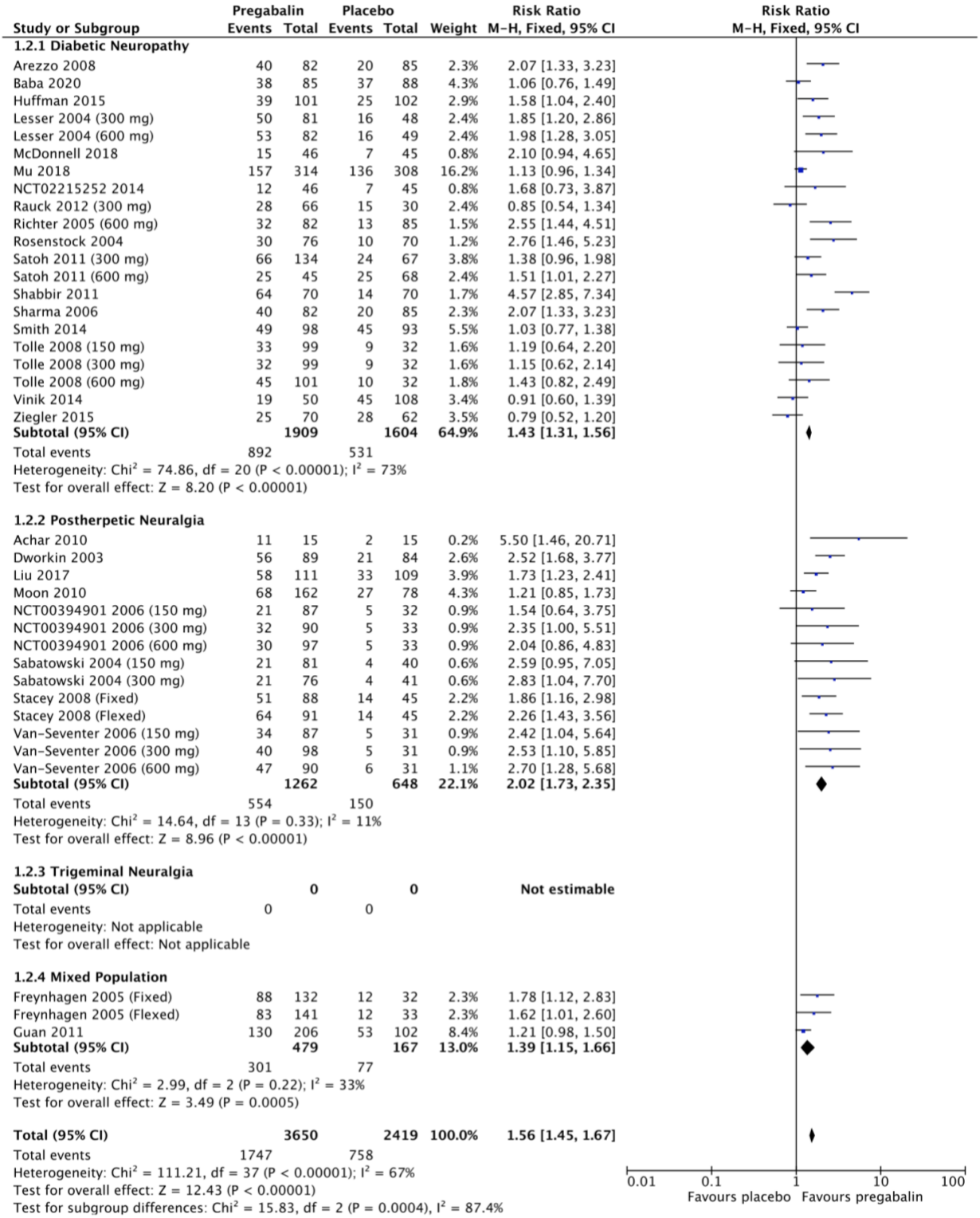
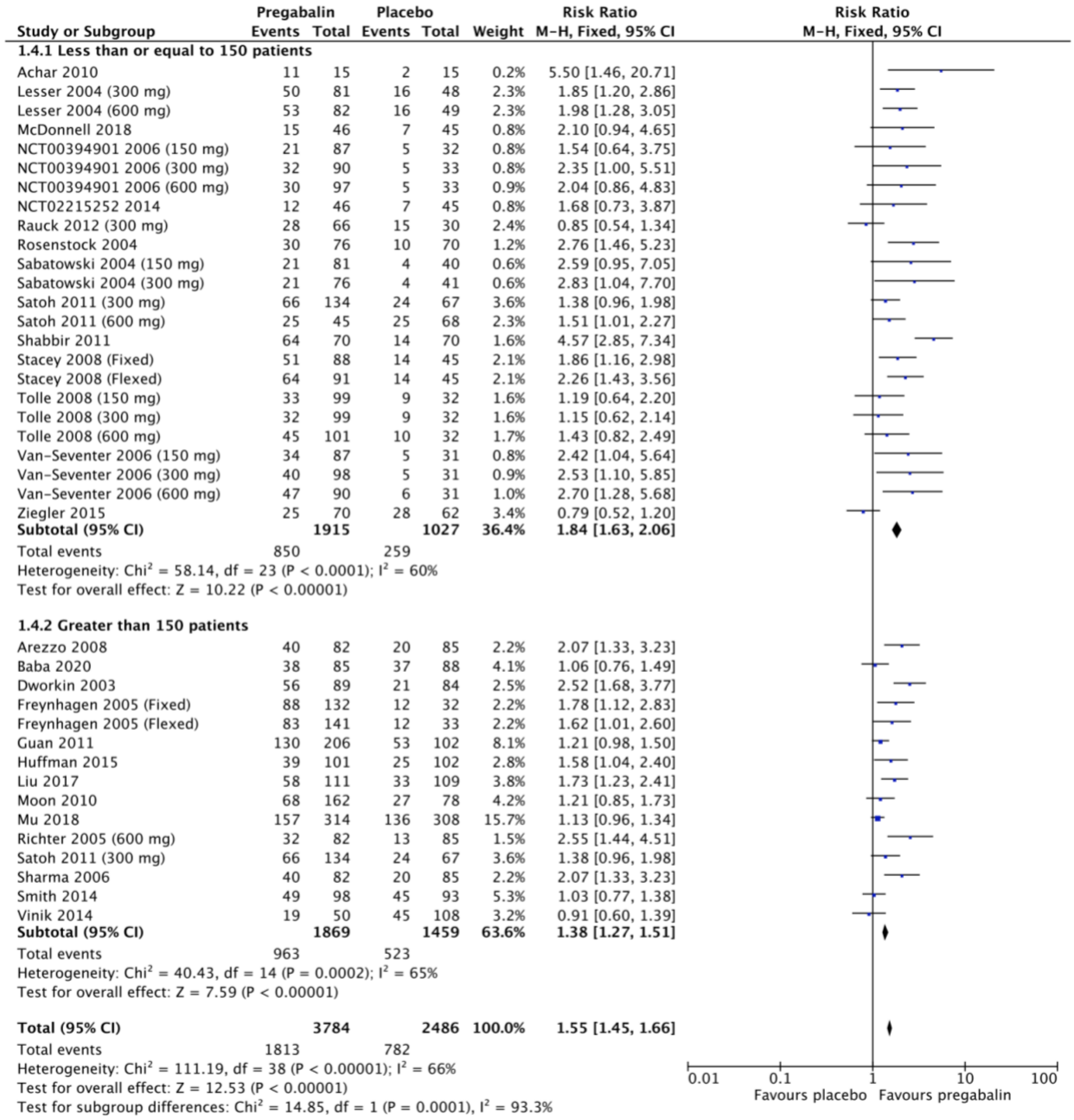


Figure 5.4: Pregabalin versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size



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

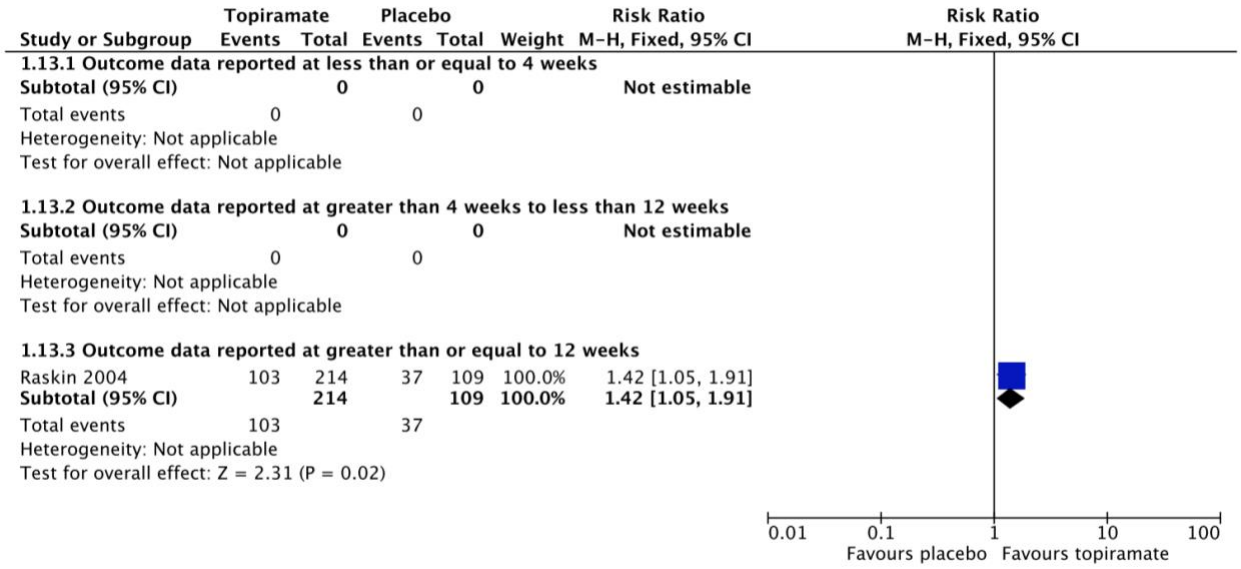


Figure 6.2: Topiramate versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source

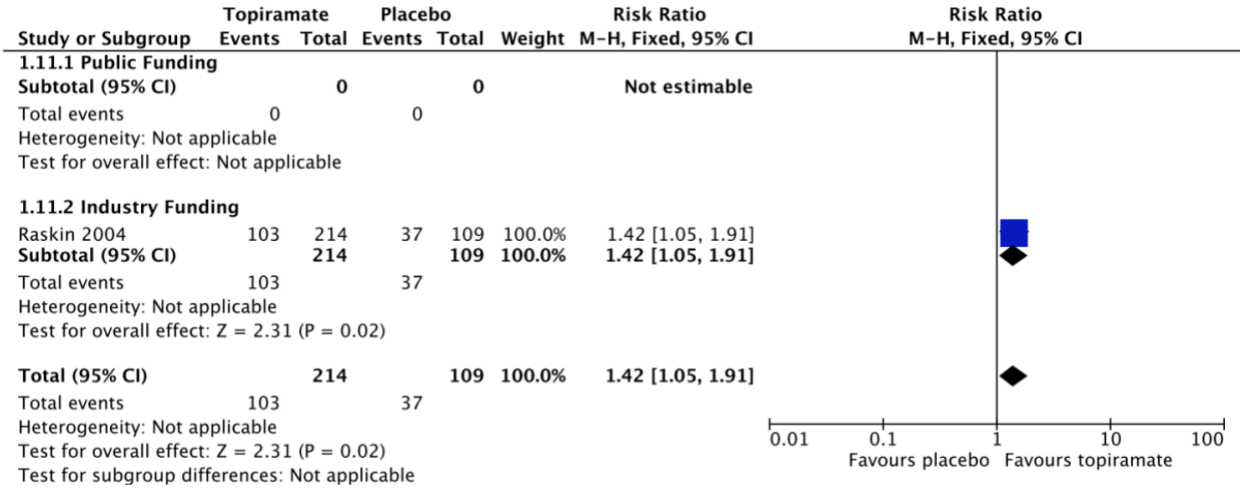


Figure 6.3: Topiramate versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by neuropathic pain type

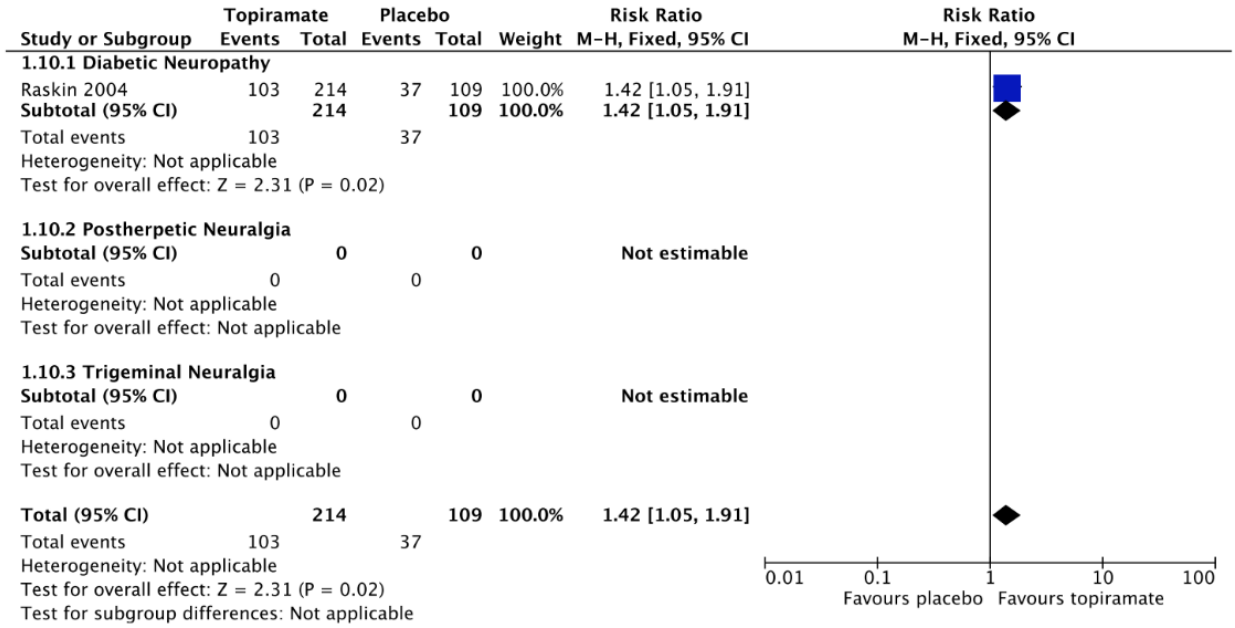
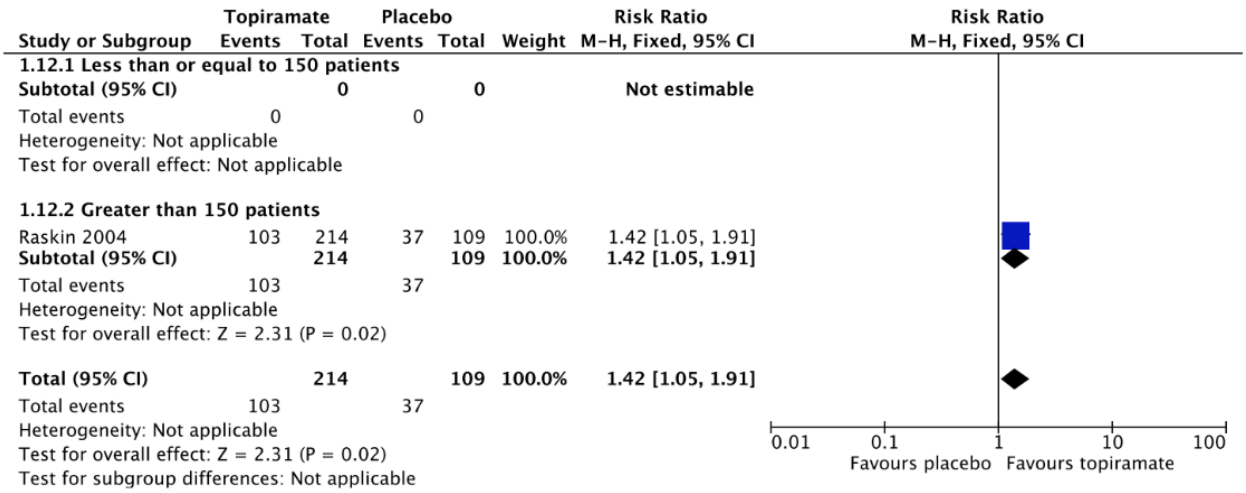


Figure 6.4: Topiramate versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size



Opioids

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

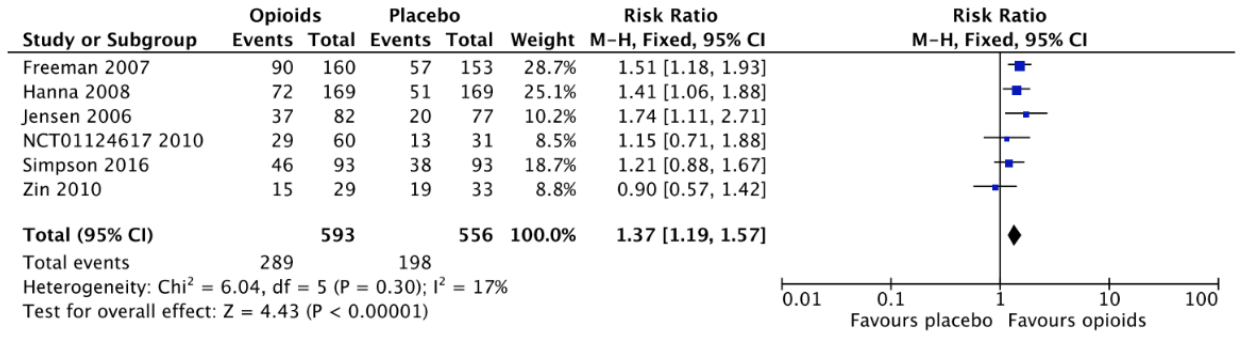


Figure 7.2: Opioids versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater

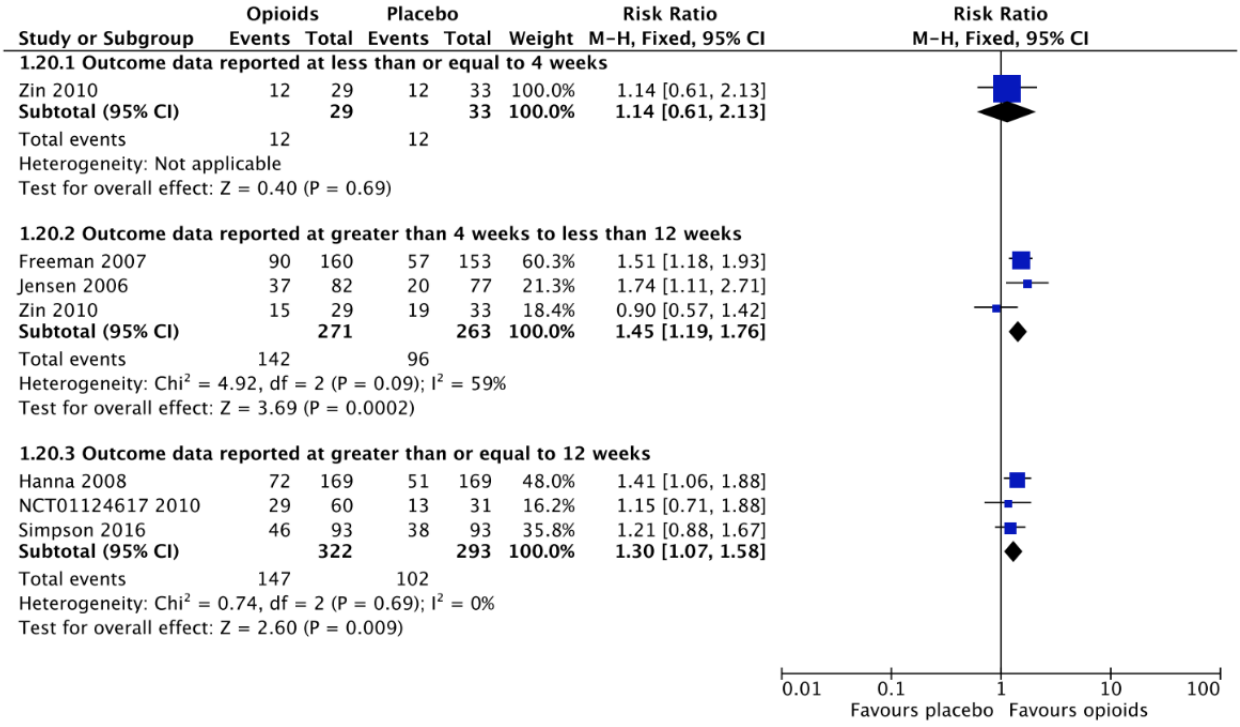


Figure 7.3: Opioids versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source

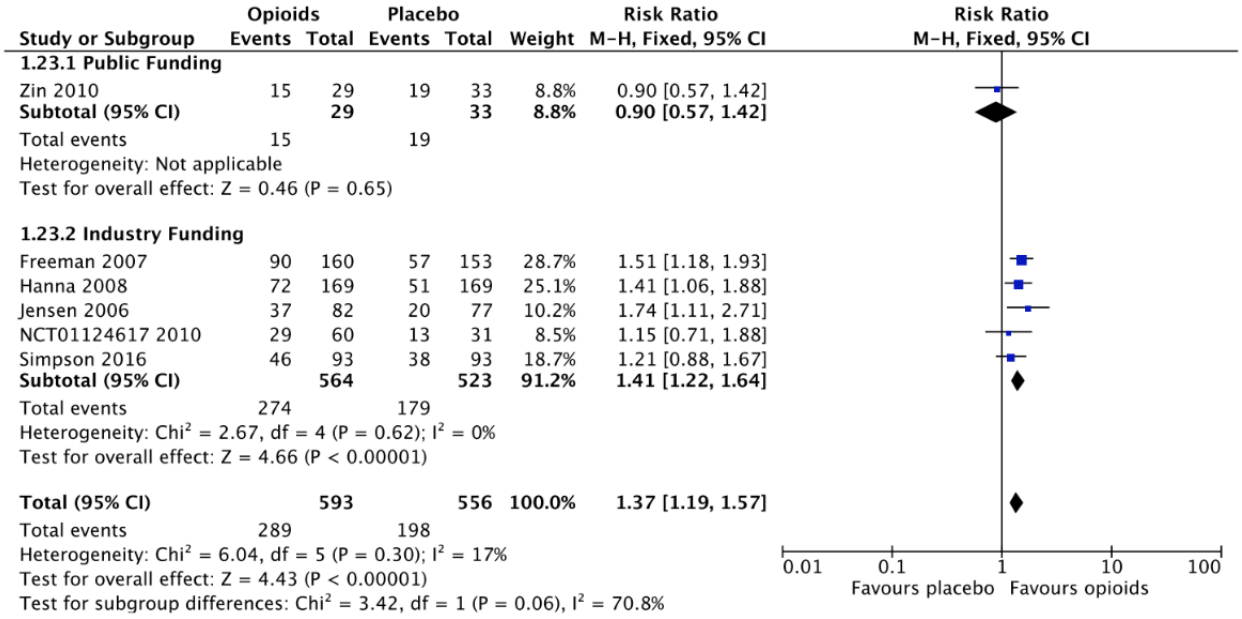
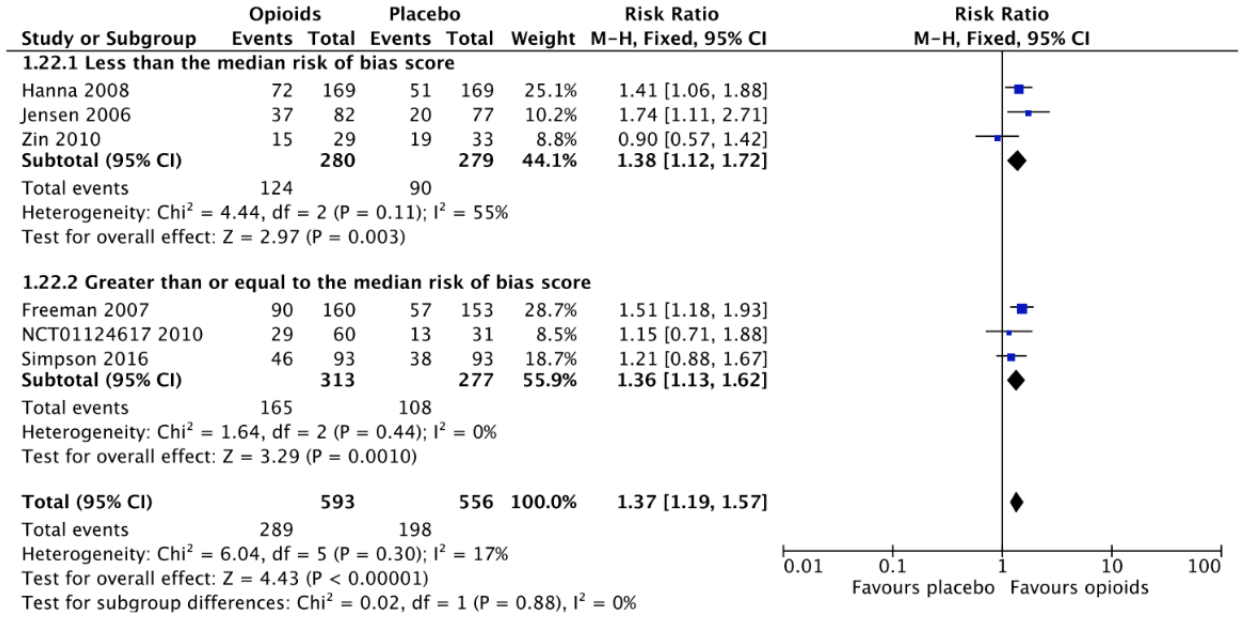


Figure 7.4: Opioids versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by median risk of bias



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

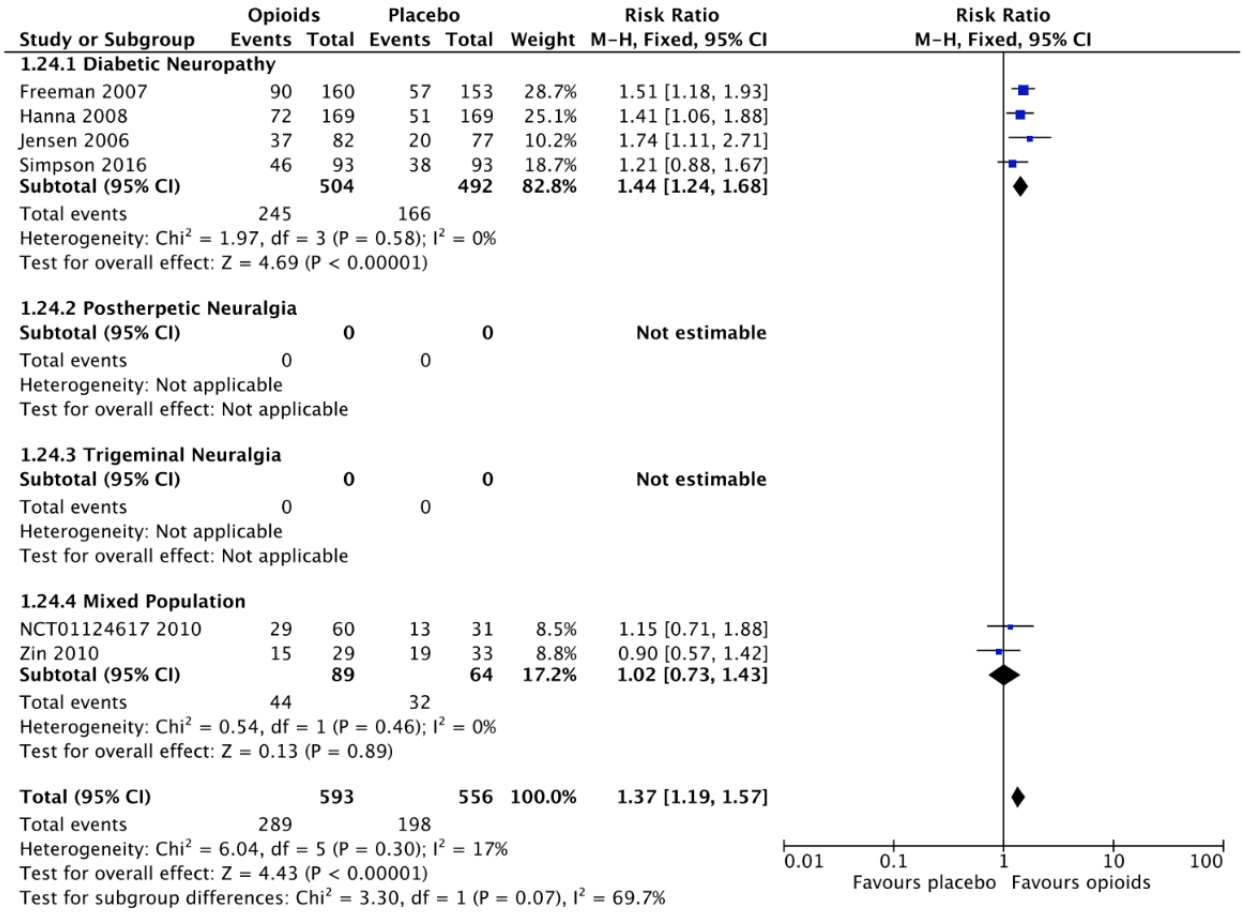
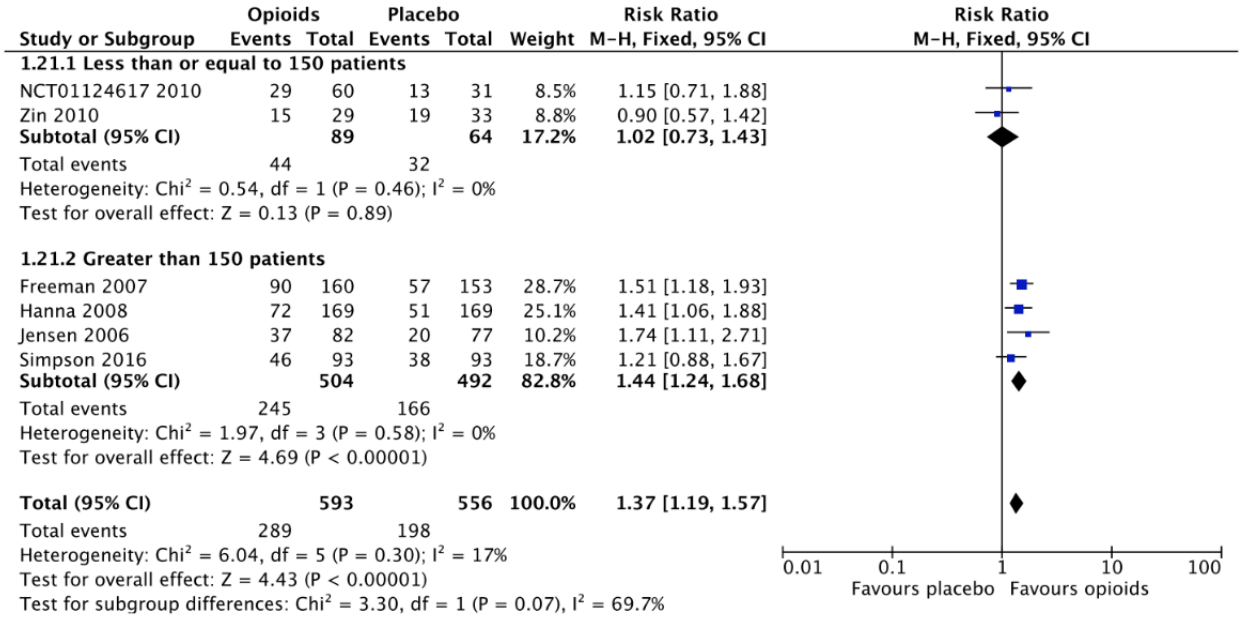
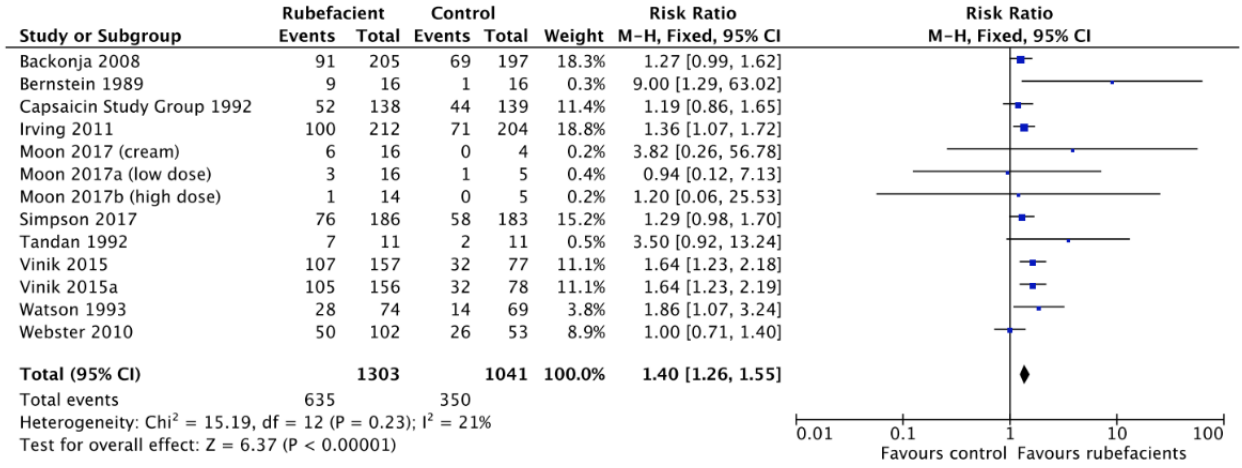


Figure 7.6: Opioids versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size



Rubefacients (Capsaicin)

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

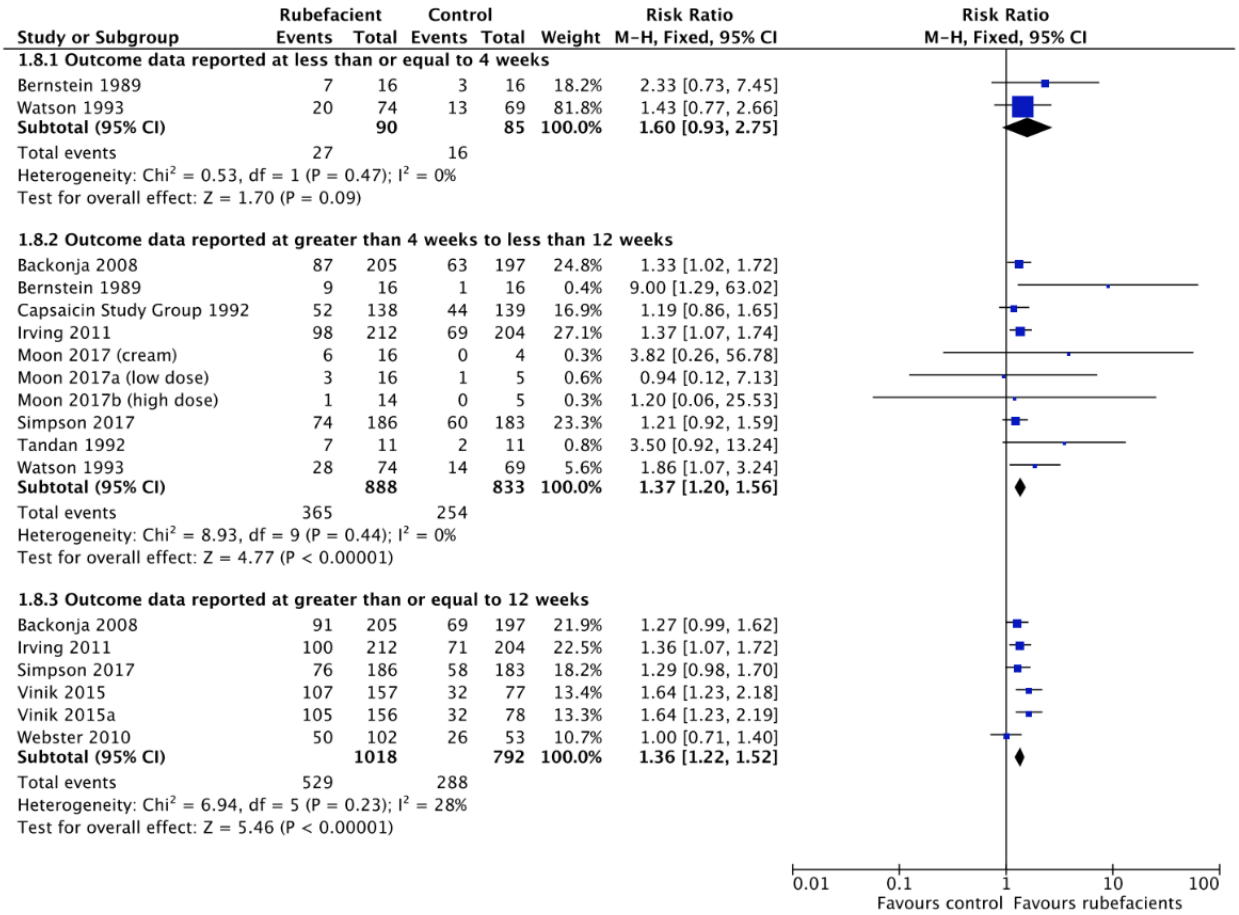


Study or Subgroup	Rubefacient Events	Rubefacient Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Backonja 2008	91	205	69	197	18.3%	1.27 [0.99, 1.62]
Bernstein 1989	9	16	1	16	0.3%	9.00 [1.29, 63.02]
Capsaicin Study Group 1992	52	138	44	139	11.4%	1.19 [0.86, 1.65]
Irving 2011	100	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); $I^2 = 21\%$

Test for overall effect: Z = 6.37 (P < 0.00001)

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



Study or Subgroup	Rubefacient Events	Rubefacient Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Outcome data reported at less than or equal to 4 weeks						
Bernstein 1989	7	16	3	16	18.2%	2.33 [0.73, 7.45]
Watson 1993	20	74	13	69	81.8%	1.43 [0.77, 2.66]
Subtotal (95% CI)		**90**		**85**	**100.0%**	**1.60 [0.93, 2.75]**
Total events	27		16			

Heterogeneity: $Chi^2 = 0.53$, df = 1 (P = 0.47); $I^2 = 0\%$

Test for overall effect: Z = 1.70 (P = 0.09)

1.8.2 Outcome data reported at greater than 4 weeks to less than 12 weeks						
Backonja 2008	87	205	63	197	24.8%	1.33 [1.02, 1.72]
Bernstein 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]
Irving 2011	98	212	69	204	27.1%	1.37 [1.07, 1.74]
Moon 2017 (cream)	6	16	0	4	0.3%	3.82 [0.26, 56.78]
Moon 2017a (low dose)	3	16	1	5	0.6%	0.94 [0.12, 7.13]
Moon 2017b (high dose)	1	14	0	5	0.3%	1.20 [0.06, 25.53]
Simpson 2017	74	186	60	183	23.3%	1.21 [0.92, 1.59]
Tandan 1992	7	11	2	11	0.8%	3.50 [0.92, 13.24]
Watson 1993	28	74	14	69	5.6%	1.86 [1.07, 3.24]
Subtotal (95% CI)		**888**		**833**	**100.0%**	**1.37 [1.20, 1.56]**
Total events	365		254			

Heterogeneity: $Chi^2 = 8.93$, df = 9 (P = 0.44); $I^2 = 0\%$

Test for overall effect: Z = 4.77 (P < 0.00001)

1.8.3 Outcome data reported at greater than or equal to 12 weeks						
Backonja 2008	91	205	69	197	21.9%	1.27 [0.99, 1.62]
Irving 2011	100	212	71	204	22.5%	1.36 [1.07, 1.72]
Simpson 2017	76	186	58	183	18.2%	1.29 [0.98, 1.70]
Vinik 2015	107	157	32	77	13.4%	1.64 [1.23, 2.18]
Vinik 2015a	105	156	32	78	13.3%	1.64 [1.23, 2.19]
Webster 2010	50	102	26	53	10.7%	1.00 [0.71, 1.40]
Subtotal (95% CI)		**1018**		**792**	**100.0%**	**1.36 [1.22, 1.52]**
Total events	529		288			

Heterogeneity: $Chi^2 = 6.94$, df = 5 (P = 0.23); $I^2 = 28\%$

Test for overall effect: Z = 5.46 (P < 0.00001)

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

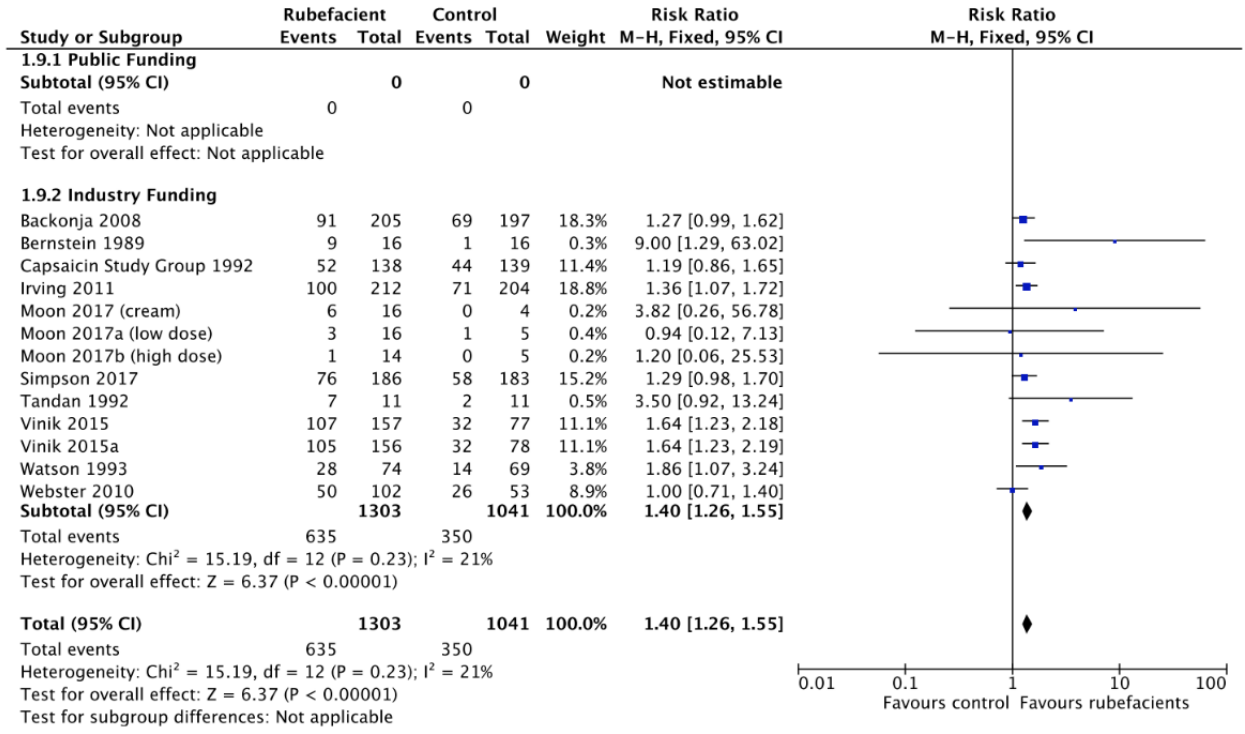
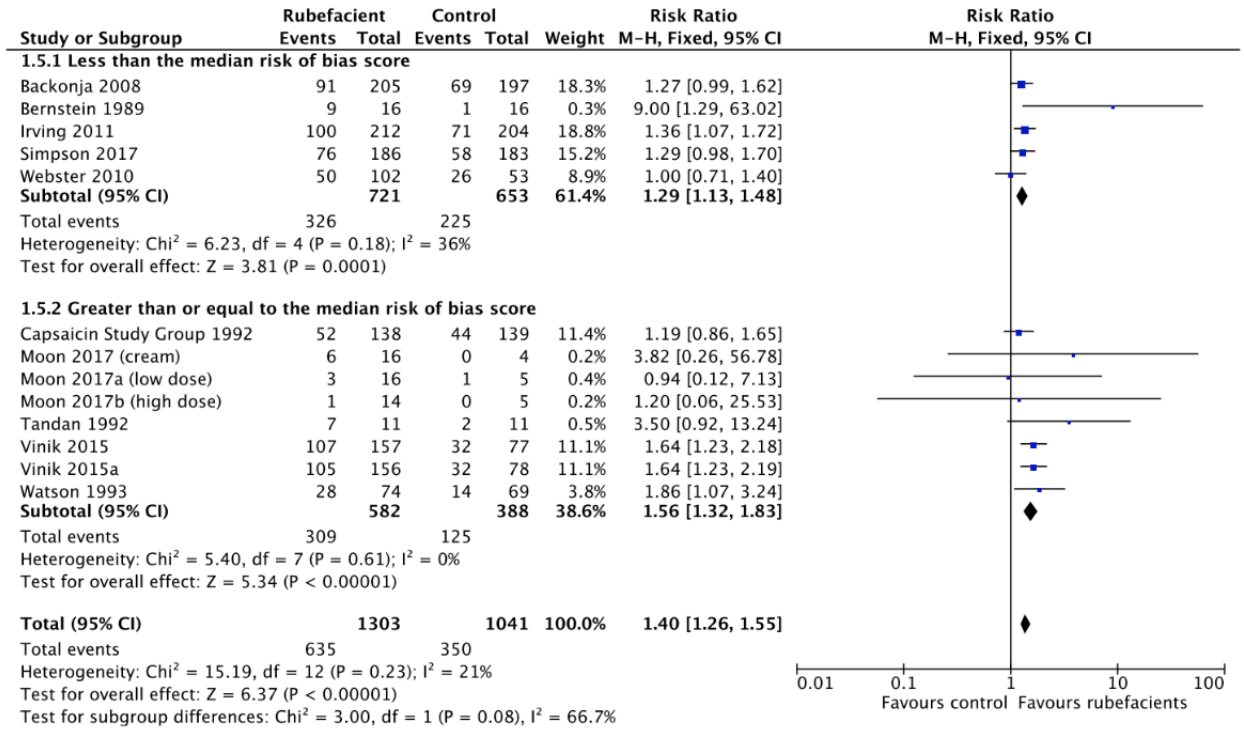


Figure 8.4: Rubefacients versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by median risk of bias



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

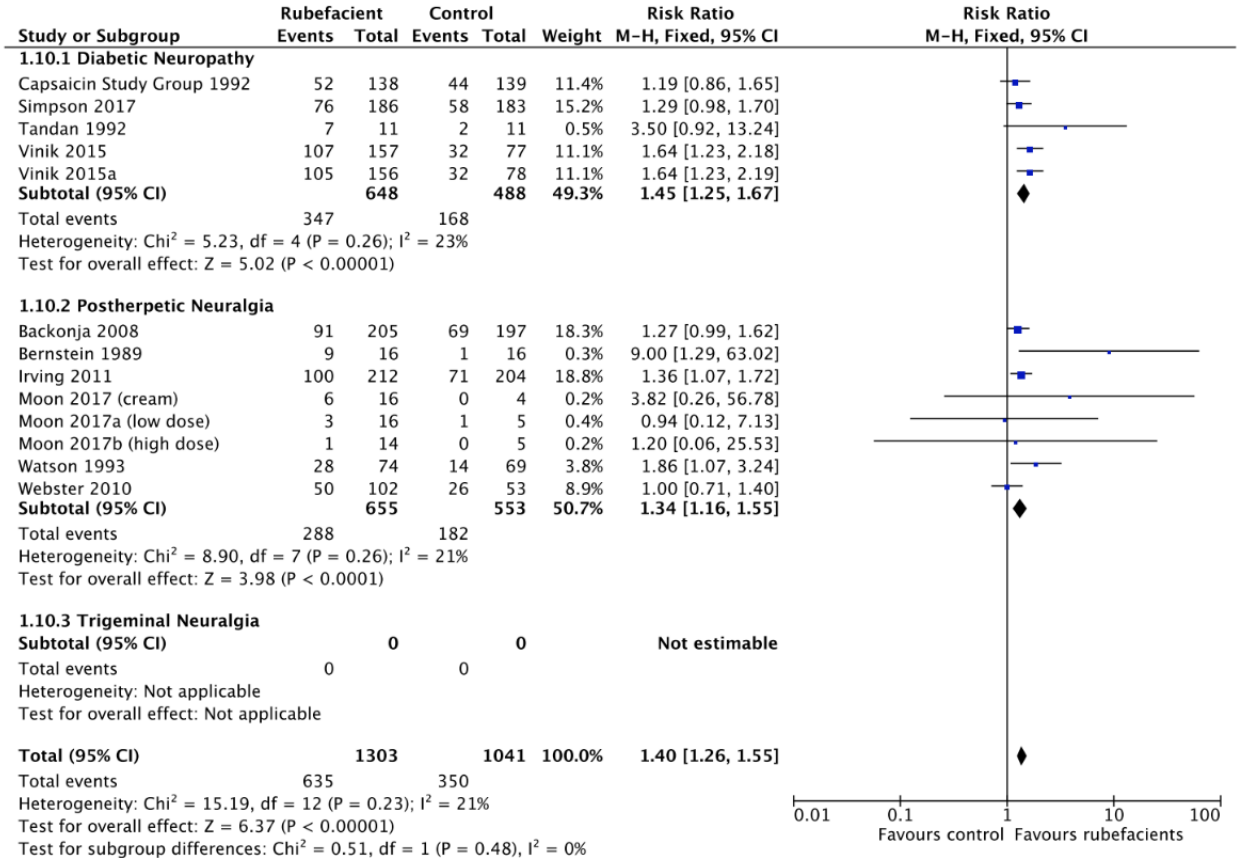


Figure 8.6: Rubefacients versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by drug type

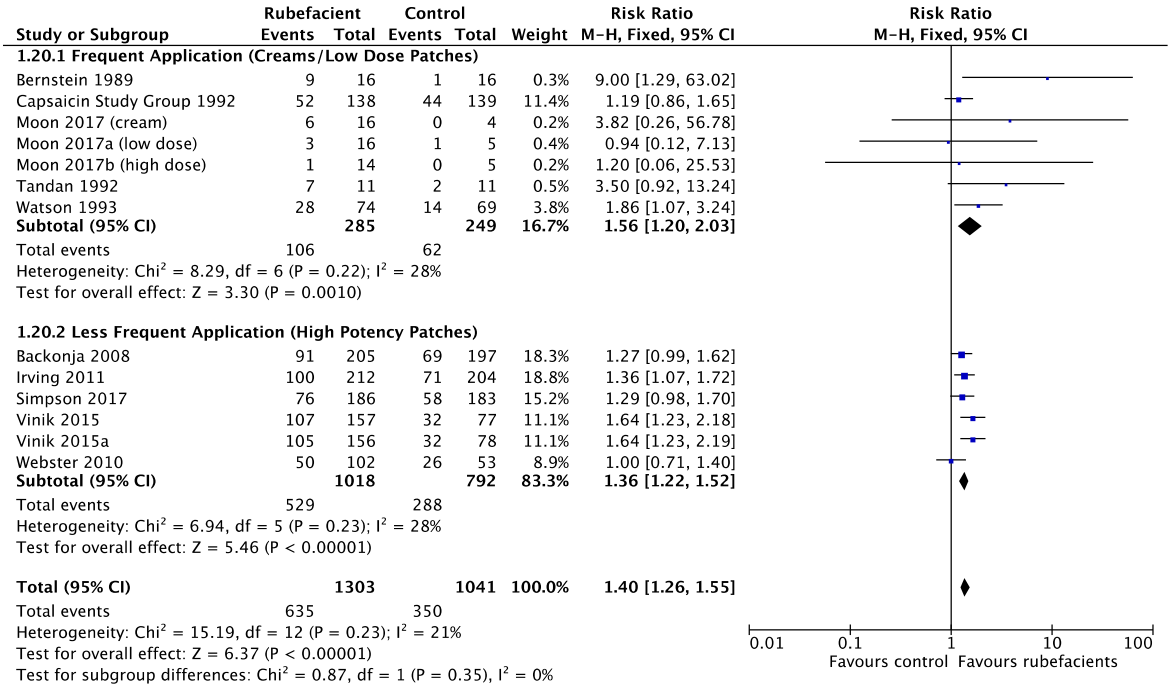
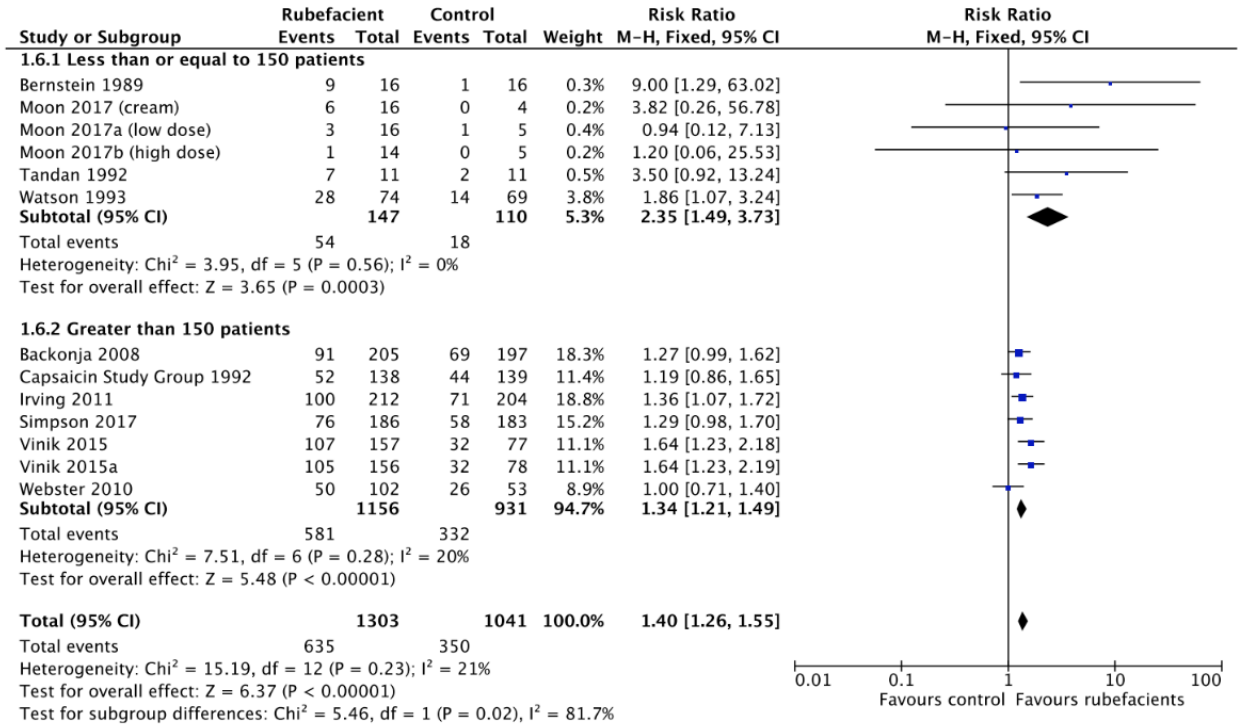


Figure 8.7: Rubefacients versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size



SNRIs

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

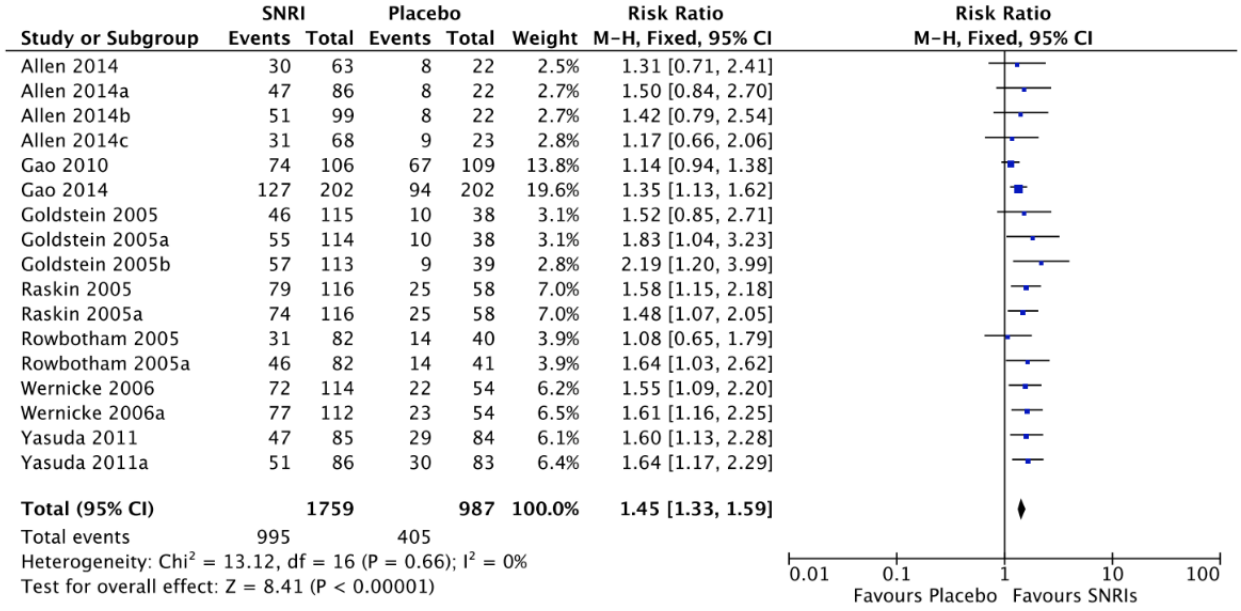


Figure 9.2: SNRIs versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater

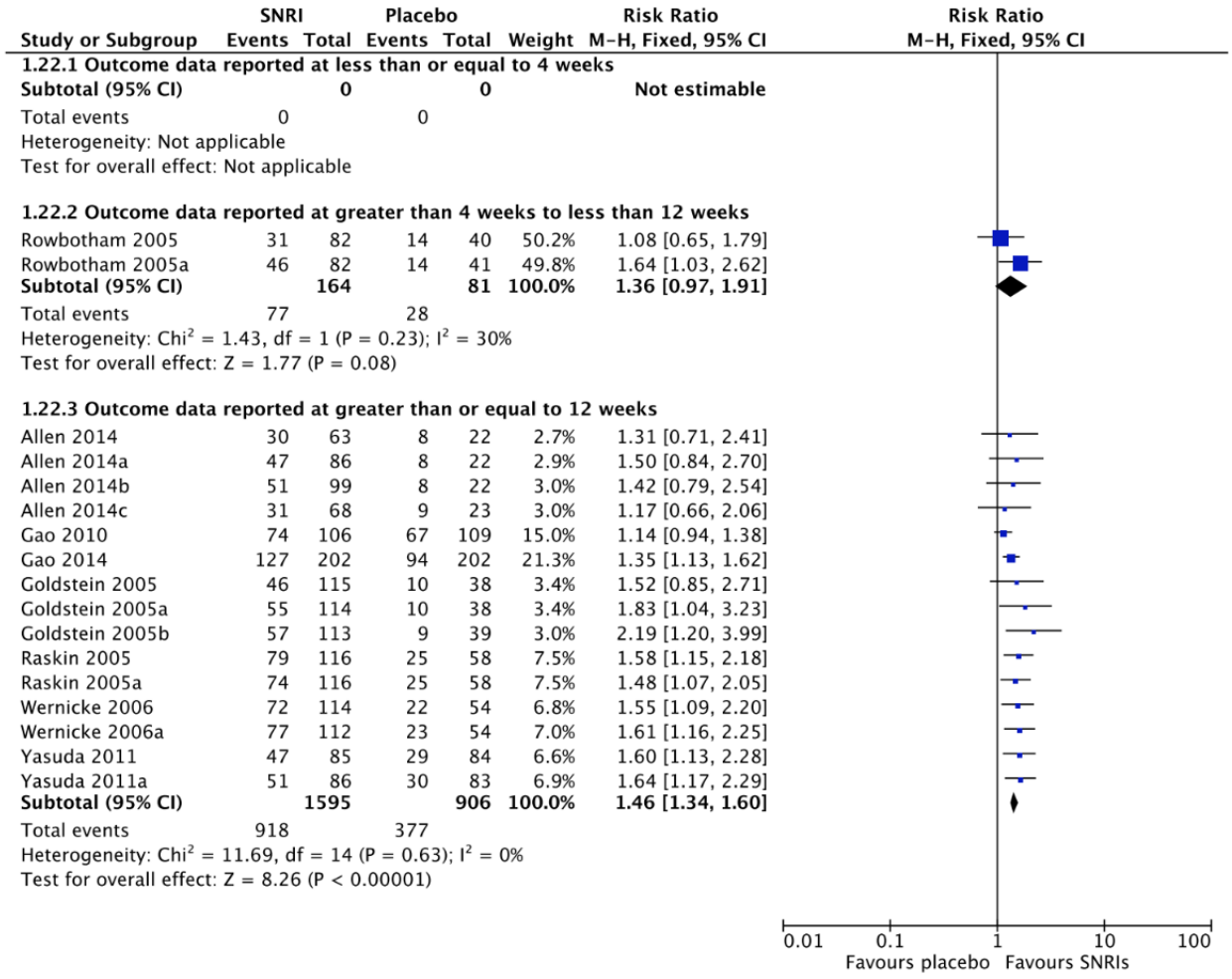


Figure 9.3: SNRIs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source

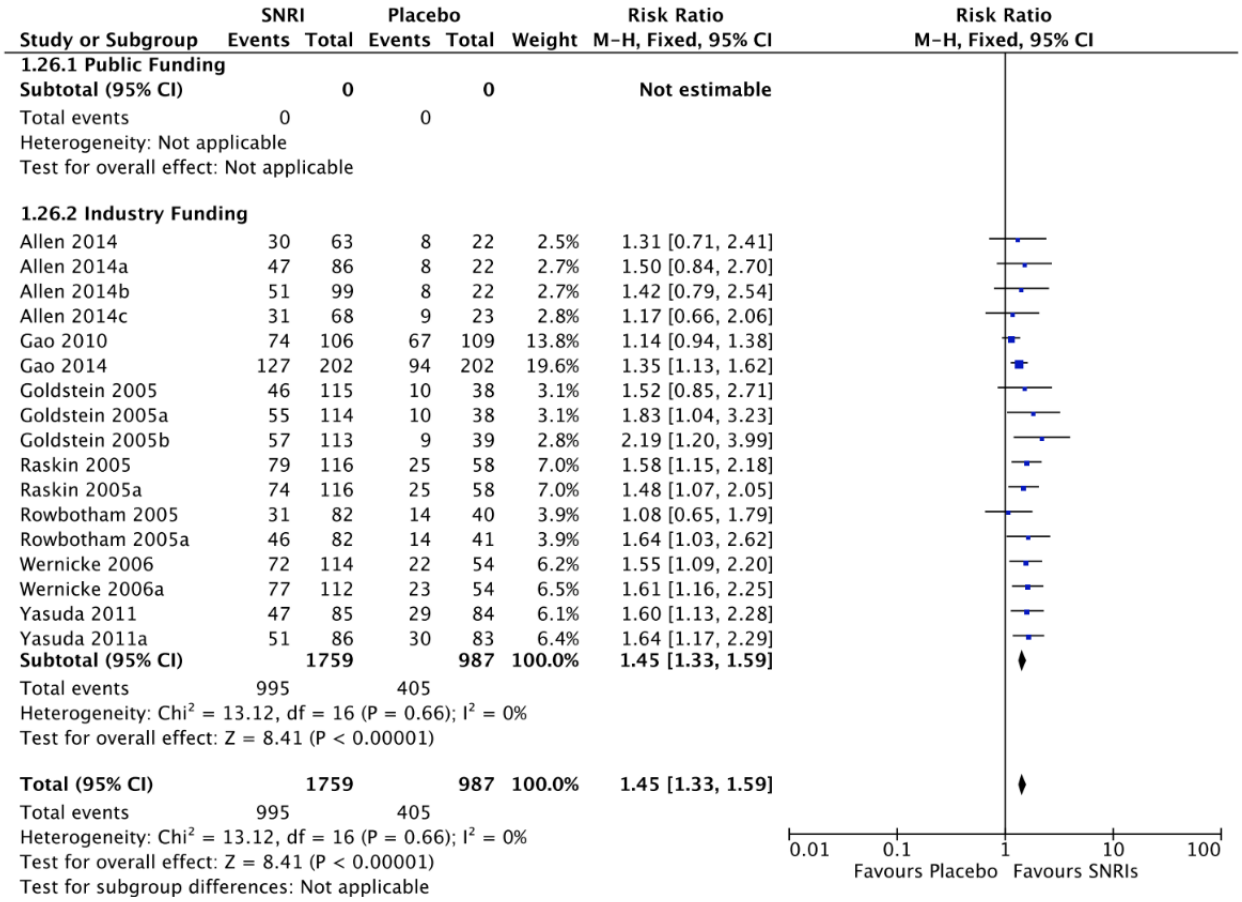
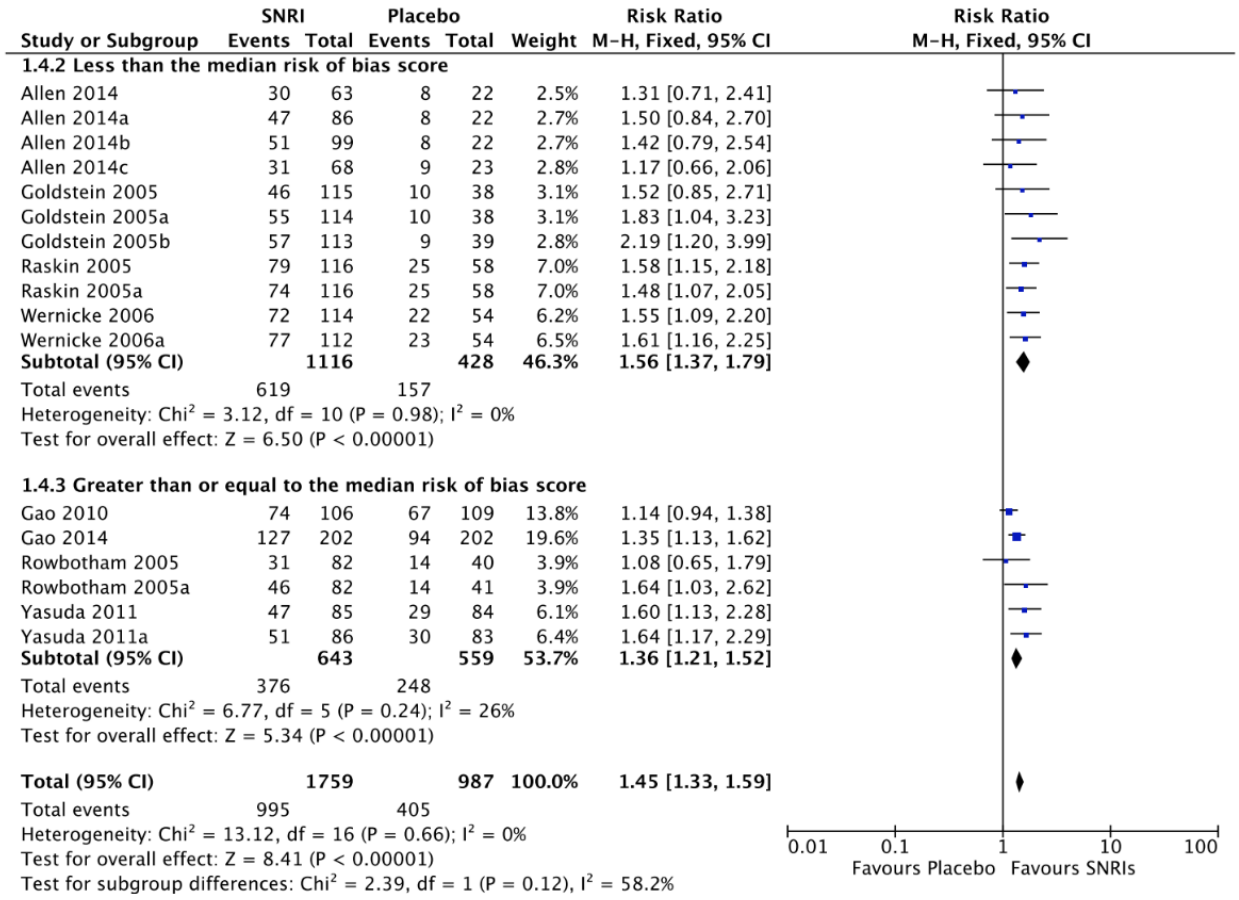


Figure 9.4: SNRIs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by median risk of bias



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)

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

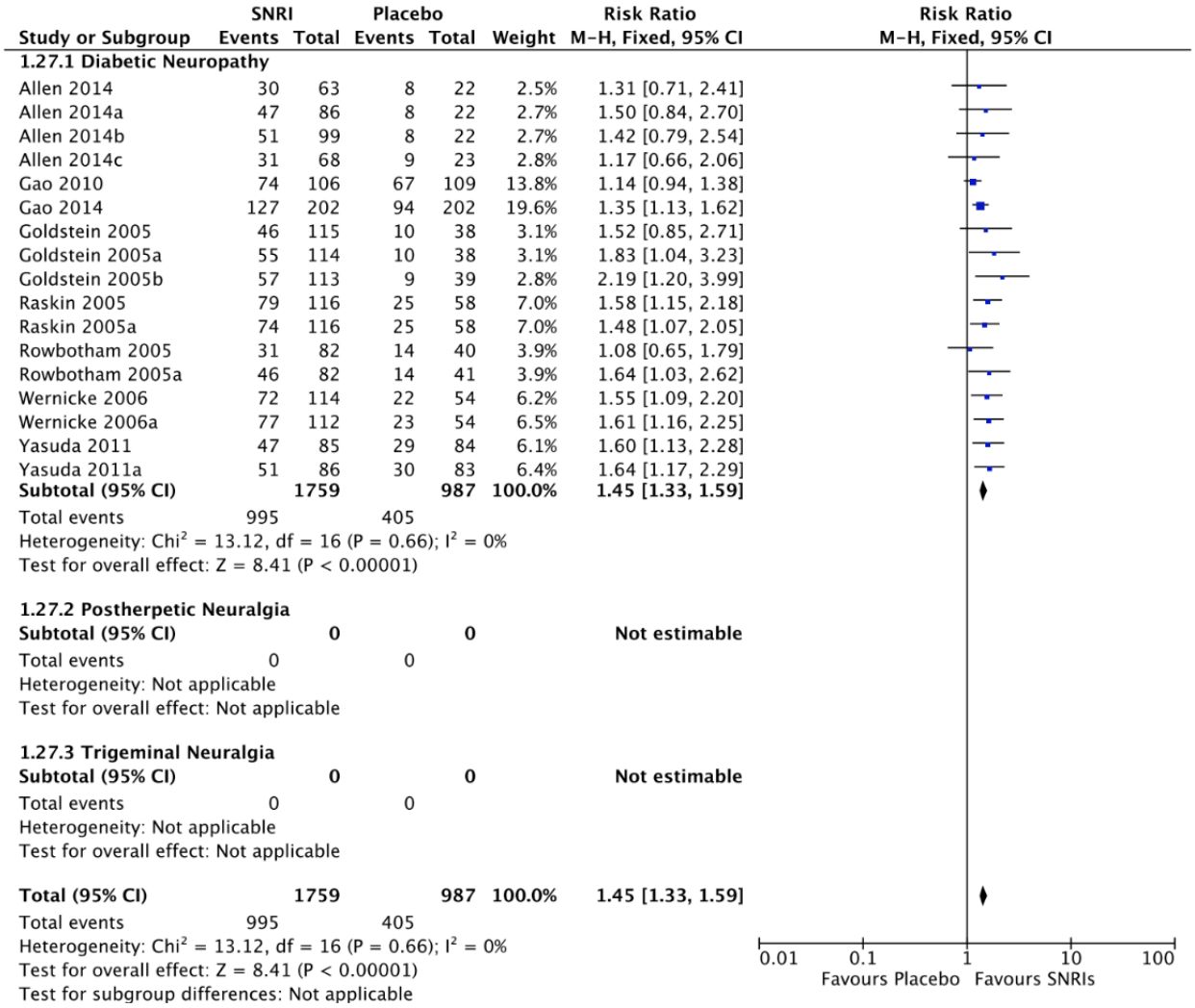


Figure 9.6: SNRIs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by drug type

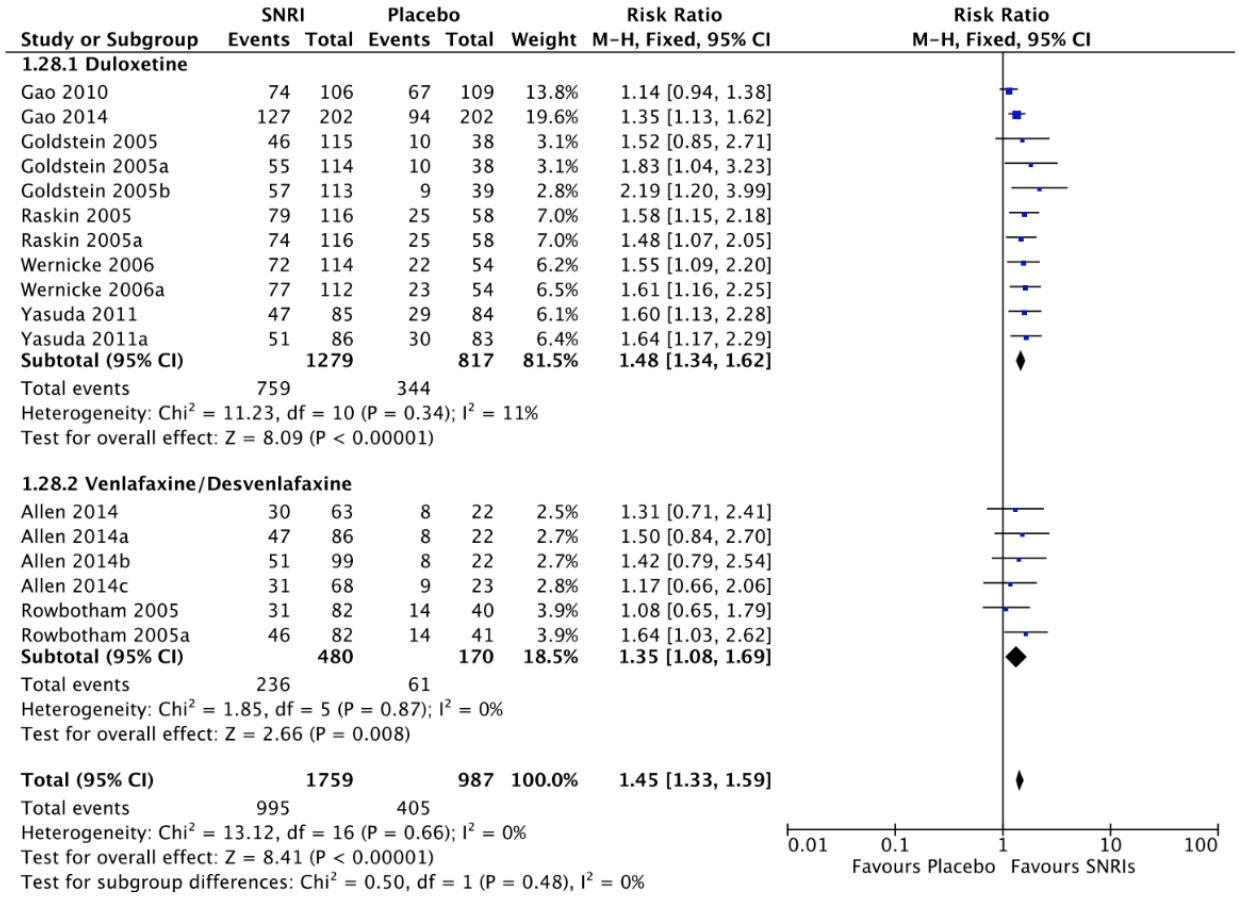
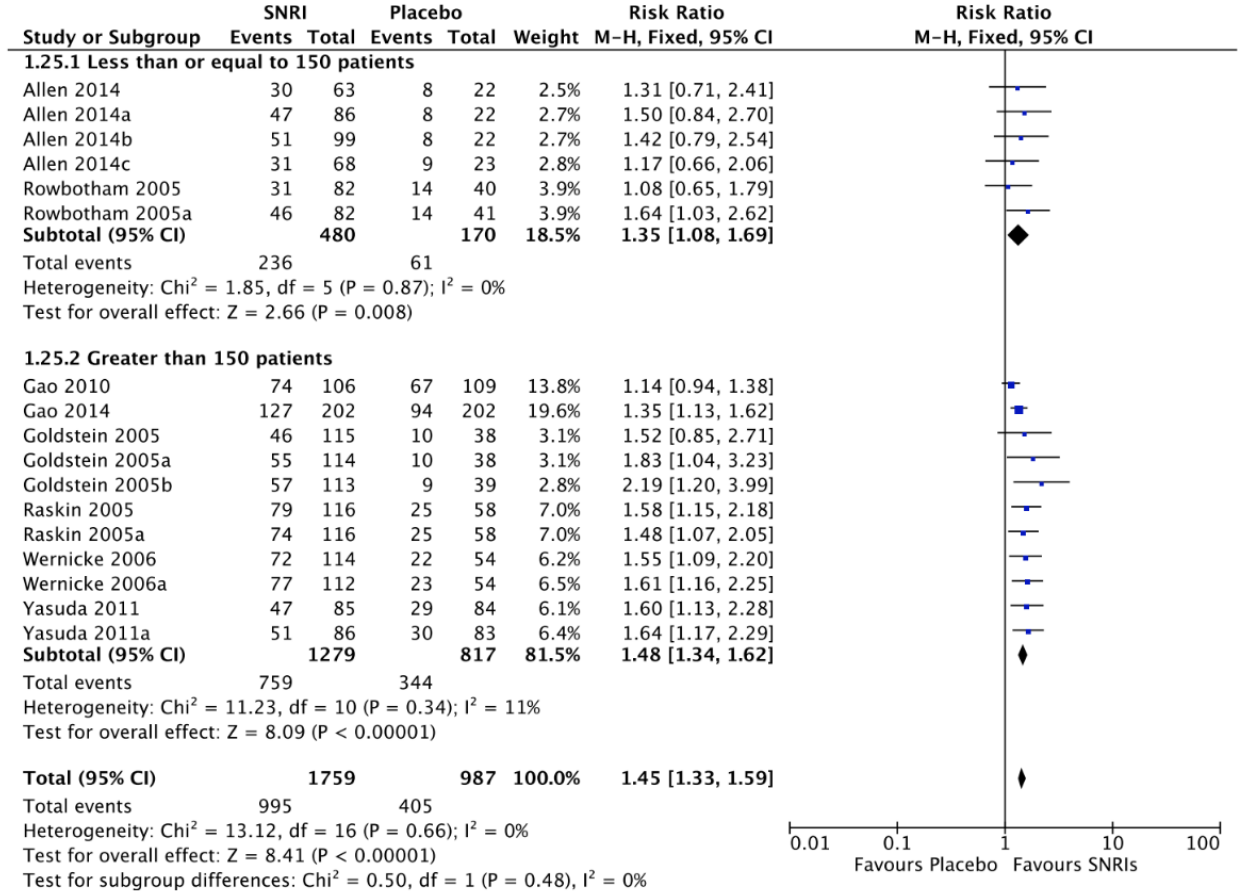


Figure 9.7: SNRIs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size



TCAs

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

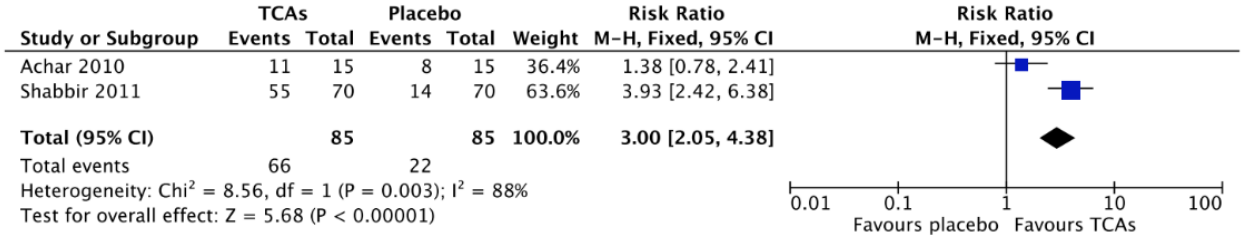


Figure 10.2: TCAs versus control; Outcome: Proportion of patients with a meaningful response to treatment (random effects)

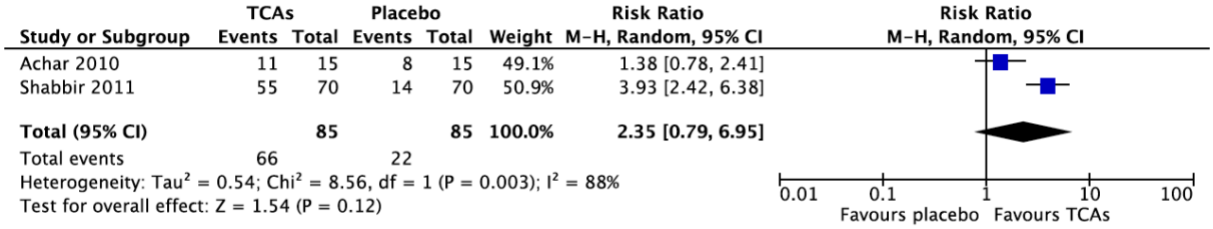


Figure 10.3: TCAs versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater (fixed effects)

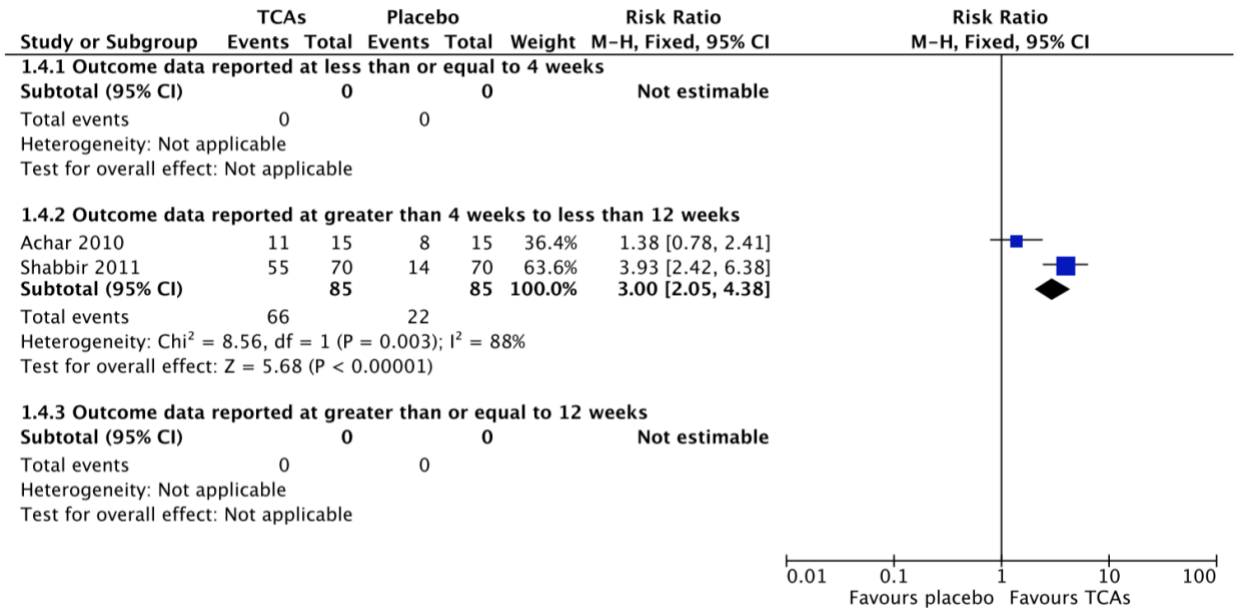


Figure 10.4: TCAs versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less, 4 weeks to 12 weeks, and 12 weeks or greater (random effects)

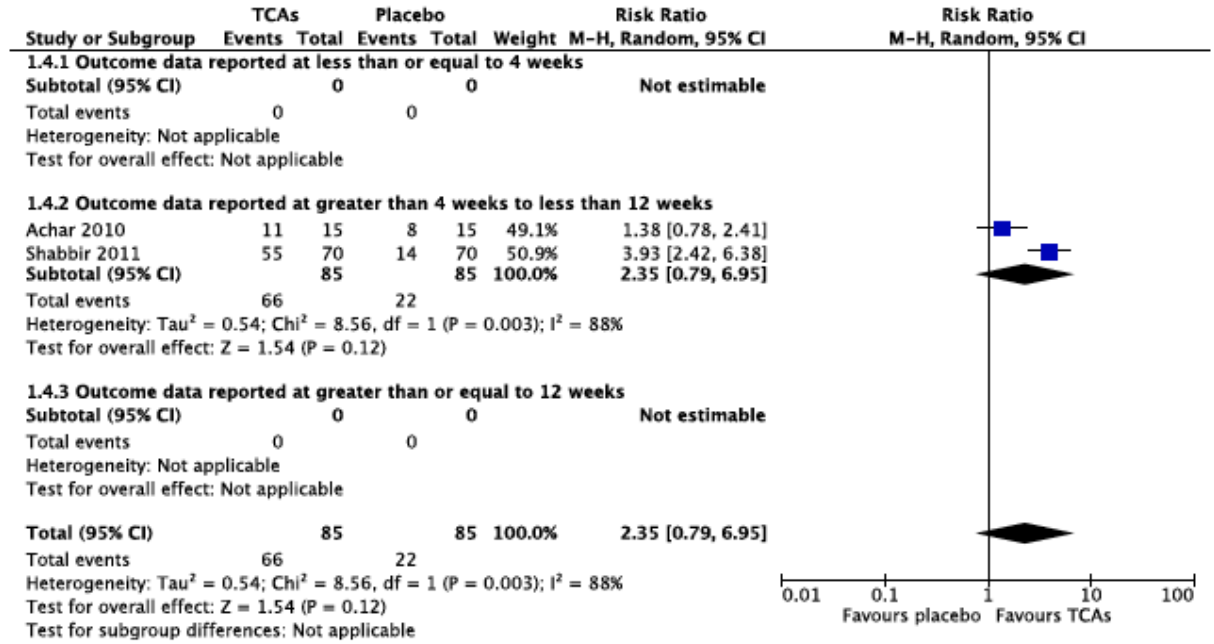


Figure 10.5: TCAs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by neuropathic pain type (fixed effects)

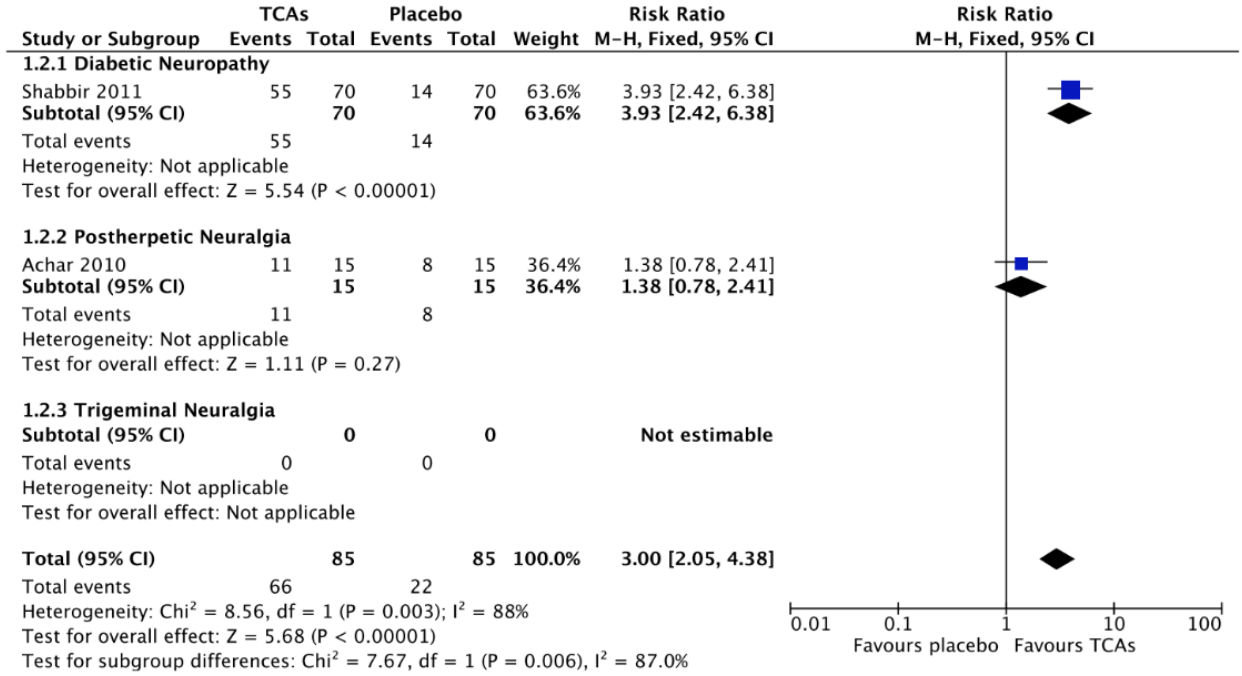


Figure 10.6: TCAs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by neuropathic pain type (random effects)

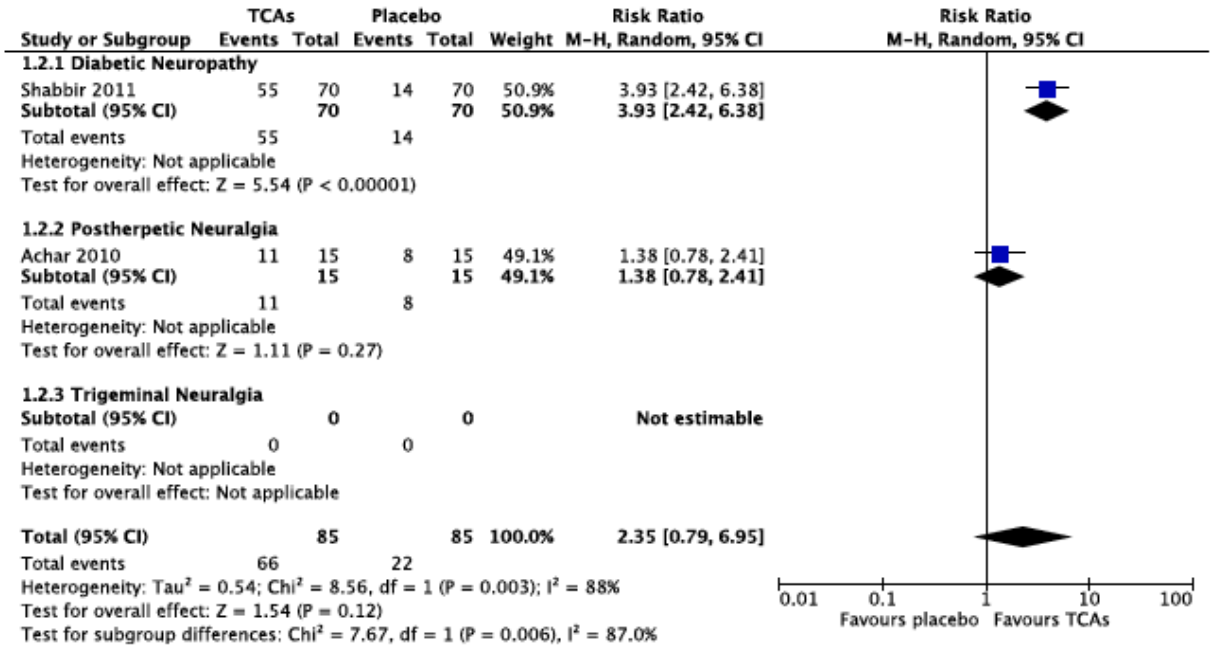


Figure 10.7: TCAs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size (fixed effects)

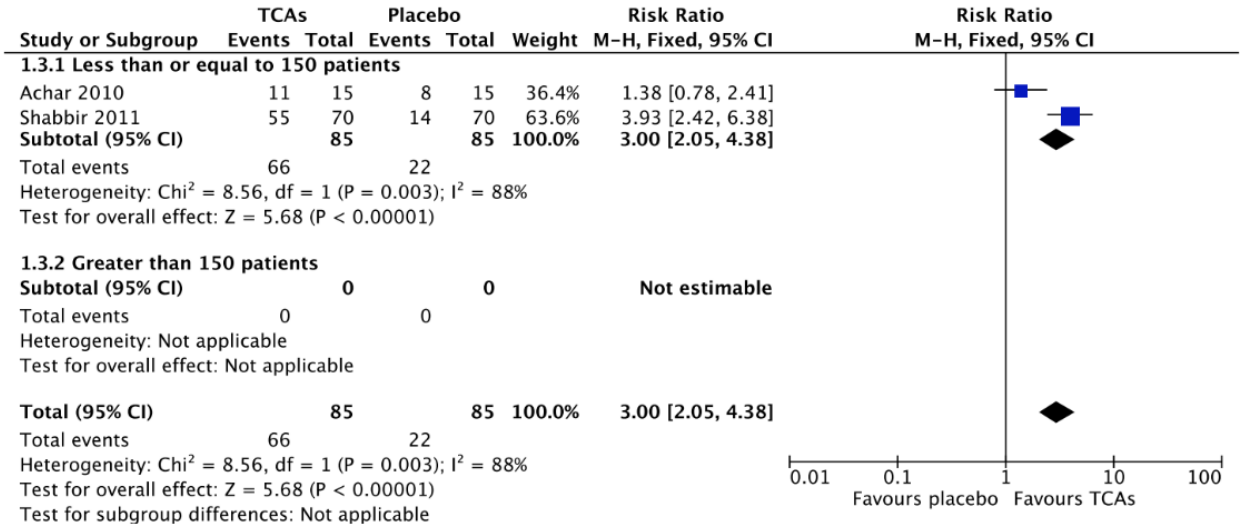
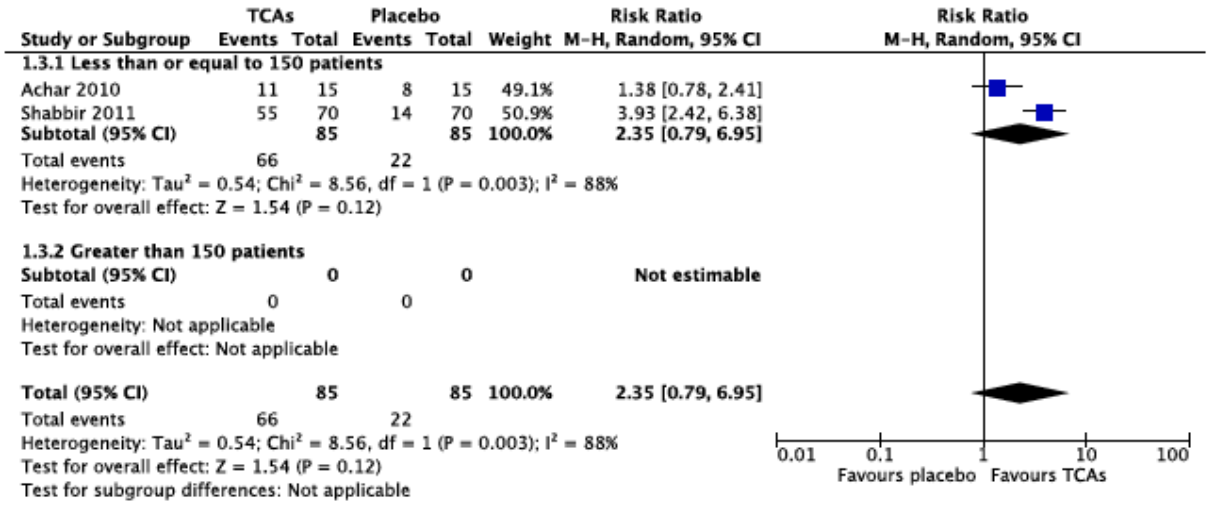


Figure 10.8: TCAs versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by sample size (random effects)



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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI	NSS

								0.04, 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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, 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI	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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI	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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI	

			Placebo					0.62, 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI	NSS

			Placebo					0.07, 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI	

			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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI	NSS

			for one, 60-minute session 0.04% Capsaicin Placebo Patch					0.19, 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI	NSS

								0.49, 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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	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% CI 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% CI 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% CI 1.92, 3.53)	12
Anticonvulsants (Gabapentin)	Arthralgia	Rauck 2012 Zhang 2013	2	695	4% (21/510)	3% (6/185)	RR 1.23 (95% CI 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% CI 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% CI 0.43, 3.19)	NSS
Anticonvulsants (Gabapentin)	Constipation	Rauck 2012 Zhang 2013	2	695	5% (26/510)	4% (8/185)	RR 1.20 (95% CI 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% CI 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% CI 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% CI 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% CI 0.71, 7.87)	NSS
Anticonvulsants (Gabapentin)	Insomnia	Backonja 2011 Zhang 2013	2	472	4% (13/323)	4% (6/149)	RR 0.97 (95% CI 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% CI 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% CI 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% CI 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% CI 0.59, 3.48)	NSS
Anticonvulsants (Oxcarbazepine)	Back Pain	CTRI476G2301 Dogra 2005	2	266	8% (10/126)	2% (3/140)	RR 3.82 (95% CI 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% CI 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% CI 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% CI 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% CI 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% CI 1.33, 4.34)	10
Anticonvulsants (Oxcarbazepine)	Diarrhea	CTRI476G2301 Dogra 2005	2	266	4% (5/126)	6% (8/140)	RR 0.67 (95% CI 0.22, 2.05)	NSS
Anticonvulsants (Oxcarbazepine)	Tremor	Beydoun 2006 Dogra 2005	2	469	5% (15/310)	2% (3/159)	RR 2.01 (95% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 0.34, 7.57)	NSS
Anticonvulsants (Pregabalin)	Contusion	NCT00394901 2006 Stacey 2008	2	640	3% (14/452)	1% (2/188)	RR 1.92 (95% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 0.11, 1.11)	NSS
Anticonvulsants (Pregabalin)	Infection	Lesser 2004 Richter 2005	5	1125	7% (51/684)	6% (27/441)	RR 1.34 (95% CI 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% CI 0.61, 2.17)	NSS
Anticonvulsants (Pregabalin)	Lethargy	Guan 2011 Stacey 2008	2	577	5% (18/385)	2% (3/192)	RR 2.63 (95% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 1.78, 3.50)	10
Opioids	Dry Mouth	Jensen 2006 NCT01124617 2010	2	250	10% (14/142)	2% (2/108)	RR 5.01 (95% CI 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% CI 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% CI 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% CI 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% CI 1.90, 6.72)	11
Opioids	Asthenia	Jensen 2006 NCT01124617 2010	2	250	8% (12/142)	6% (6/108)	RR 1.68 (95% CI 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% CI 0.57, 3.26)	NSS
Opioids	Generalized Pain	Freeman 2007 NCT01124617 2010	2	404	2% (4/220)	5% (9/184)	RR 0.38 (95% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 1.46, 4.91)	22
Rubefacients	Sinusitis	Backonja 2008 Irving 2011	2	818	3% (12/417)	0.5% (2/401)	RR 5.77 (95% CI 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% CI 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% CI 2.79, 7.72)	5
Rubefacients	Vomiting	Backonja 2008 Irving 2011	2	818	3% (12/417)	0.7% (3/401)	RR 3.43 (95% CI 1.06, 11.14)	47
Rubefacients	Back Pain	Backonja 2008 Webster 2010	2	557	3% (9/307)	2% (5/250)	RR 1.47 (95% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 1.47, 7.86)	24
SNRIs	Asthenia	Gao 2010 Gao 2014	2	619	5% (16/308)	0.3% (1/311)	RR 11.16 (95% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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

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

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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 2.69, 3.92)	8

		Huffman 2015 Lesser 2004 Liu 2017 McDonnell 2018 Mu 2018 NCT00394901 2006 NCT02215252 2014 Rauck 2012 Richter 2005 Rosenstock 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 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% CI 2.71, 4.21)	10
Opioids	Constipation	Freeman 2007 Hanna 2008	5	963	24% (122/500)	7% (31/463)	RR 3.72 (95% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 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% CI 2.31, 4.13)	9

Table 14: Withdrawals Due to Adverse Events

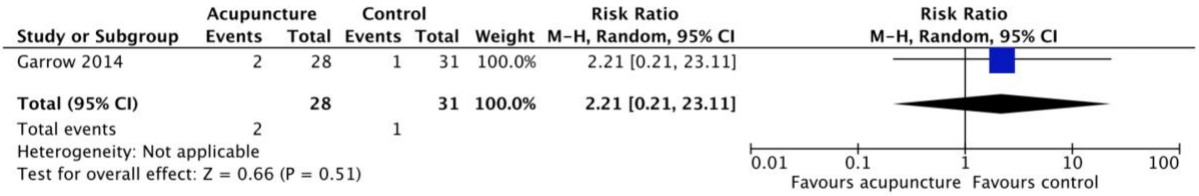
Intervention Type	Number of RCTs	Intervention Event Rate	Control Event Rate	Risk Ratio (95% CI)	NNH
Acupuncture	1	7% (2/28)	3% (1/31)	RR 2.21 (95% CI 0.21, 23.11)	NSS
Anticonvulsants (Gabapentin)	8	13% (184/1470)	8% (72/911)	RR 1.47 (95% CI 1.13, 1.91)	22
Anticonvulsants (Oxcarbazepine)	3	26% (102/395)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

CI: 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



Anticonvulsants (Gabapentin)

Figure 12.1 Gabapentin versus control; Withdrawals due to Adverse Events

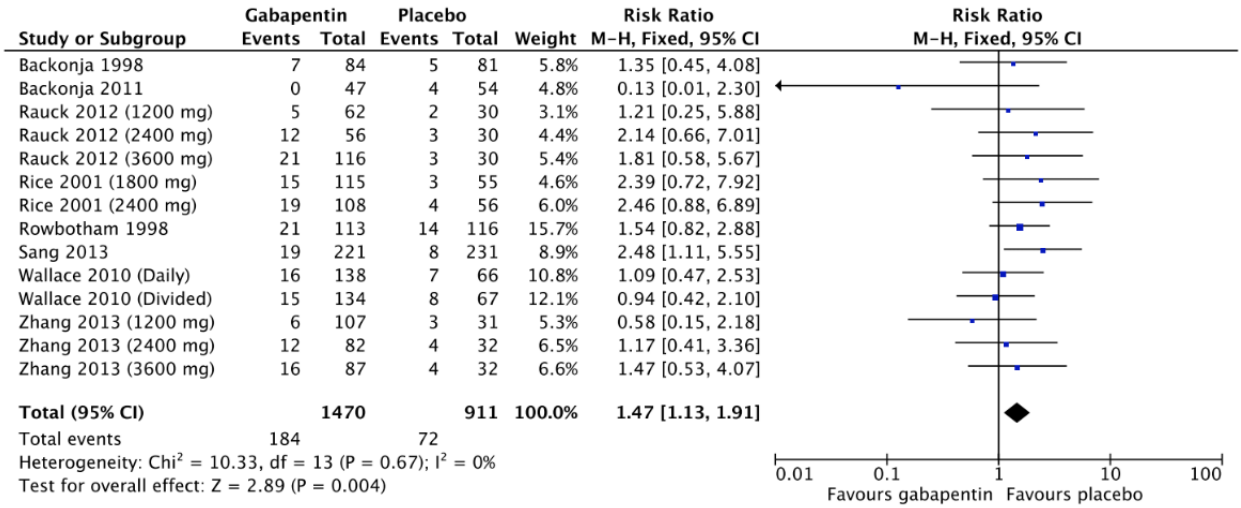


Figure 12.2 Gabapentin versus control; Adverse Event: Arthralgia

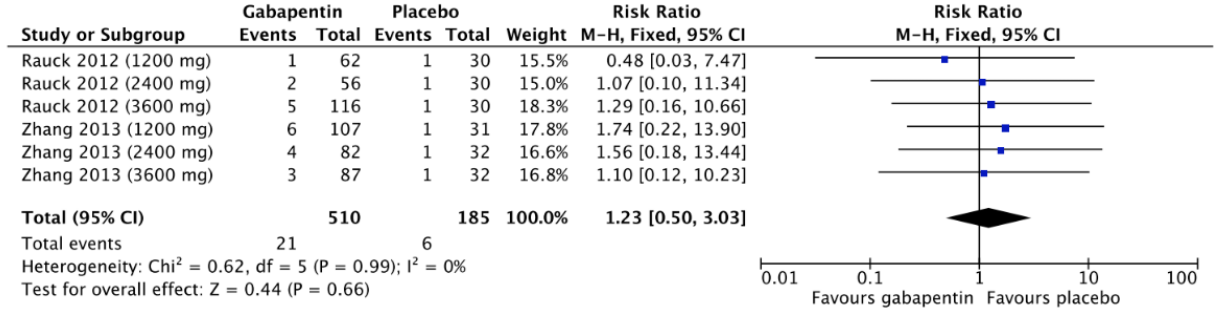


Figure 12.3 Gabapentin versus control; Adverse Event: Back Pain

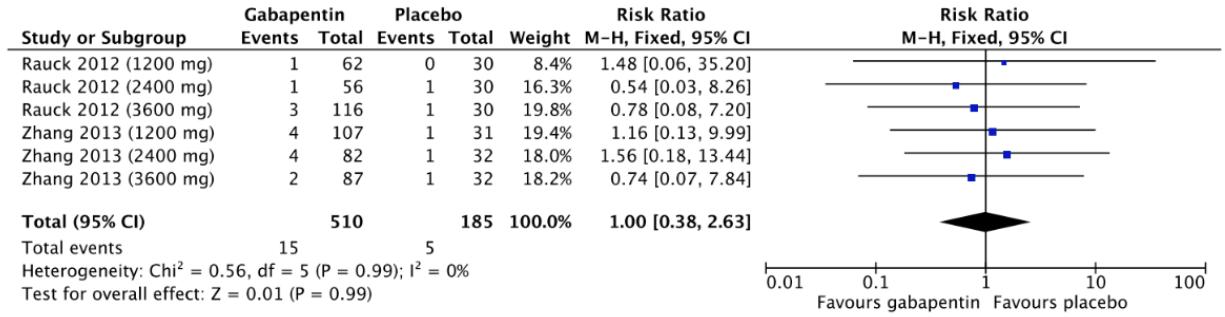


Figure 12.4 Gabapentin versus control; Adverse Event: Blurred Vision

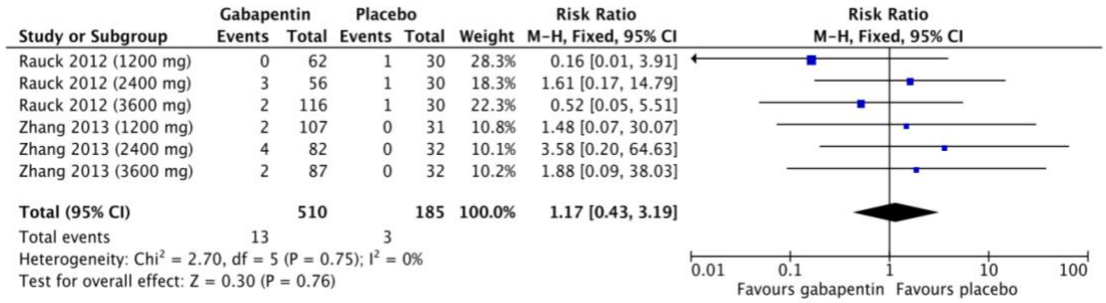


Figure 12.5 Gabapentin versus control; Adverse Event: Constipation

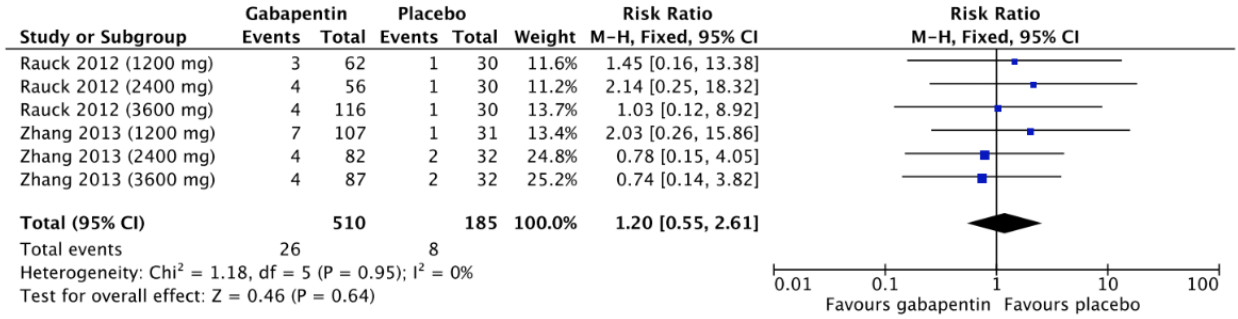


Figure 12.6 Gabapentin versus control; Adverse Event: Diarrhea

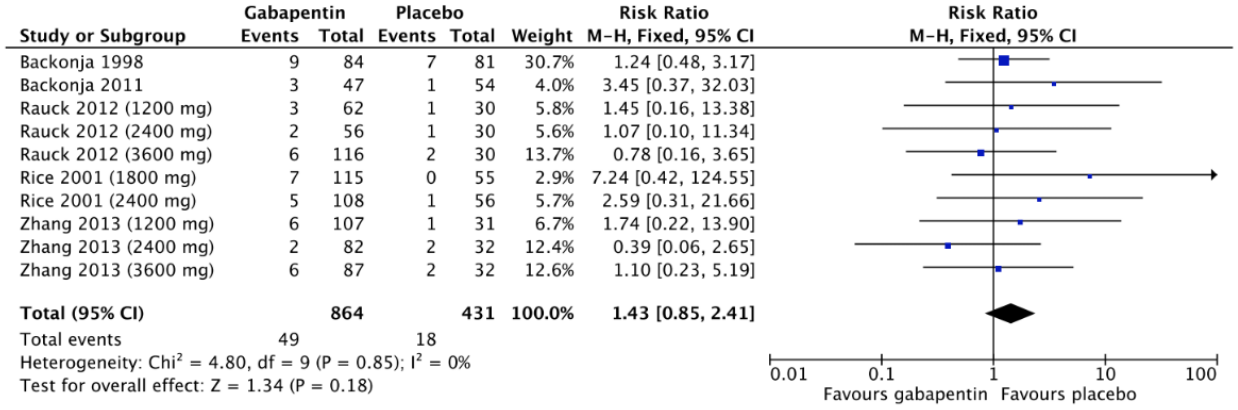


Figure 12.7 Gabapentin versus control; Adverse Event: Dizziness

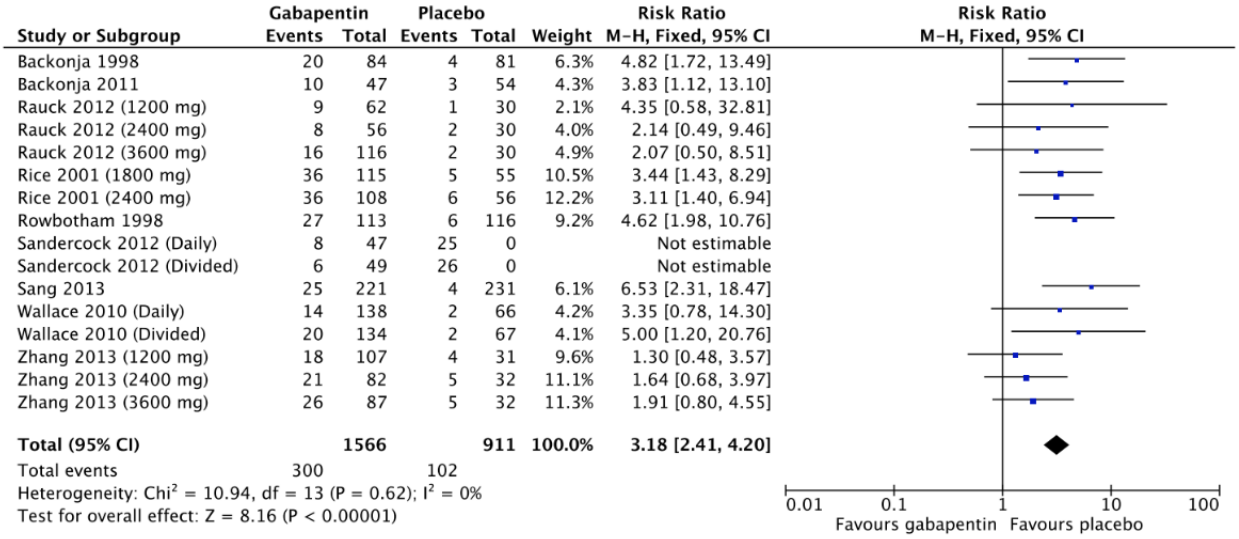


Figure 12.8 Gabapentin versus control; Adverse Event: Dry Mouth

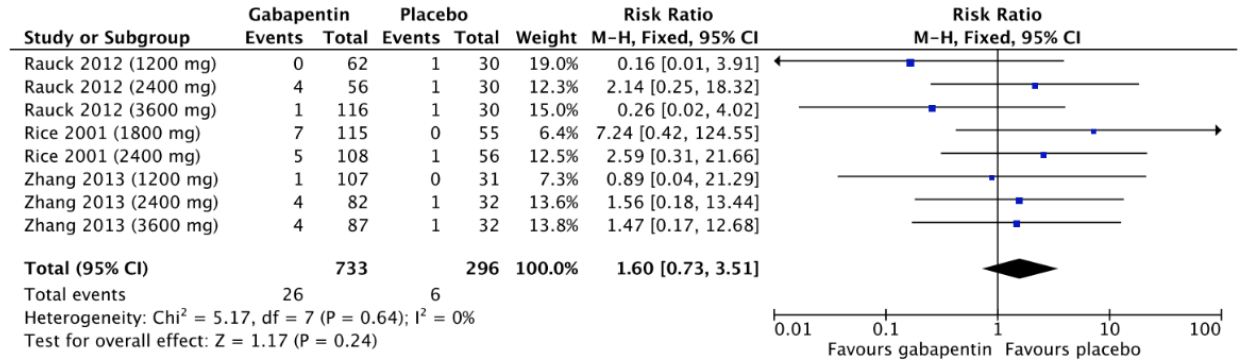


Figure 12.9 Gabapentin versus control; Adverse Event: Headache

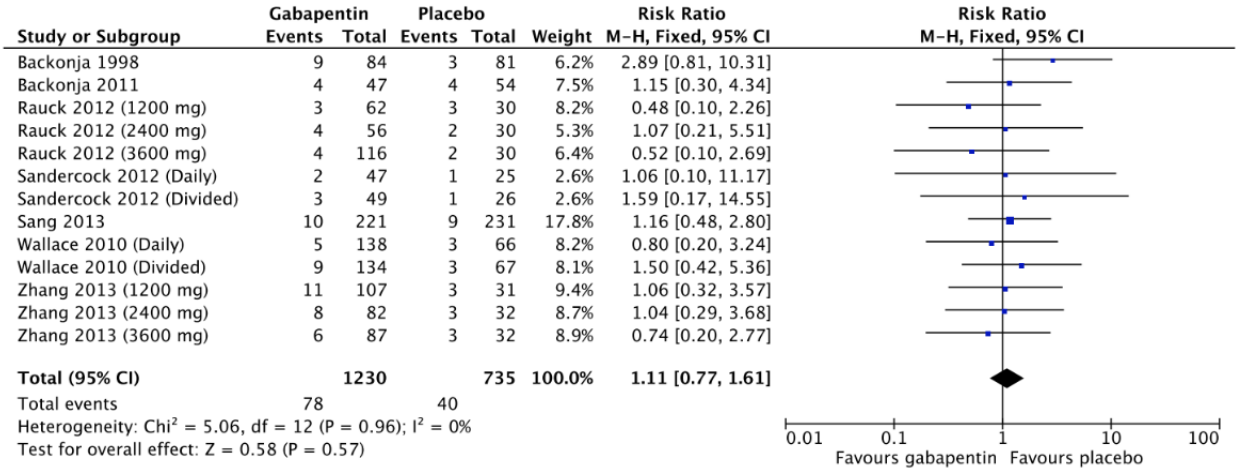


Figure 12.10 Gabapentin versus control; Adverse Event: Increased Weight

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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); $I^2 = 0\%$
Test for overall effect: Z = 1.40 (P = 0.16)

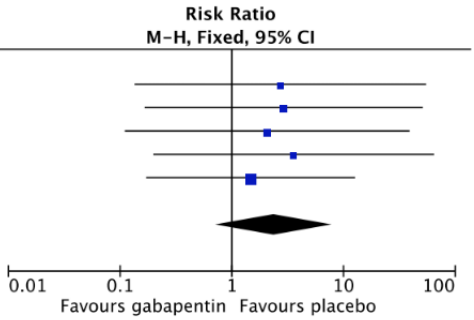


Figure 12.11 Gabapentin versus control; Adverse Event: Insomnia

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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 (P = 0.40); $I^2 = 0\%$
Test for overall effect: Z = 0.06 (P = 0.95)

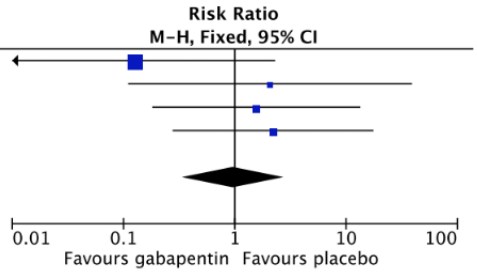


Figure 12.12 Gabapentin versus control; Adverse Event: Nasopharyngitis

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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]
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]
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)

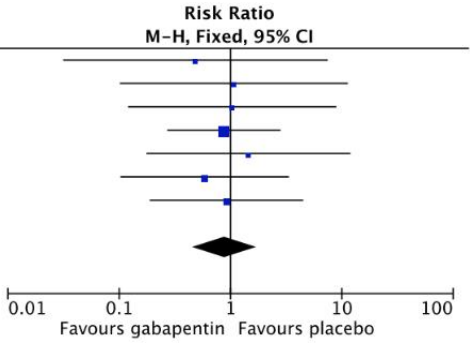


Figure 12.13 Gabapentin versus control; Adverse Event: Nausea

Study or Subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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]
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 = 0.98); $I^2 = 0\%$
Test for overall effect: Z = 1.34 (P = 0.18)

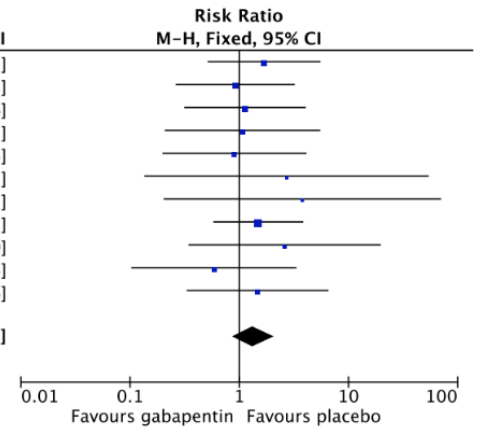


Figure 12.14 Gabapentin versus control; Adverse Event: Peripheral Edema

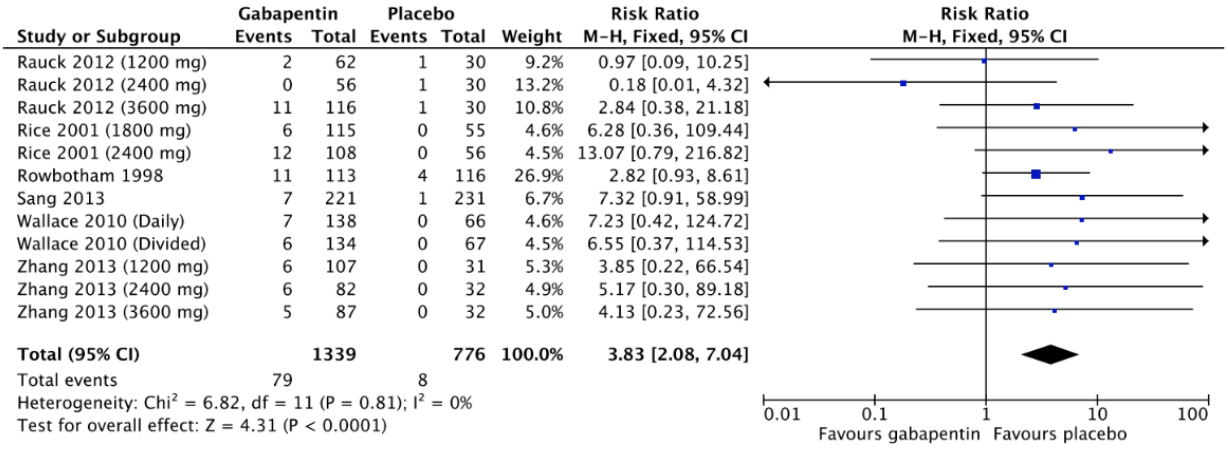


Figure 12.15 Gabapentin versus control; Adverse Event: Serious Adverse Events

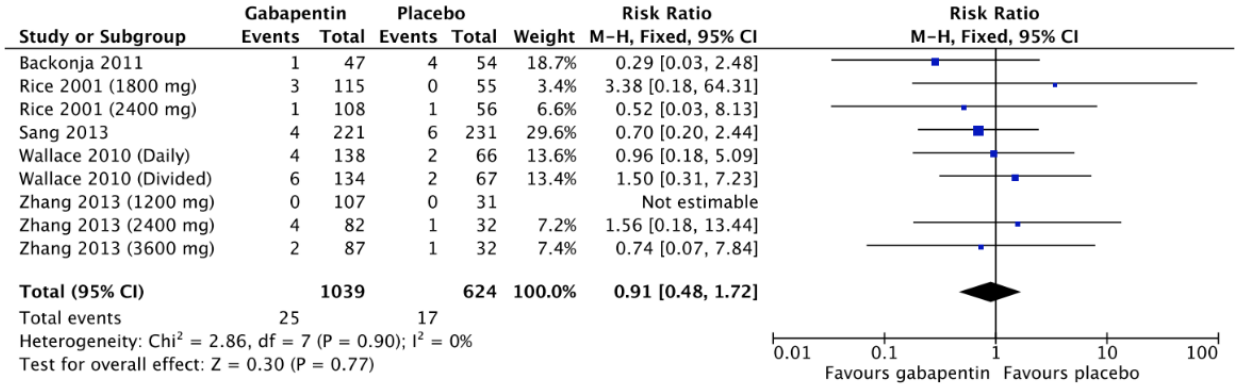


Figure 12.16 Gabapentin versus control; Adverse Event: Somnolence and Fatigue

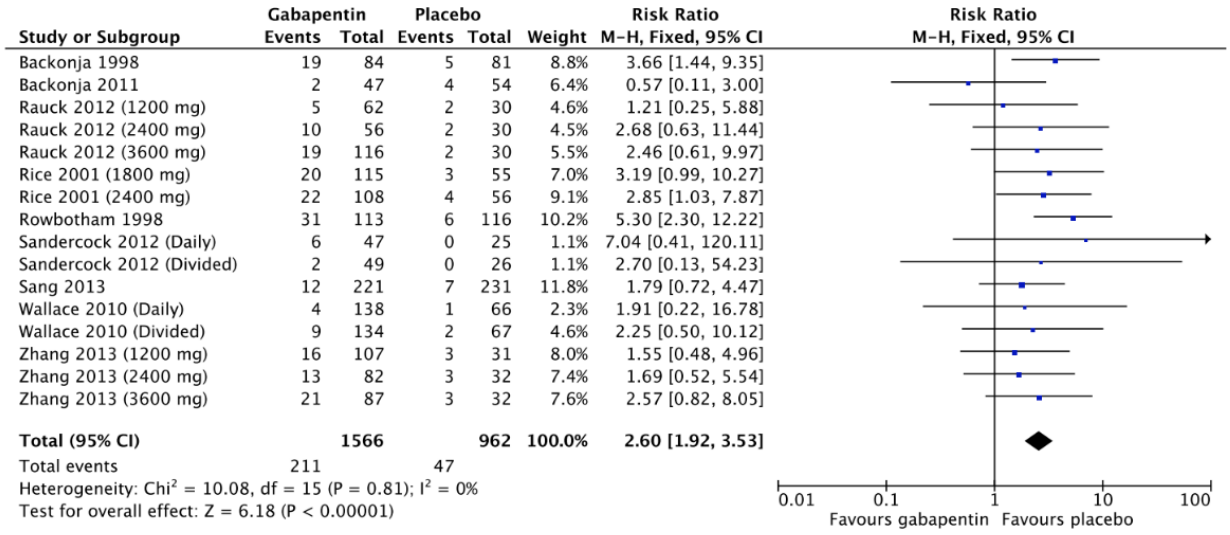
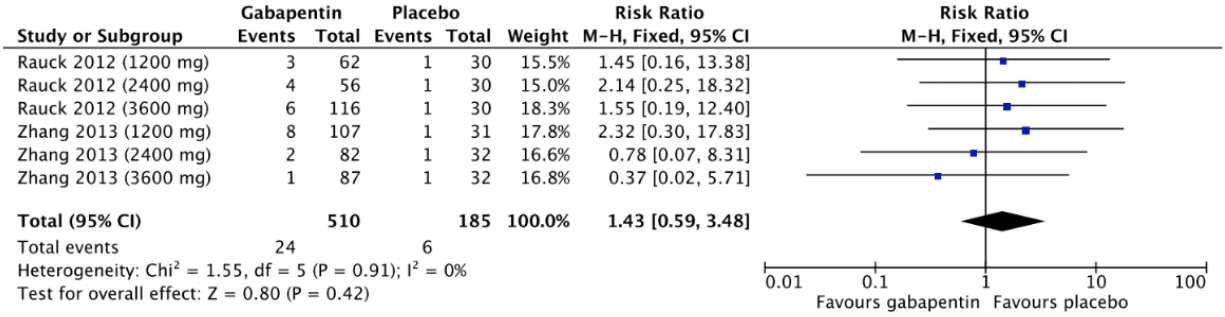


Figure 12.17 Gabapentin versus control; Adverse Event: Urinary Tract Infection



Anticonvulsants (Oxcarbazepine)

Figure 13.1 Oxcarbazepine versus control; Withdrawals due to Adverse Events

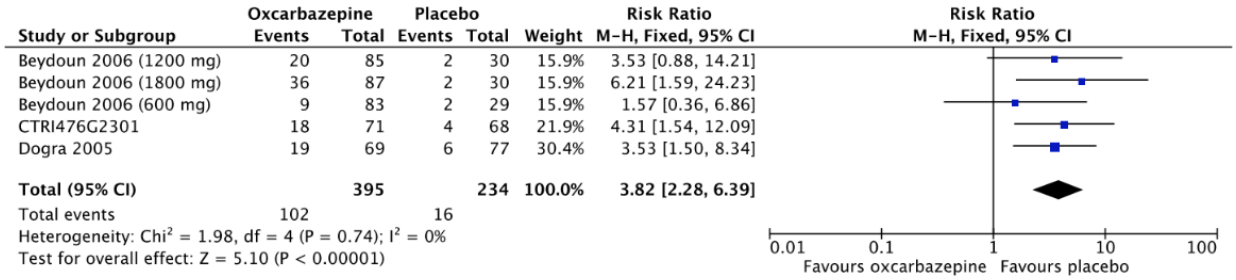


Figure 13.2 Oxcarbazepine versus control; Adverse Event: Back Pain

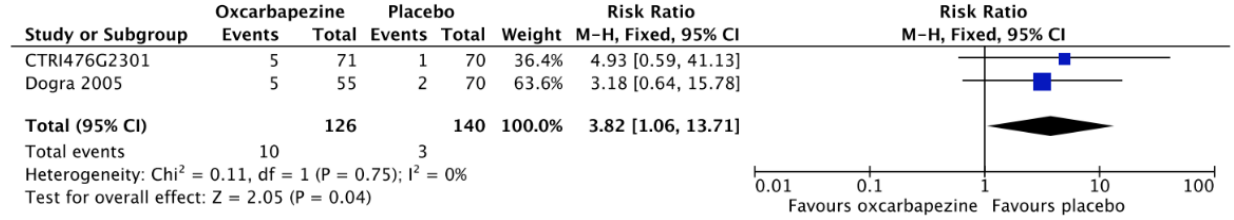


Figure 13.3 Oxcarbazepine versus control; Adverse Event: Diarrhea

Figure 13.4 Oxcarbazepine versus control; Adverse Event: Dizziness

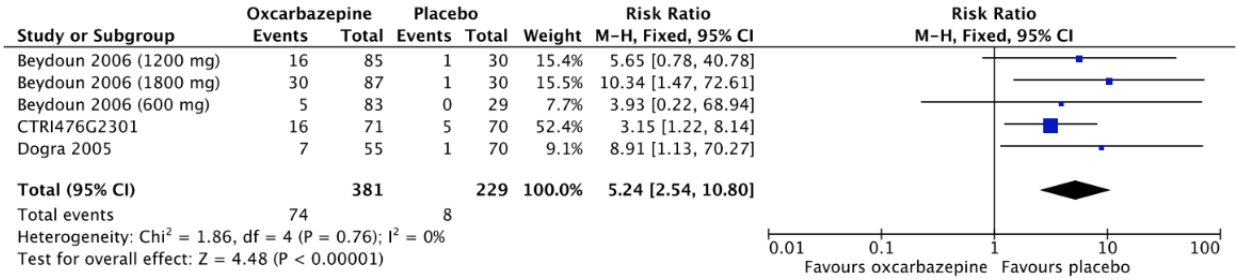


Figure 13.5 Oxcarbazepine versus control; Adverse Event: Headache

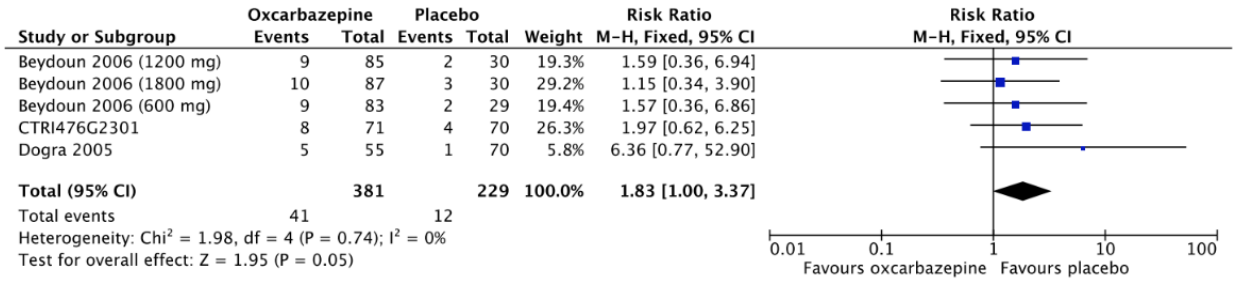


Figure 13.6 Oxcarbazepine versus control; Adverse Event: Nausea

Study or Subgroup	Oxcarbazepine Events	Oxcarbazepine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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); $I^2 = 8\%$
Test for overall effect: Z = 3.41 (P = 0.0007)

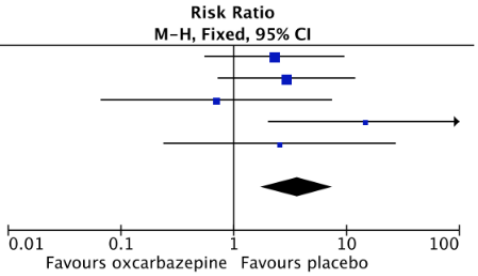


Figure 13.7 Oxcarbazepine versus control; Adverse Event: Serious Adverse Events

Study or Subgroup	Oxcarbazepine Events	Oxcarbazepine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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); $I^2 = 0\%$
Test for overall effect: Z = 2.61 (P = 0.009)

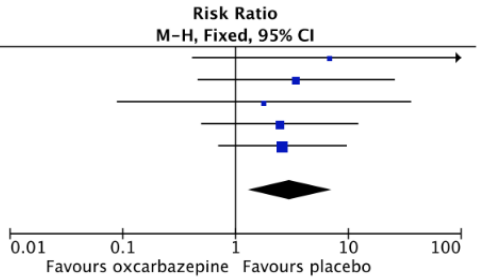


Figure 13.8 Oxcarbazepine versus control; Adverse Event: Somnolence and Fatigue

Study or Subgroup	Oxcarbazepine Events	Oxcarbazepine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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 = 2.92 (P = 0.003)

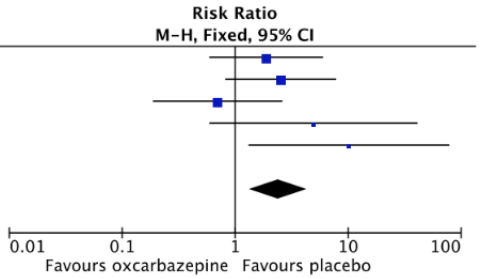
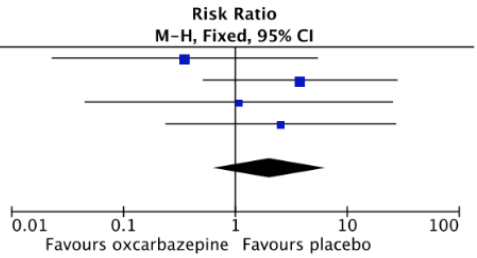


Figure 13.9 Oxcarbazepine versus control; Adverse Event: Tremor

Study or Subgroup	Oxcarbazepine Events	Oxcarbazepine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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]
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 = 0.24)



Anticonvulsants (Pregabalin)

Figure 14.1 Pregabalin versus control; Withdrawals due to Adverse Events

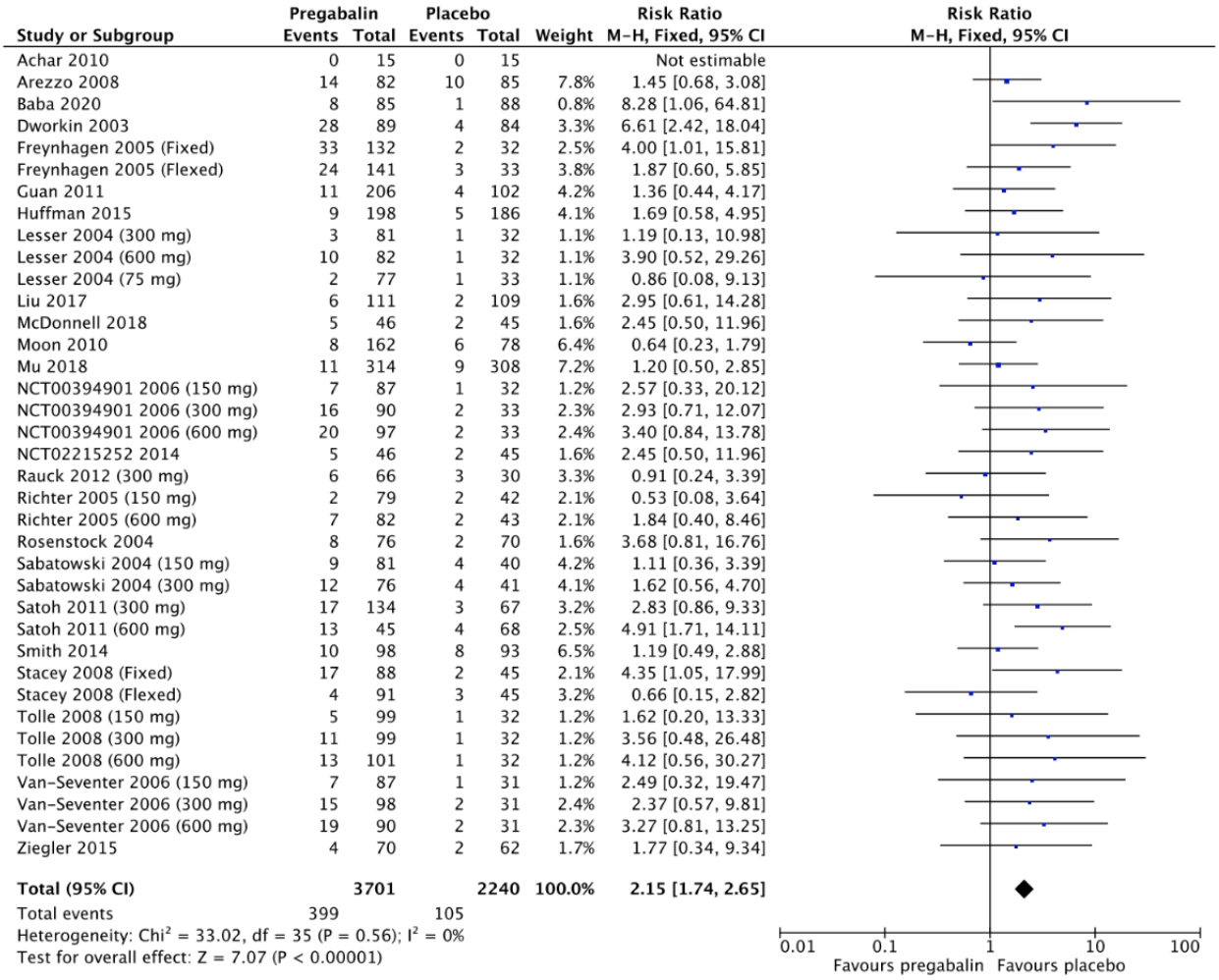


Figure 14.2 Pregabalin versus control; Adverse Event: Abnormal Coordination

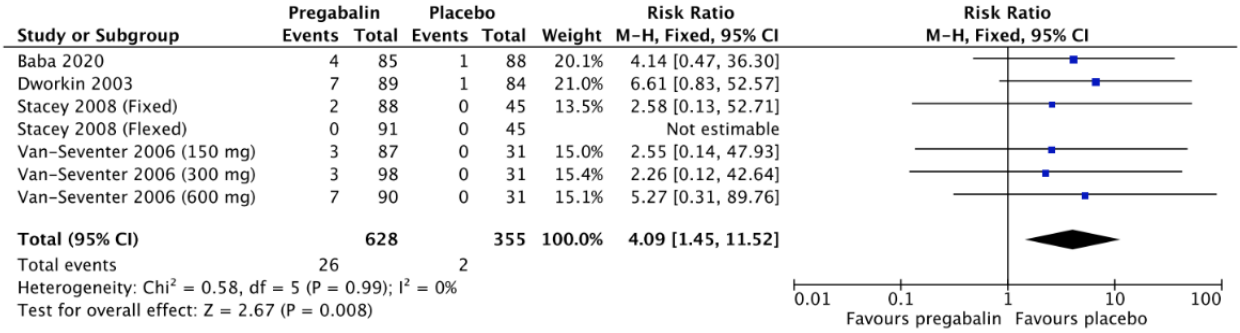


Figure 14.3 Pregabalin versus control; Adverse Event: Abnormal Thinking

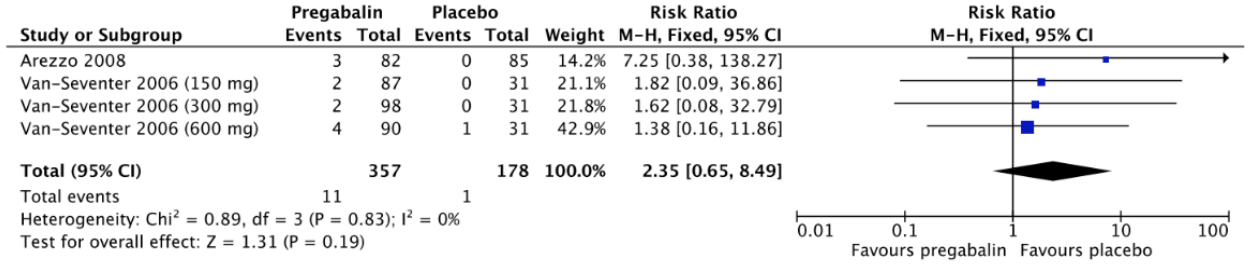


Figure 14.4 Pregabalin versus control; Adverse Event: Amblyopia

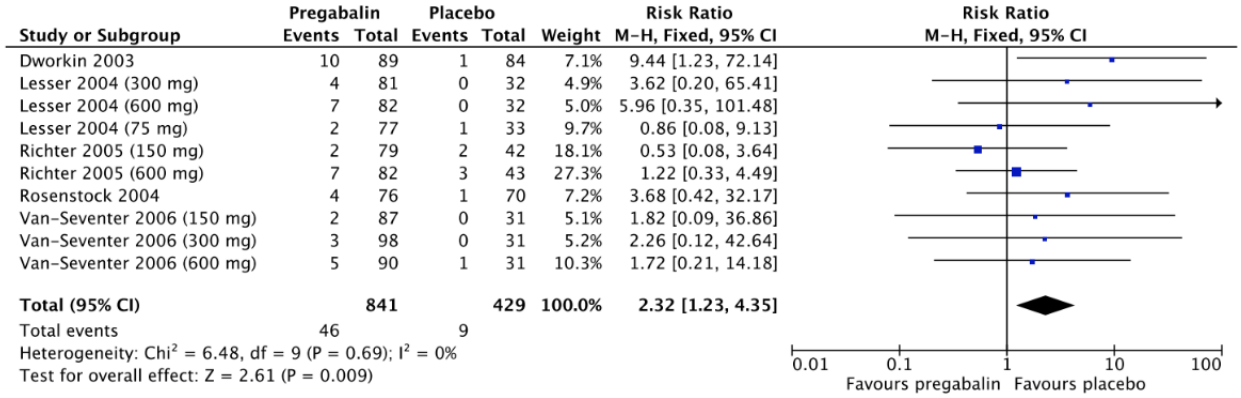


Figure 14.5 Pregabalin versus control; Adverse Event: Amnesia

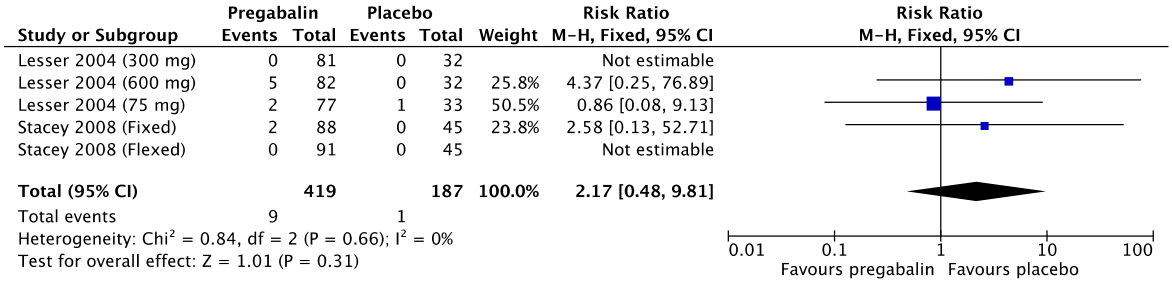


Figure 14.6 Pregabalin versus control; Adverse Event: Asthenia

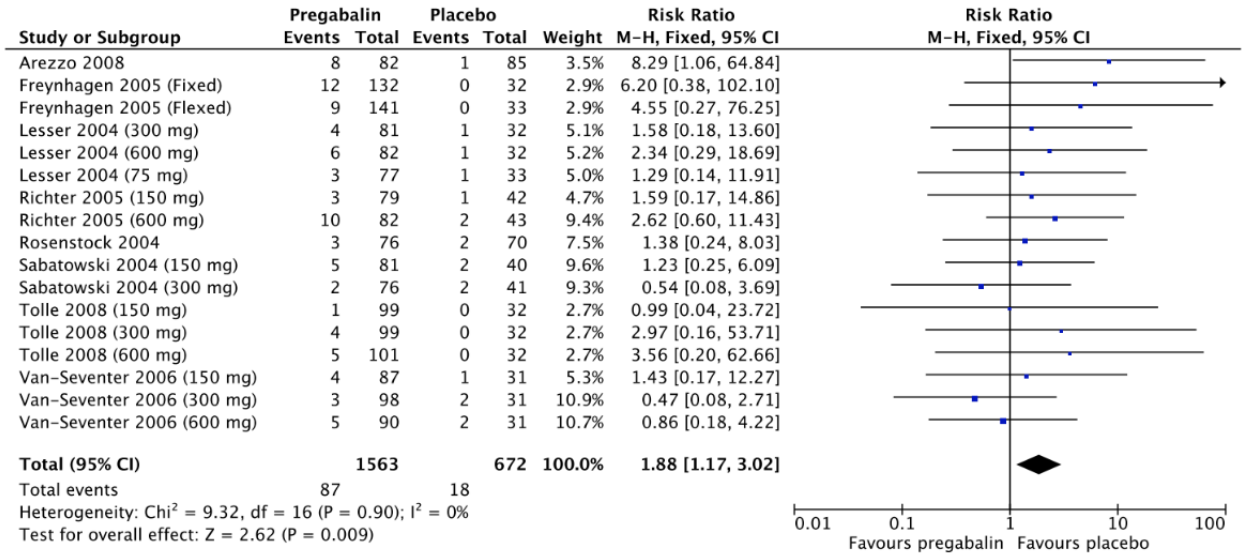


Figure 14.7 Pregabalin versus control; Adverse Event: Ataxia

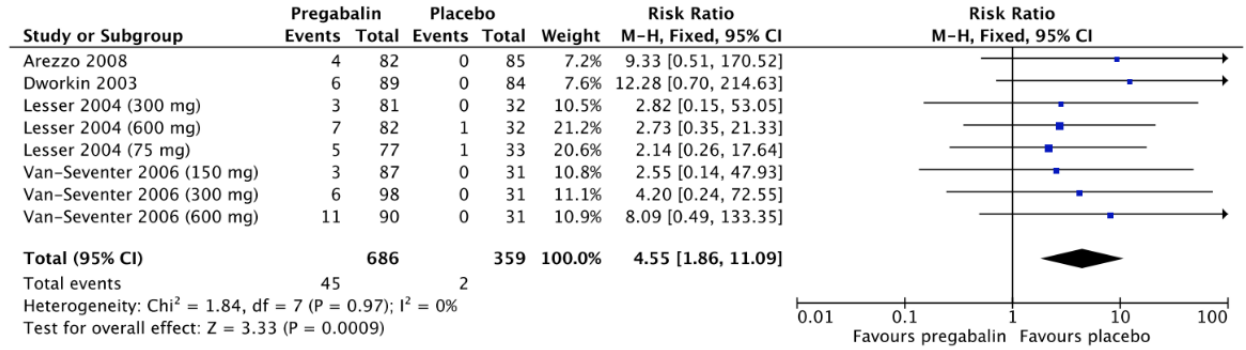


Figure 14.8 Pregabalin versus control; Adverse Event: Back Pain

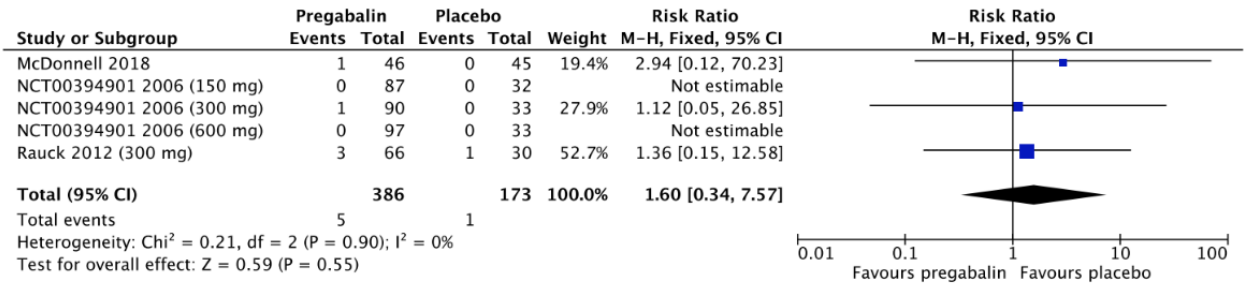


Figure 14.9 Pregabalin versus control; Adverse Event: Balance Disorder

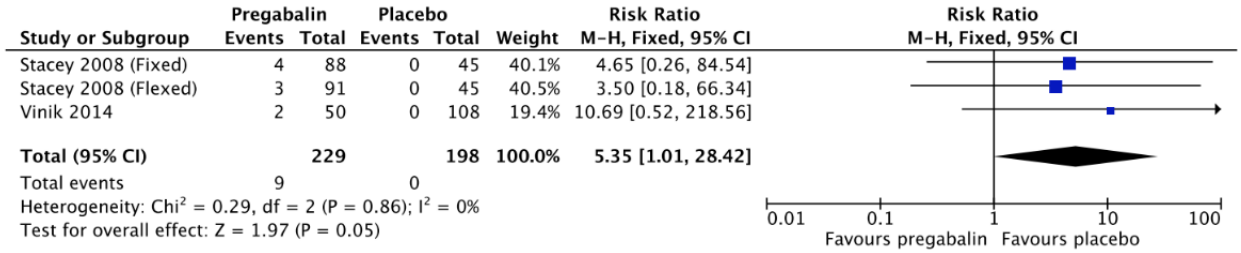


Figure 14.10 Pregabalin versus control; Adverse Event: Confusion

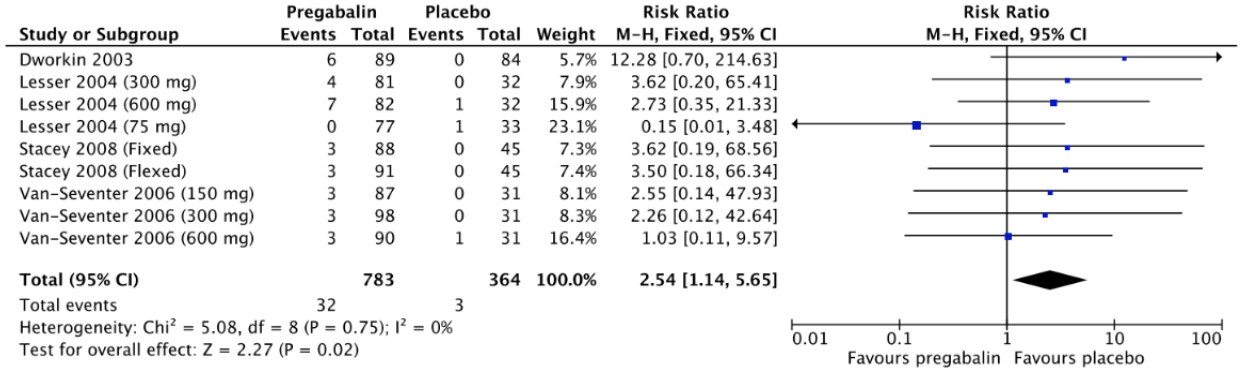


Figure 14.11 Pregabalin versus control; Adverse Event: Constipation

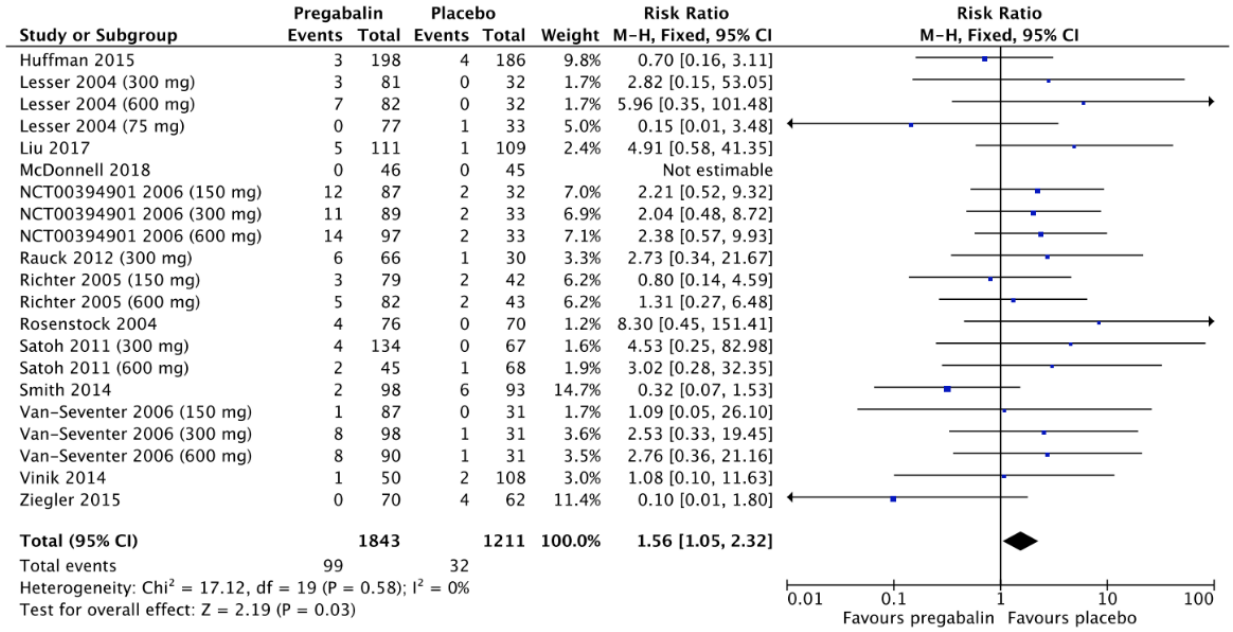


Figure 14.12 Pregabalin versus control; Adverse Event: Contusion

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio 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]
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: Chi² = 0.67, df = 3 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.05 (P = 0.29)

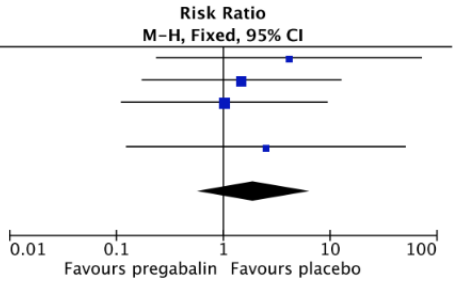


Figure 14.13 Pregabalin versus control; Adverse Event: Diarrhea

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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]
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]**
Total events	55		38			

Heterogeneity: Chi² = 10.18, df = 16 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)

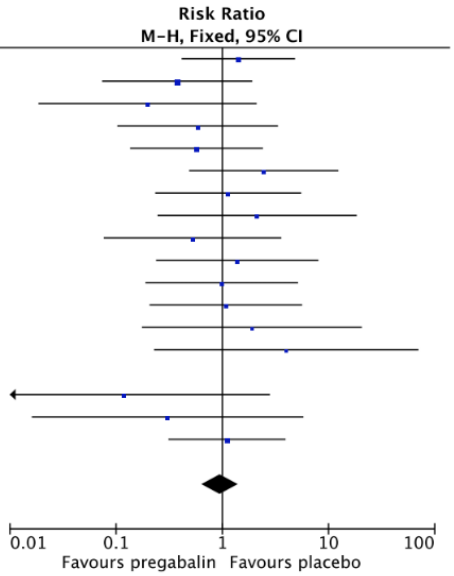


Figure 14.14 Pregabalin versus control; Adverse Event: Diplopia

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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: Chi² = 0.36, df = 4 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.53 (P = 0.13)

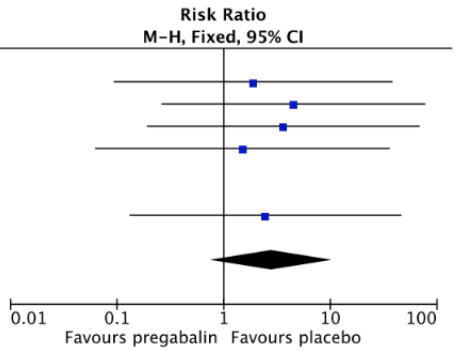


Figure 14.15 Pregabalin versus control; Adverse Event: Disturbance in Attention

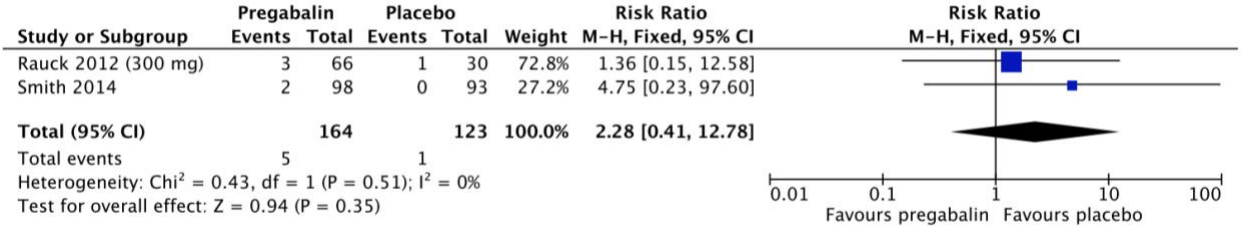


Figure 14.16 Pregabalin versus control; Adverse Event: Dizziness

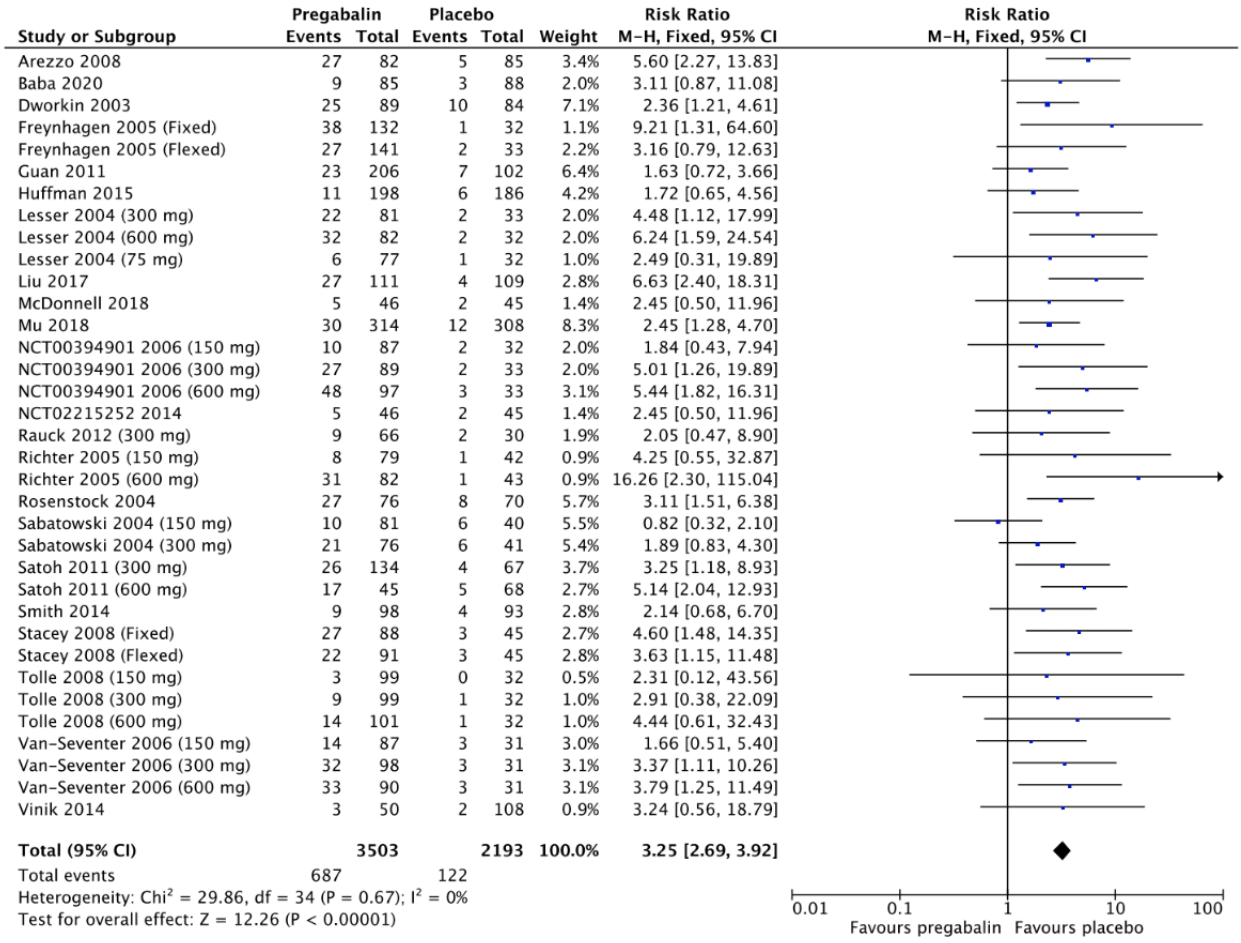


Figure 14.17 Pregabalin versus control; Adverse Event: Dry Mouth

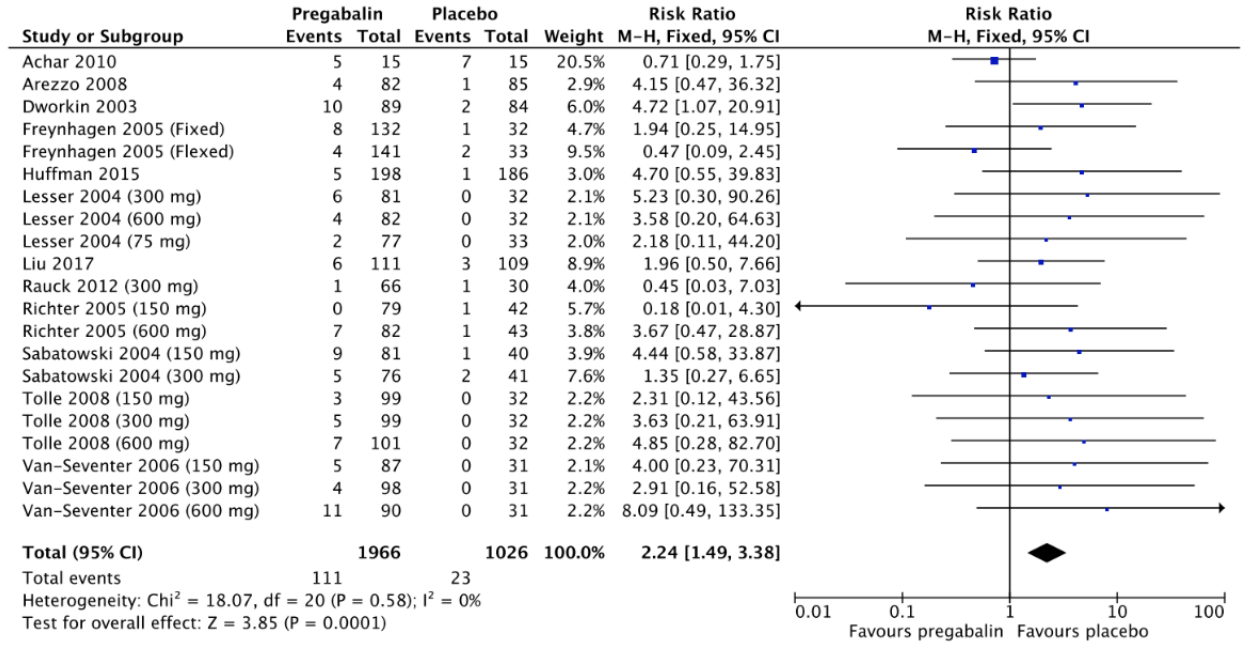


Figure 14.18 Pregabalin versus control; Adverse Event: Euphoria

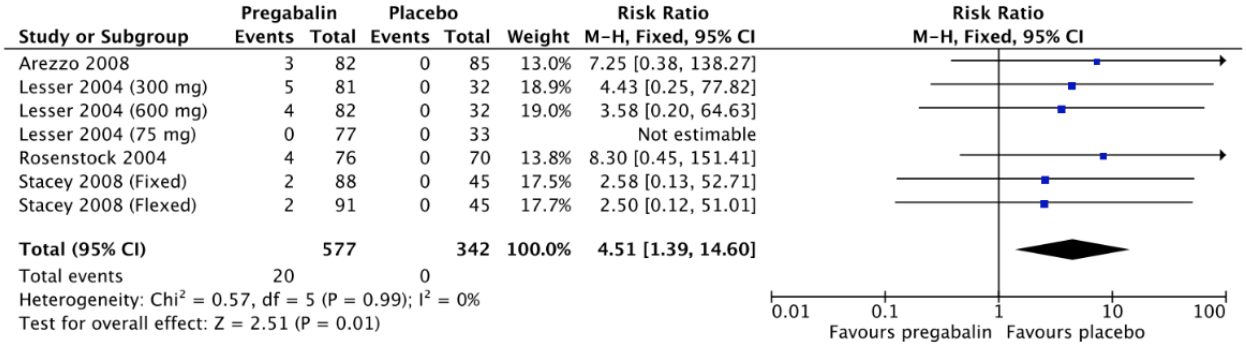


Figure 14.19 Pregabalin versus control; Adverse Event: Facial Edema

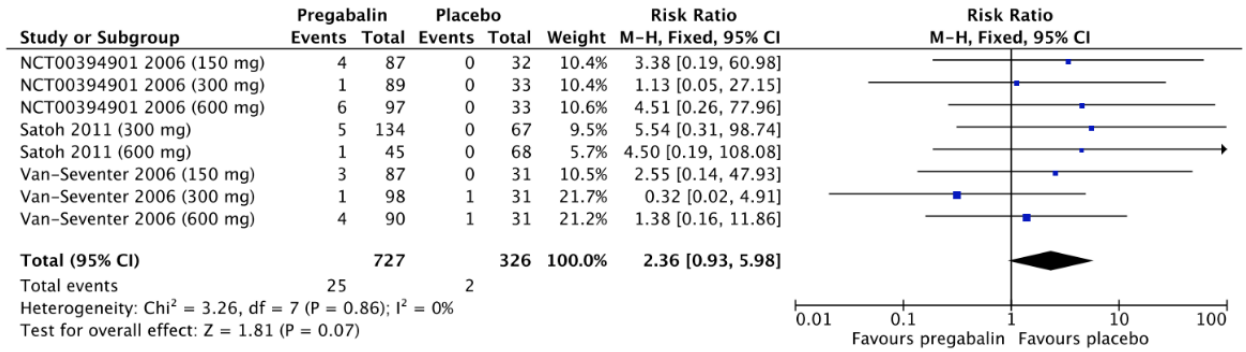


Figure 14.20 Pregabalin versus control; Adverse Event: Falls

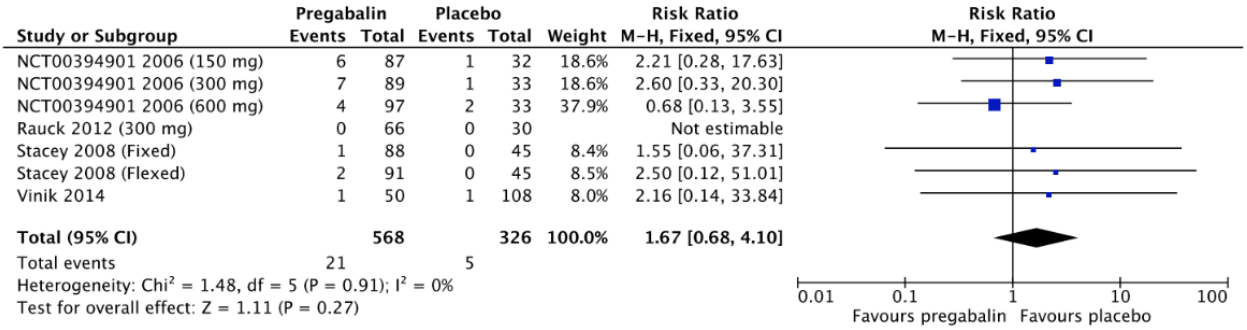


Figure 14.21 Pregabalin versus control; Adverse Event: Flatulence

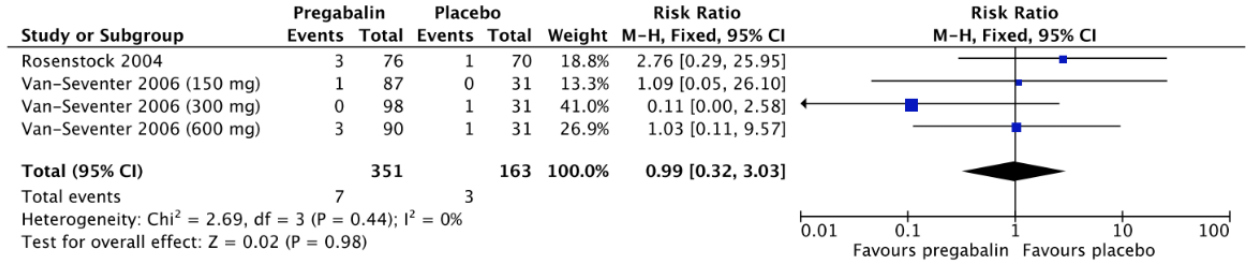


Figure 14.22 Pregabalin versus control; Adverse Event: Generalized Edema

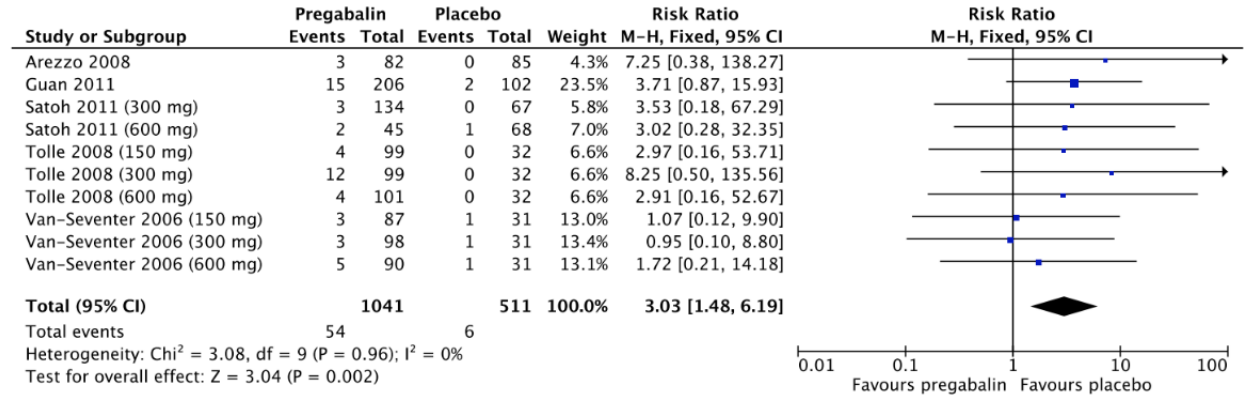


Figure 14.23 Pregabalin versus control; Adverse Event: Headache

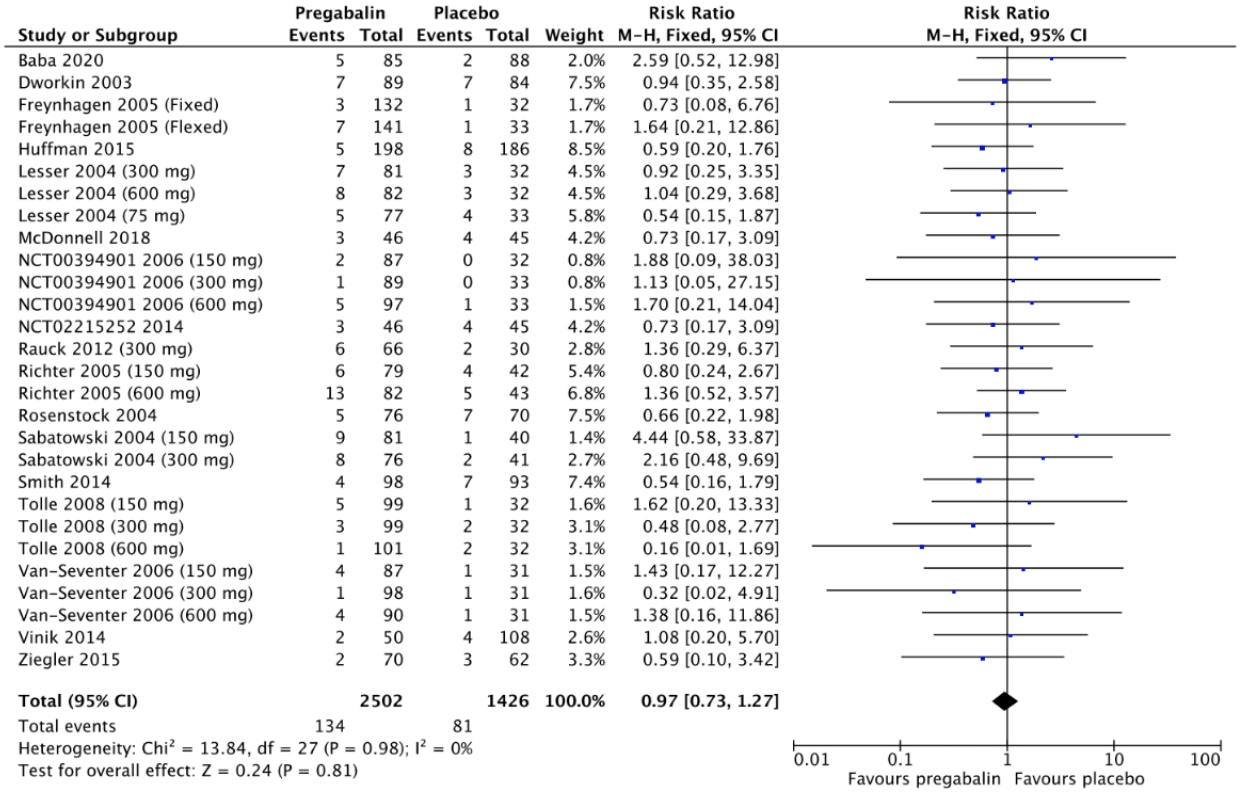


Figure 14.24 Pregabalin versus control; Adverse Event: Hyperglycemia

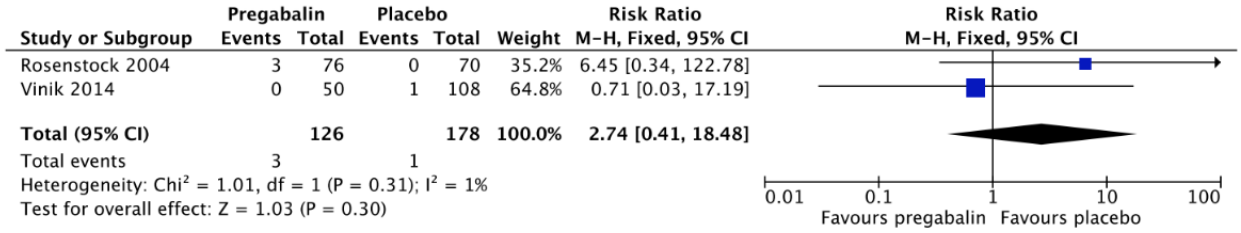


Figure 14.25 Pregabalin versus control; Adverse Event: Increased Appetite

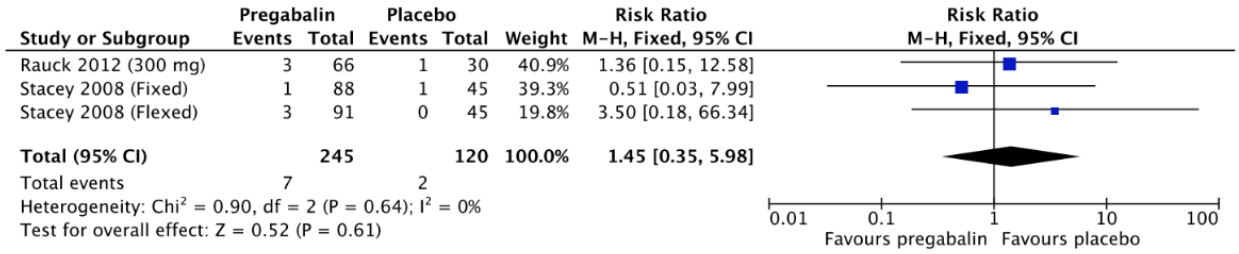


Figure 14.26 Pregabalin versus control; Adverse Event: Increased Pain

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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: Chi² = 5.06, df = 9 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)

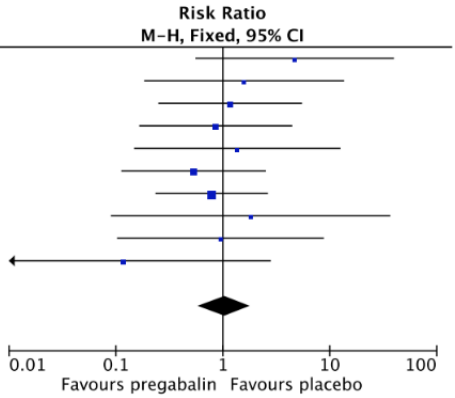


Figure 14.27 Pregabalin versus control; Adverse Event: Increased Sweating

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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: Chi² = 2.89, df = 4 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.78 (P = 0.07)

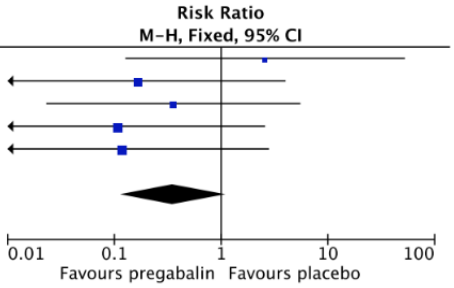


Figure 14.28 Pregabalin versus control; Adverse Event: Infection

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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]
Total (95% CI)		**684**		**441**	**100.0%**	**1.34 [0.86, 2.09]**
Total events	51		27			

Heterogeneity: Chi² = 8.77, df = 8 (P = 0.36); I² = 9%
Test for overall effect: Z = 1.29 (P = 0.20)

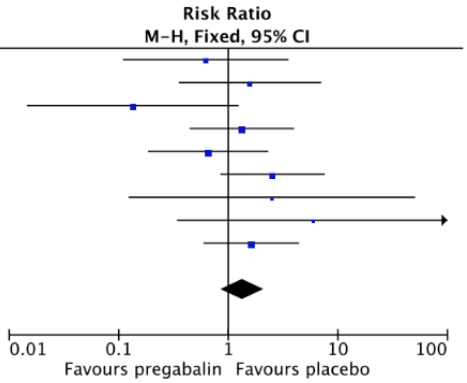


Figure 14.29 Pregabalin versus control; Adverse Event: Injury

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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: Chi² = 2.88, df = 6 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)

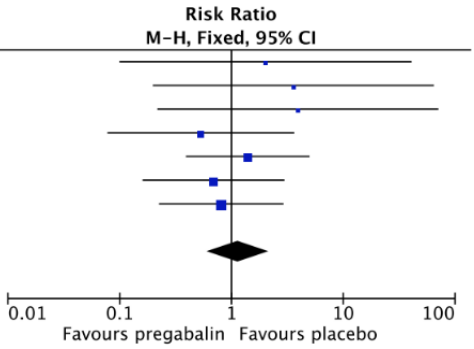


Figure 14.30 Pregabalin versus control; Adverse Event: Lethargy

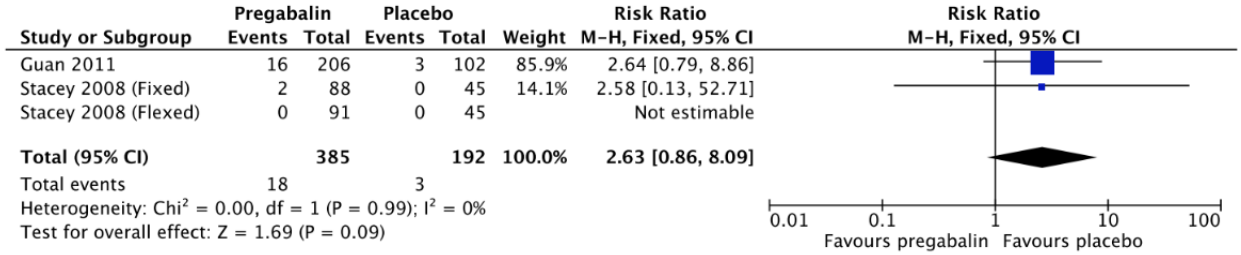


Figure 14.31 Pregabalin versus control; Adverse Event: Muscle Spasm

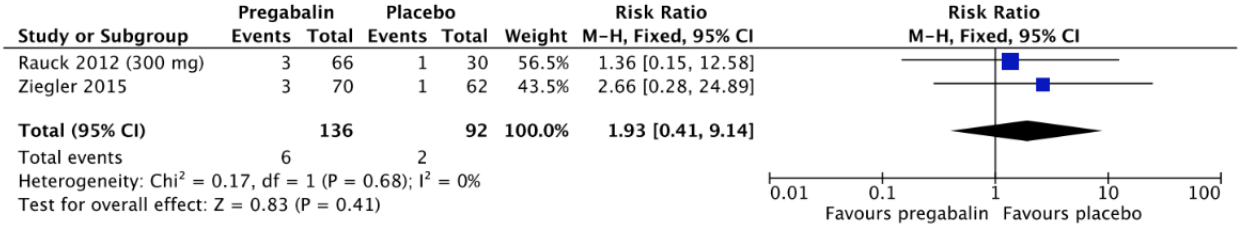


Figure 14.32 Pregabalin versus control; Adverse Event: Nasopharyngitis

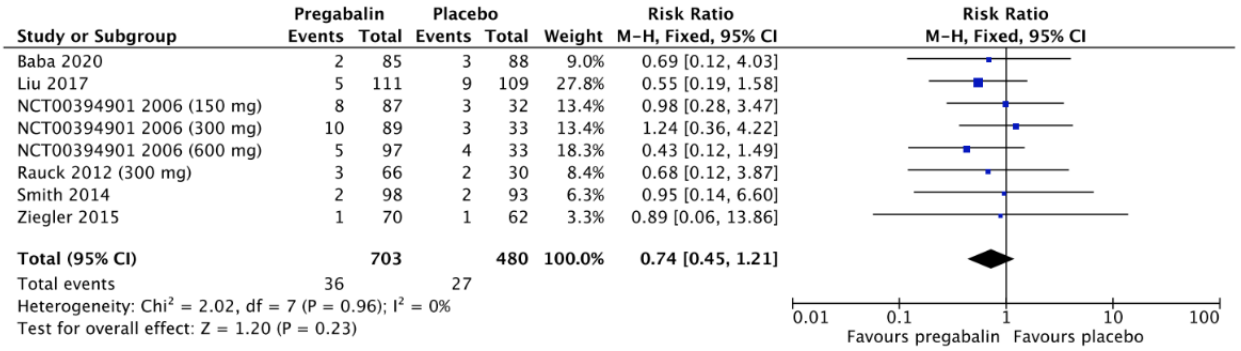


Figure 14.33 Pregabalin versus control; Adverse Event: Nausea

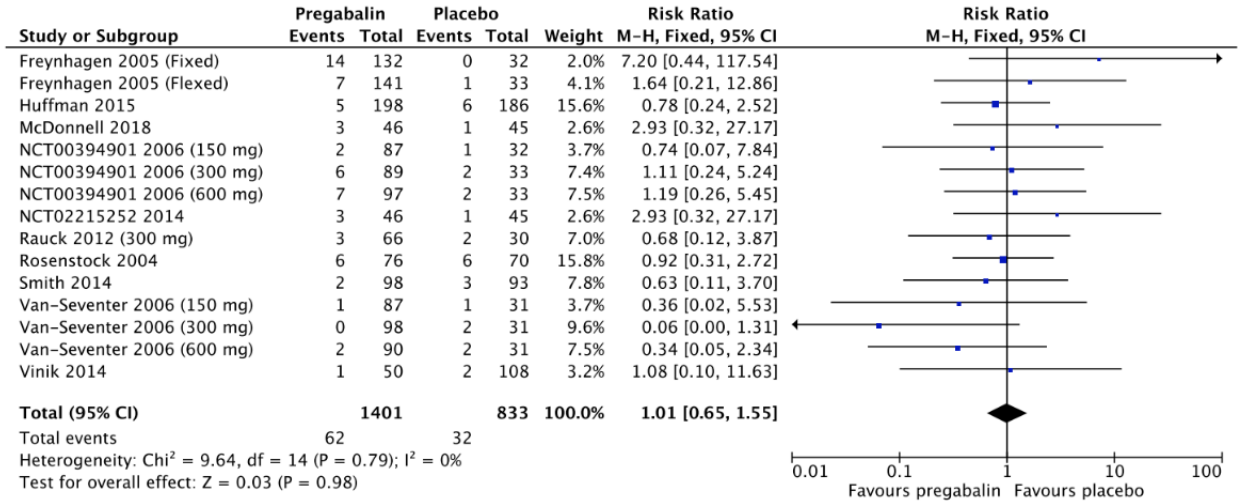


Figure 14.34 Pregabalin versus control; Adverse Event: Peripheral Edema

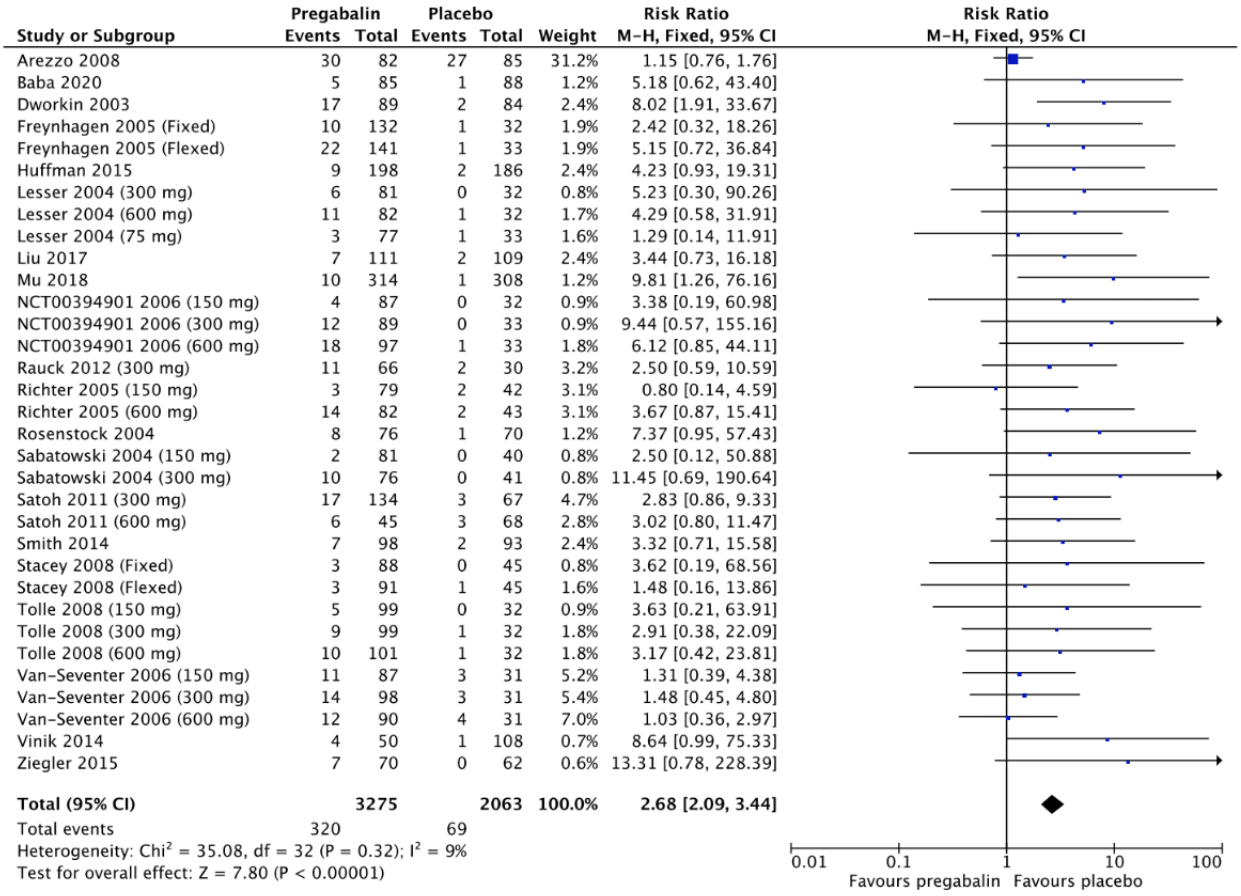


Figure 14.35 Pregabalin versus control; Adverse Event: Serious Adverse Events

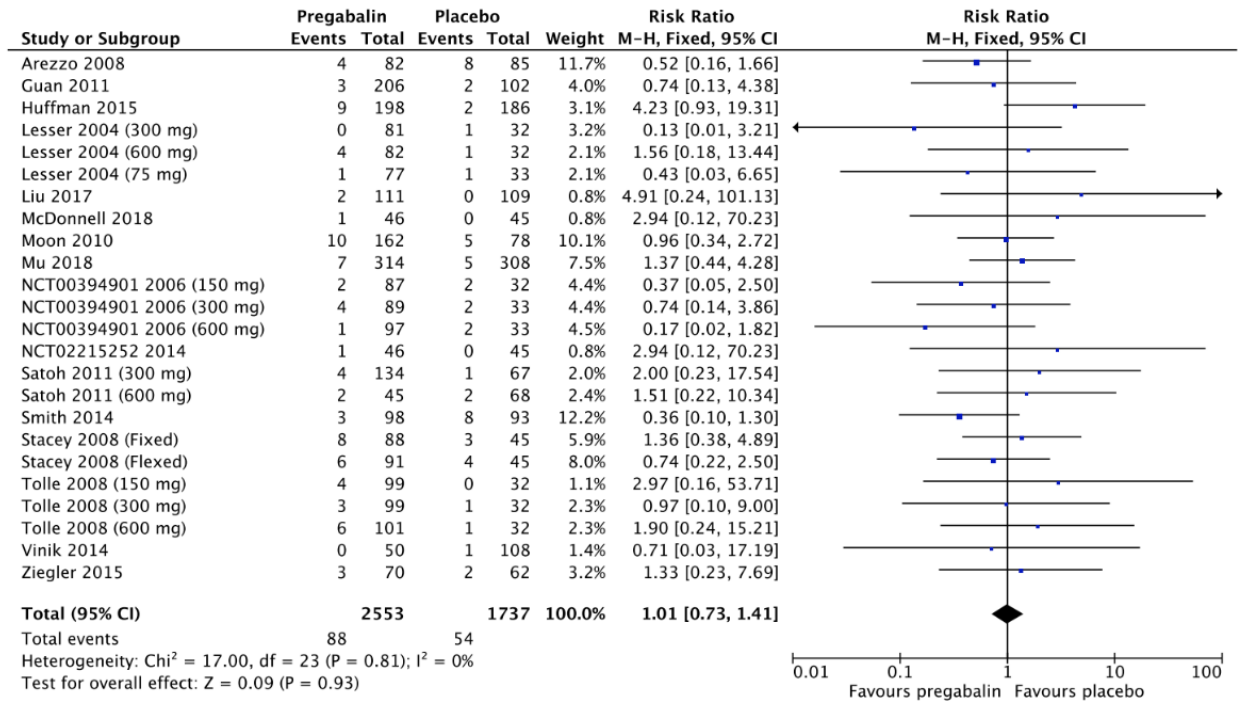


Figure 14.36 Pregabalin versus control; Adverse Event: Somnolence and Fatigue

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Arezzo 2008	11	82	5	85	4.6%	2.28 [0.83, 6.28]
Baba 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	0.8%	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]
Lesser 2004 (300 mg)	19	81	1	32	1.3%	7.51 [1.05, 53.76]
Lesser 2004 (600 mg)	22	82	1	32	1.4%	8.59 [1.21, 61.07]
Lesser 2004 (75 mg)	3	77	2	33	2.6%	0.64 [0.11, 3.67]
Liu 2017	11	111	6	109	5.7%	1.80 [0.69, 4.70]
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%	11.25 [1.57, 80.80]
Stacey 2008 (Flexed)	18	91	2	45	2.5%	4.45 [1.08, 18.35]
Tolle 2008 (150 mg)	5	99	0	32	0.7%	3.63 [0.21, 63.91]
Tolle 2008 (300 mg)	4	99	0	32	0.7%	2.97 [0.16, 53.71]
Tolle 2008 (600 mg)	8	101	1	32	1.4%	2.53 [0.33, 19.50]
Van-Seventer 2006 (150 mg)	8	87	1	31	1.4%	2.85 [0.37, 21.88]
Van-Seventer 2006 (300 mg)	11	98	1	31	1.4%	3.48 [0.47, 25.89]
Van-Seventer 2006 (600 mg)	23	90	2	31	2.8%	3.96 [0.99, 15.84]
Vinik 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 = 33 (P = 0.99); $I^2 = 0\%$

Test for overall effect: Z = 10.80 (P < 0.00001)

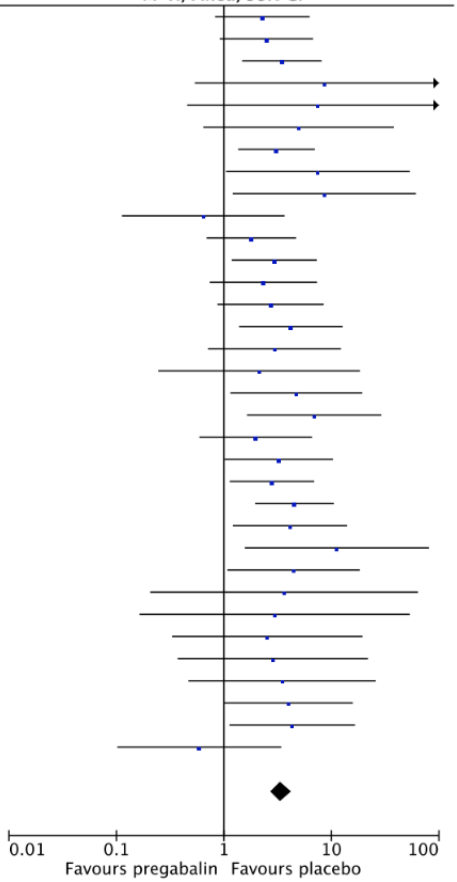


Figure 14.37 Pregabalin versus control; Adverse Event: Upper Respiratory Tract Infection

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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
Total (95% CI)		**360**		**338**	**100.0%**	**0.48 [0.19, 1.16]**
Total events	7		14			

Heterogeneity: $Chi^2 = 0.36$, df = 2 (P = 0.83); $I^2 = 0\%$

Test for overall effect: Z = 1.63 (P = 0.10)

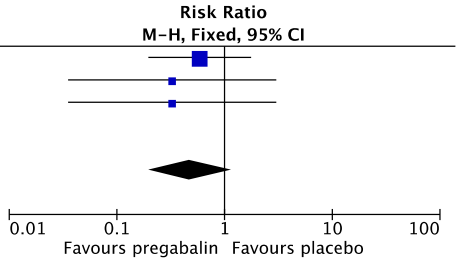


Figure 14.38 Pregabalin versus control; Adverse Event: Urinary Tract Infection

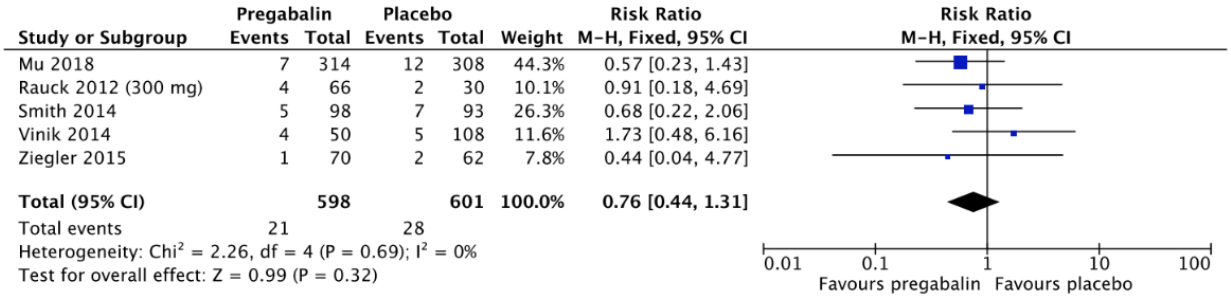


Figure 14.39 Pregabalin versus control; Adverse Event: Vertigo

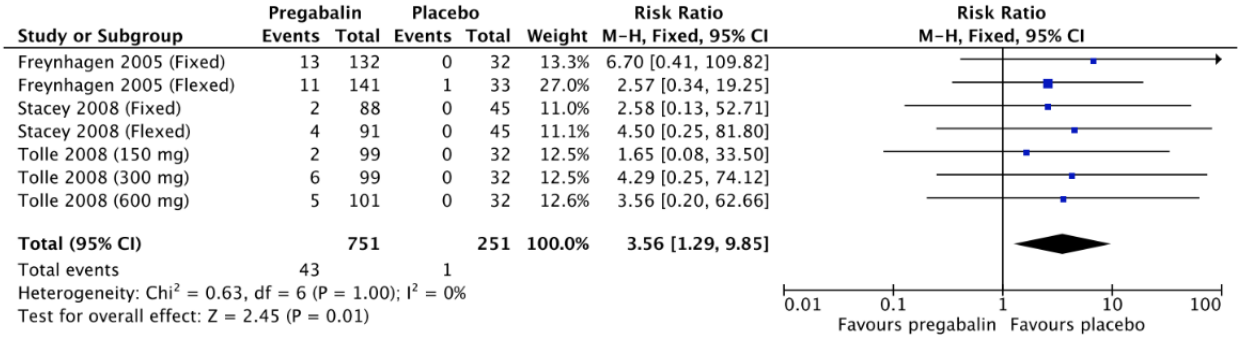


Figure 14.40 Pregabalin versus control; Adverse Event: Vision Problems

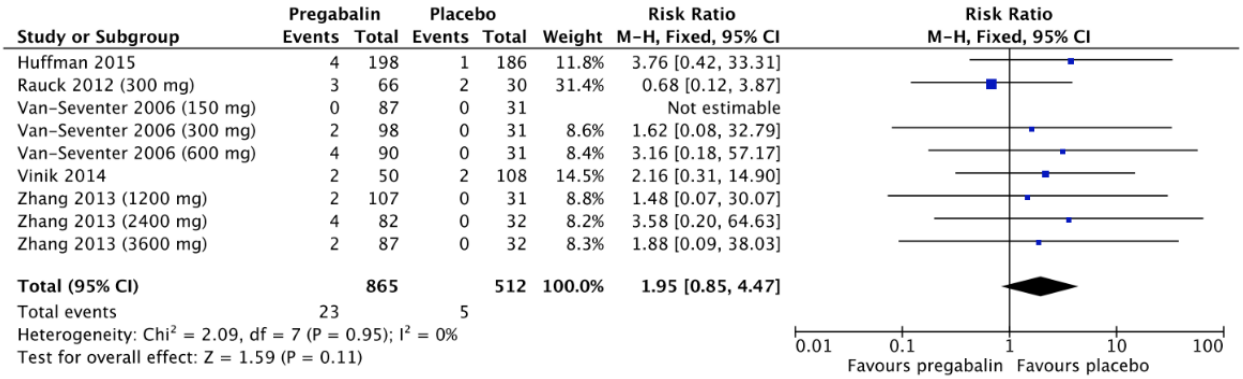


Figure 14.41 Pregabalin versus control; Adverse Event: Vomiting

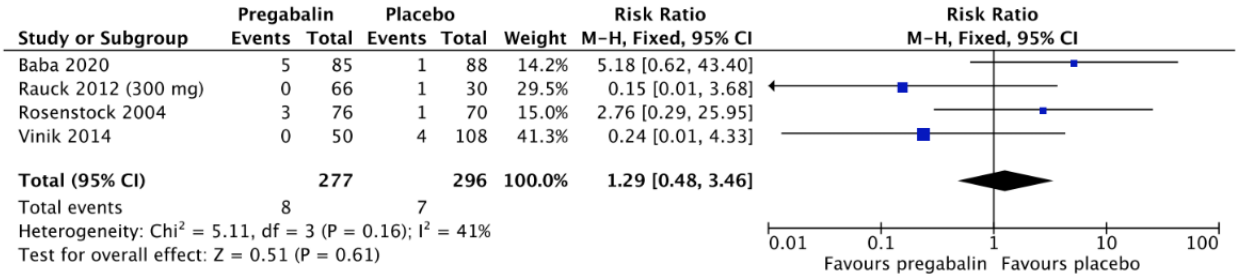
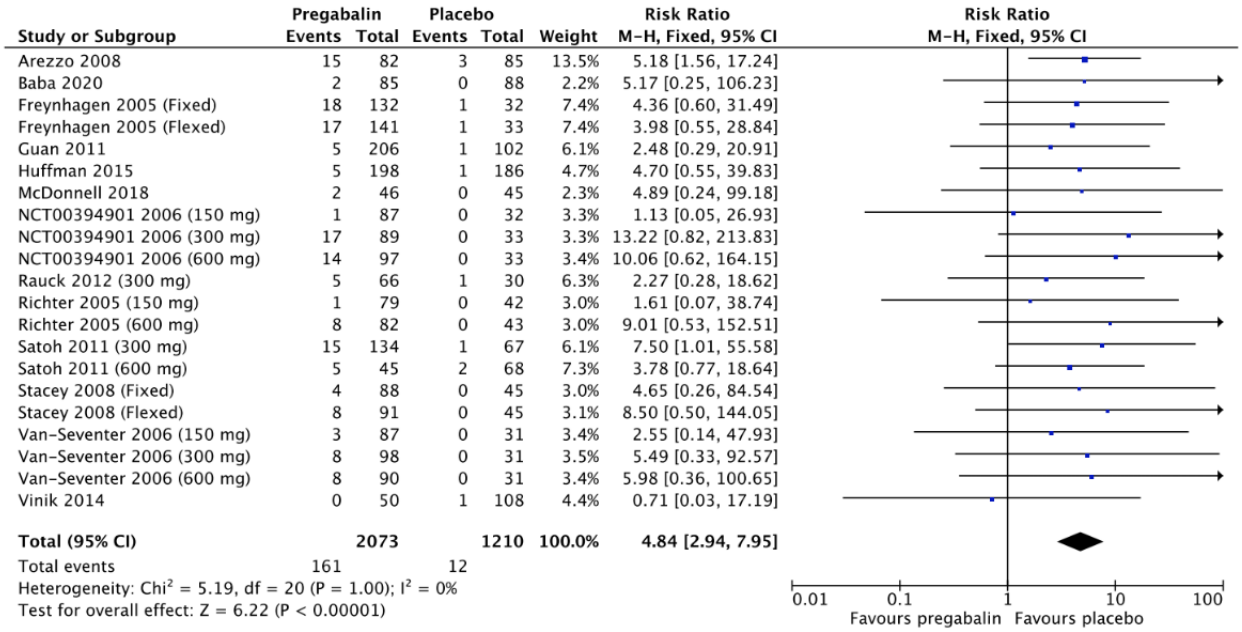
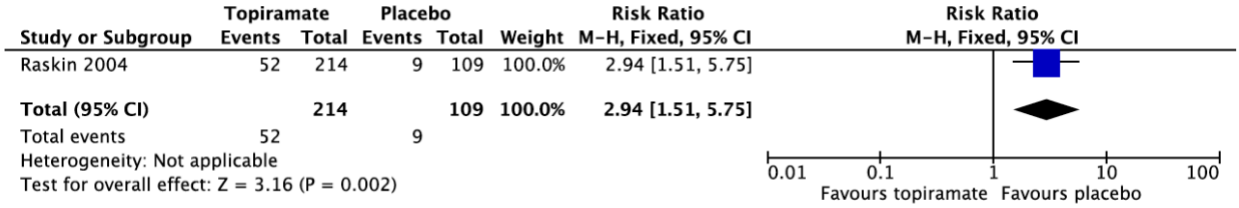


Figure 14.42 Pregabalin versus control; Adverse Event: Weight Gain



Anticonvulsants (Topiramate)

Figure 15.1 Topiramate versus control; Withdrawals due to Adverse Events



Opioids

Figure 16.1 Opioids versus control; Withdrawals due to Adverse Events

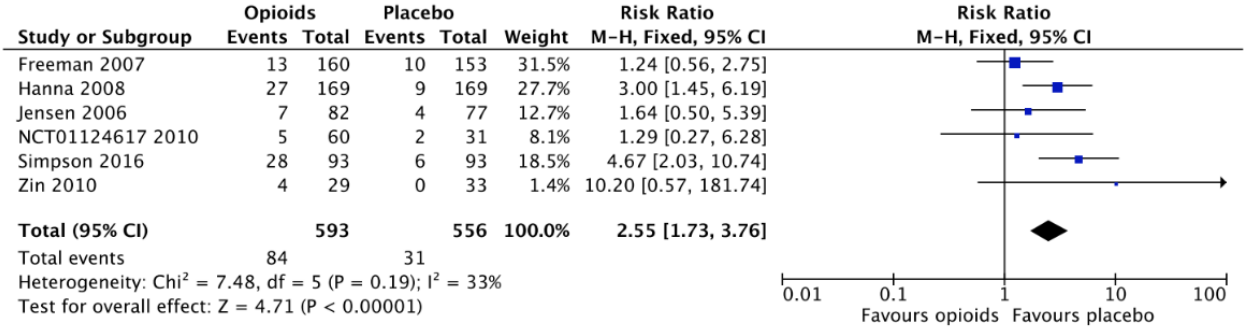


Figure 16.2 Opioids versus control; Adverse Event: Asthenia

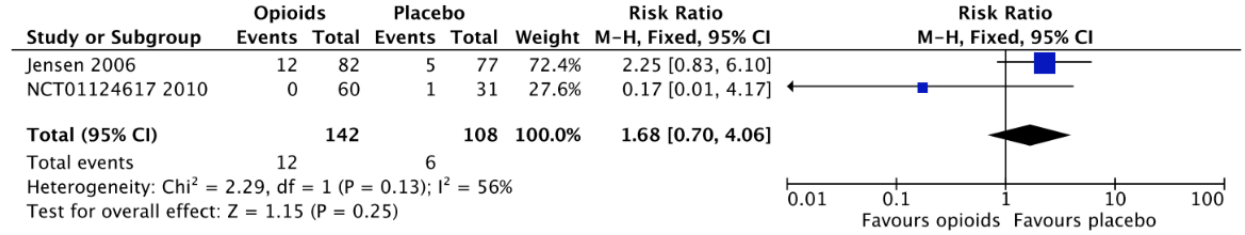


Figure 16.3 Opioids versus control; Adverse Event: Constipation

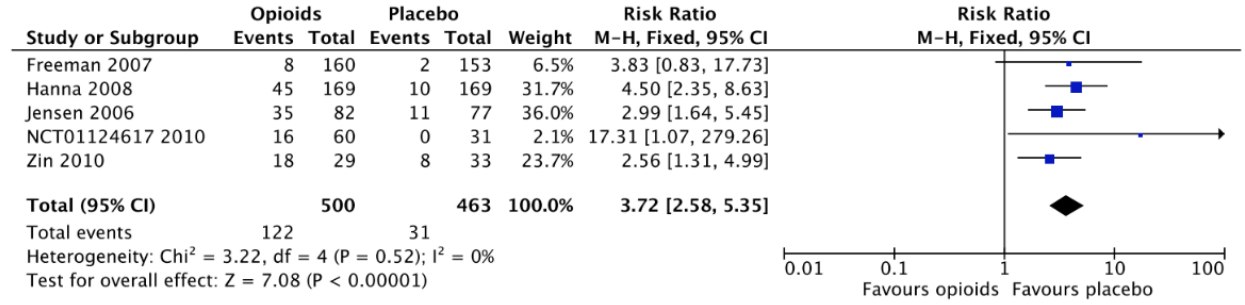


Figure 16.4 Opioids versus control; Adverse Event: Diarrhea

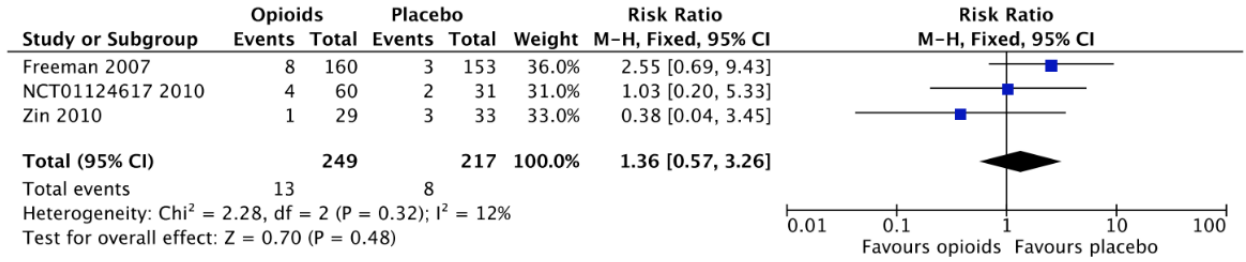


Figure 16.5 Opioids versus control; Adverse Event: Dizziness

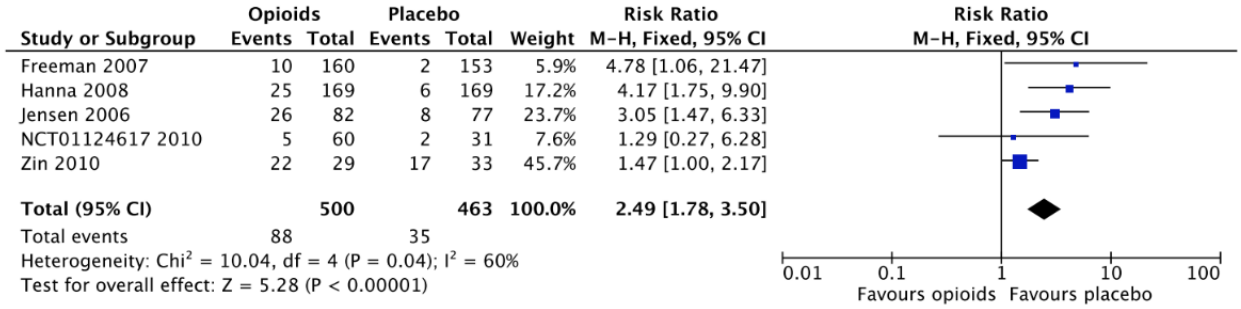


Figure 16.6 Opioids versus control; Adverse Event: Dry Mouth

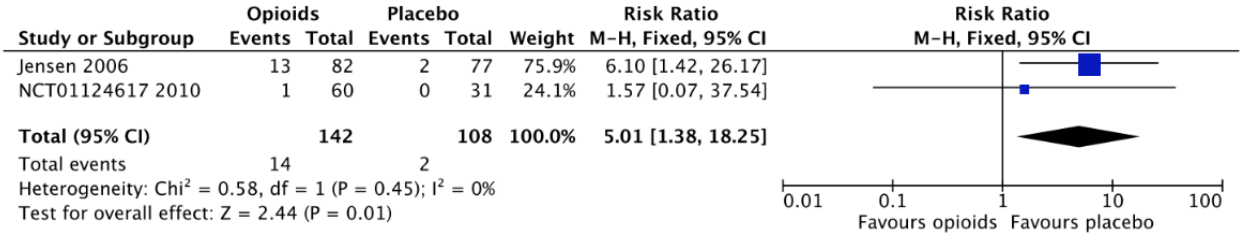


Figure 16.7 Opioids versus control; Adverse Event: Generalized Pain

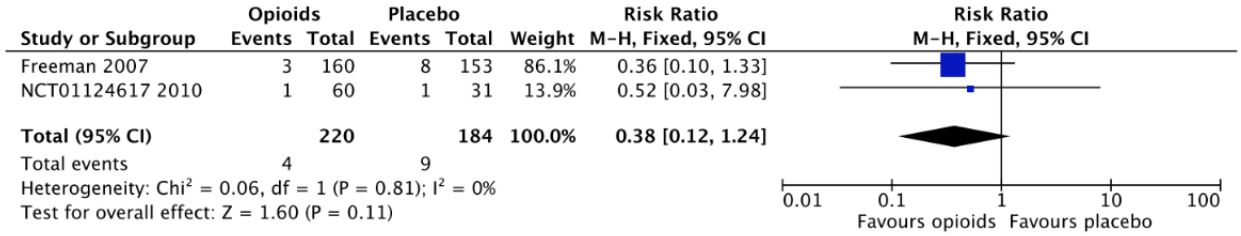


Figure 16.8 Opioids versus control; Adverse Event: Headache

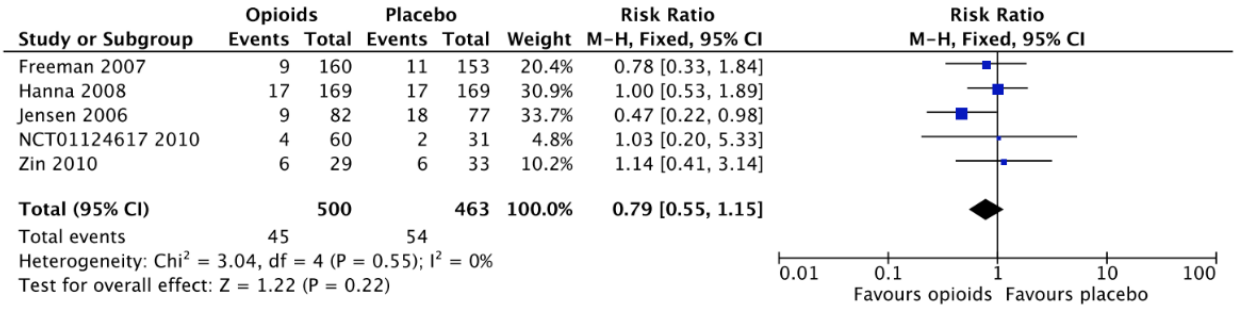


Figure 16.9 Opioids versus control; Adverse Event: Nausea

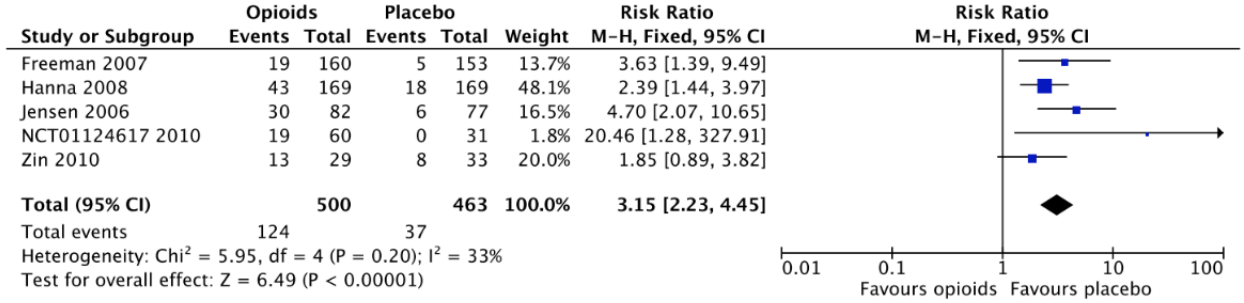


Figure 16.10 Opioids versus control; Adverse Event: Pruritus

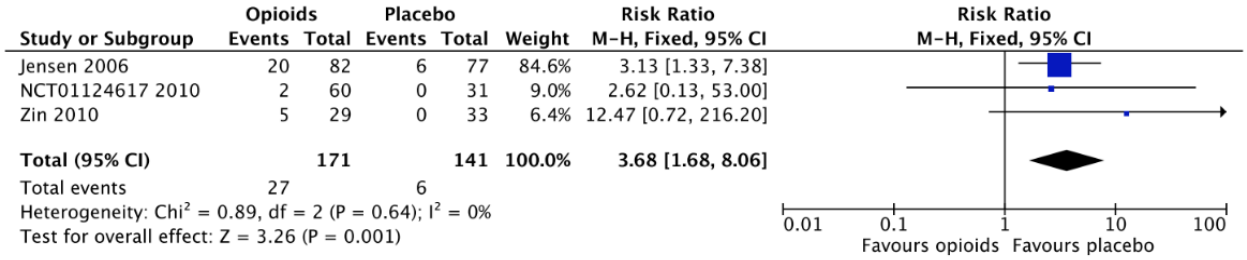


Figure 16.11 Opioids versus control; Adverse Event: Serious Adverse Events

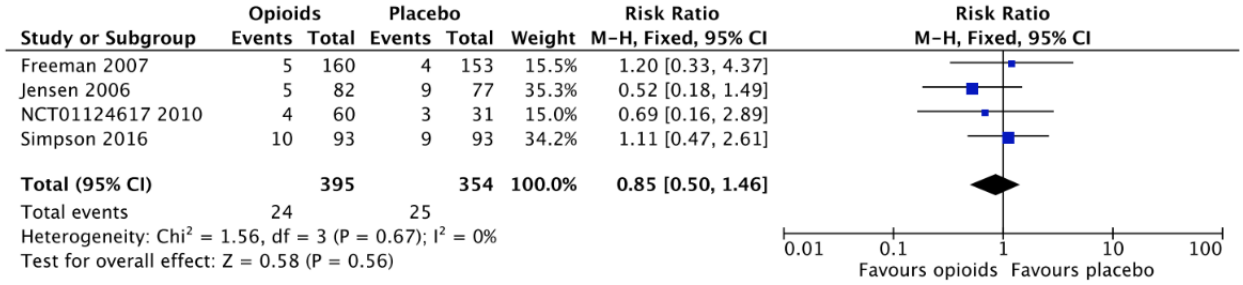


Figure 16.12 Opioids versus control; Adverse Event: Somnolence and Fatigue

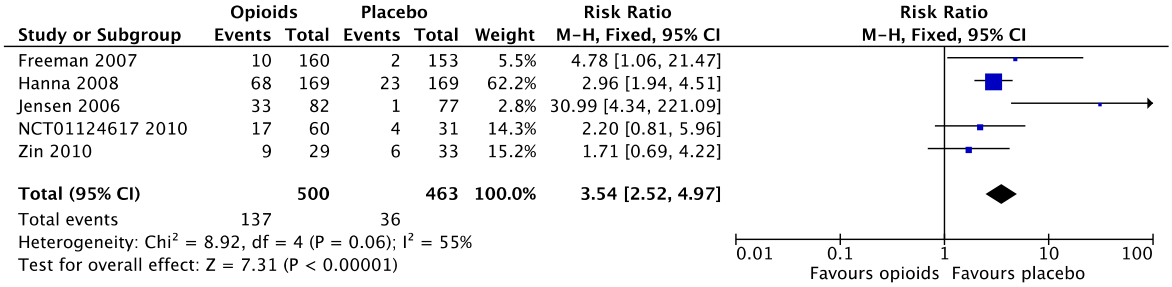


Figure 16.13 Opioids versus control; Adverse Event: Upper Respiratory Tract Infection

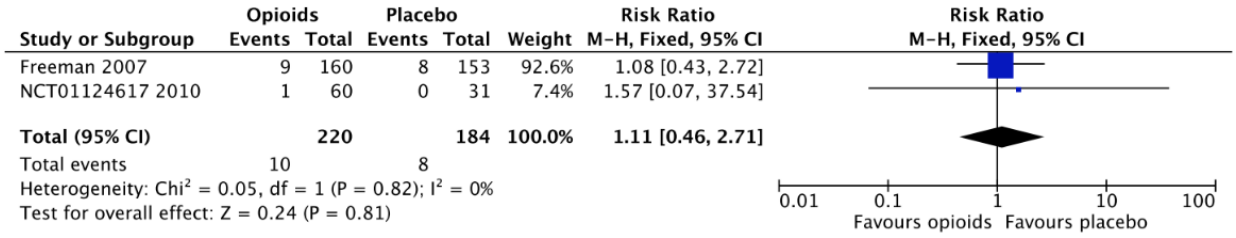
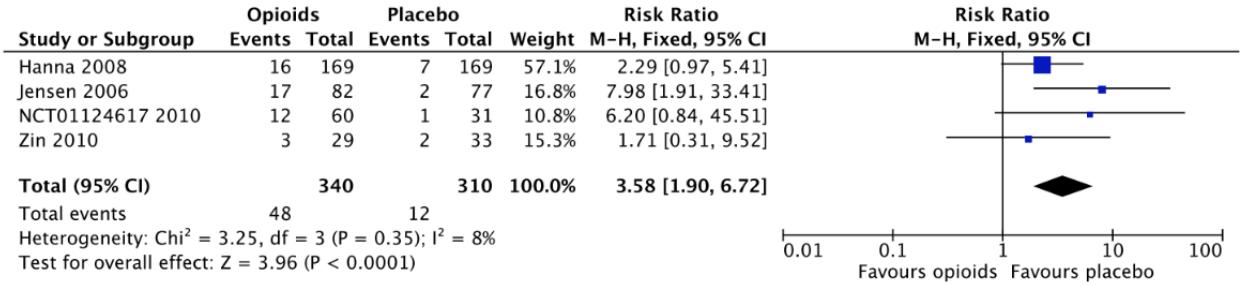


Figure 16.14 Opioids versus control; Adverse Event: Vomiting



Rubefacients (Capsaicin)

Figure 17.1 Rubefacients versus control; Withdrawals due to Adverse Events

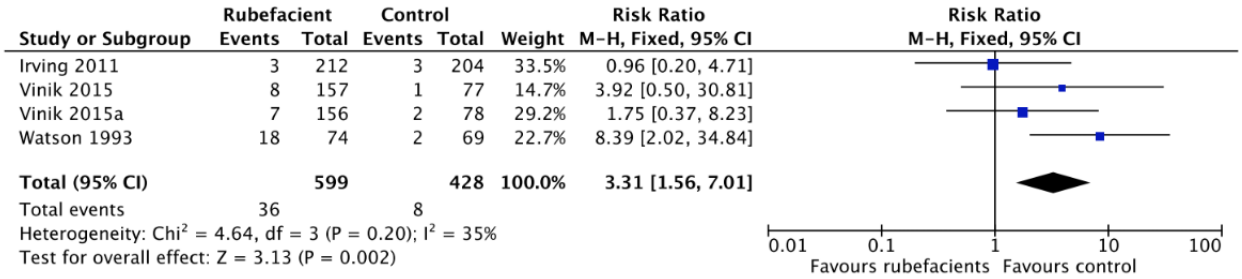


Figure 17.2 Rubefacients versus control; Adverse Event: Back Pain

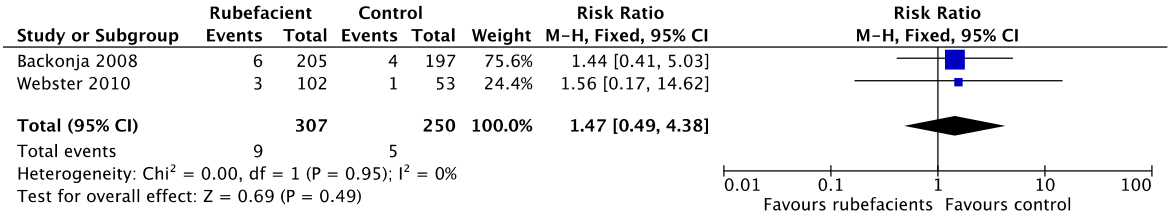


Figure 17.3 Rubefacients versus control; Adverse Event: Coughing and/or Sneezing

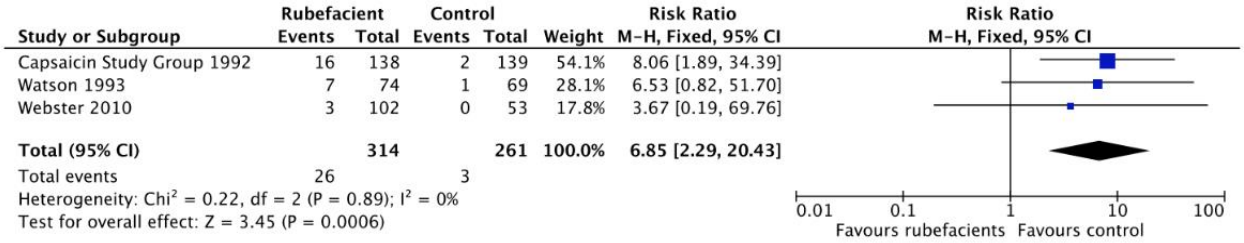


Figure 17.4 Rubefacients versus control; Adverse Event: Dizziness

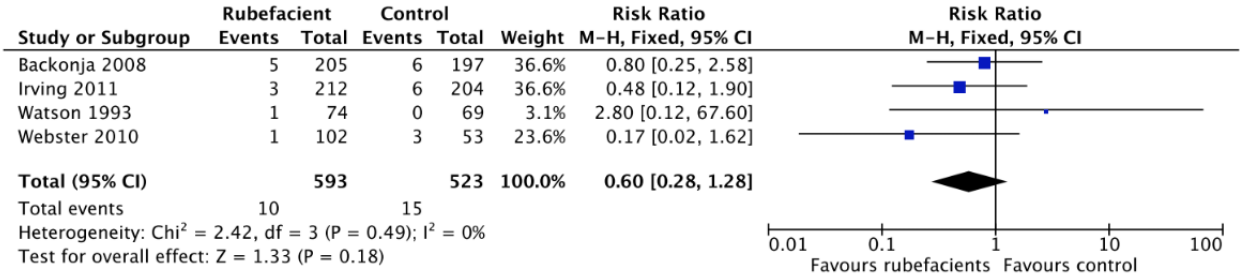


Figure 17.5 Rubefacients versus control; Adverse Event: Headache

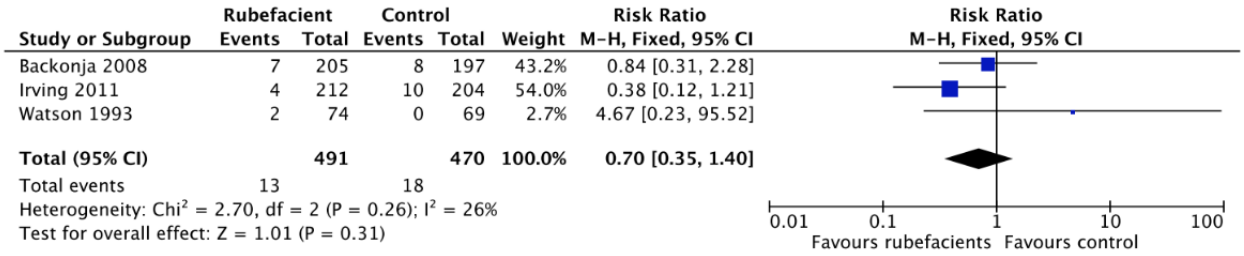


Figure 17.6 Rubefacients versus control; Adverse Event: Increased Blood Pressure

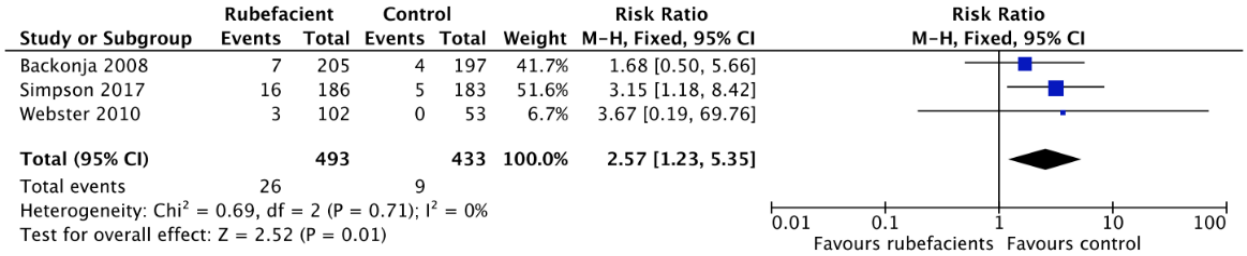


Figure 17.7 Rubefacients versus control; Adverse Event: Local Reaction (Burning, Stinging, and/or Erythema)

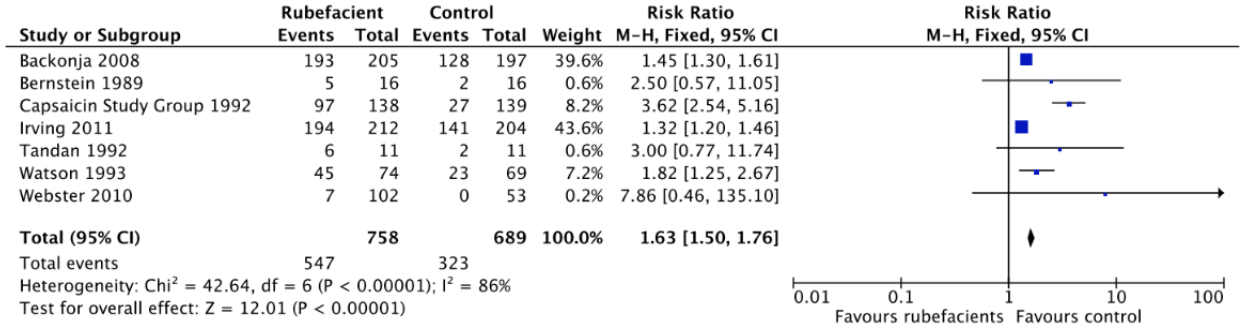


Figure 17.8 Rubefacients versus control; Adverse Event: Nasopharyngitis

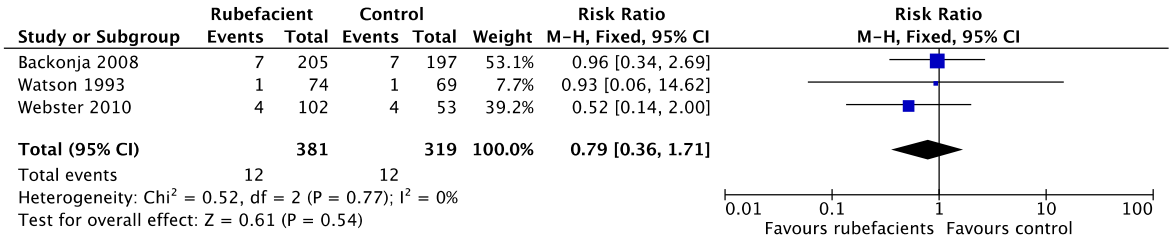


Figure 17.9 Rubefacients versus control; Adverse Event: Nausea

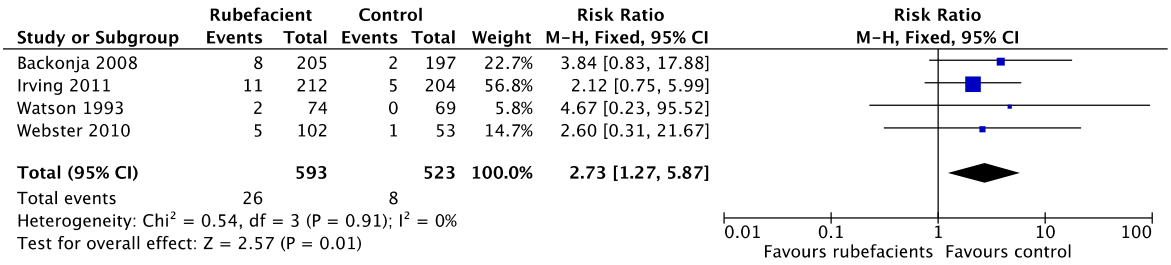


Figure 17.10 Rubefacients versus control; Adverse Event: Pain at Application Site

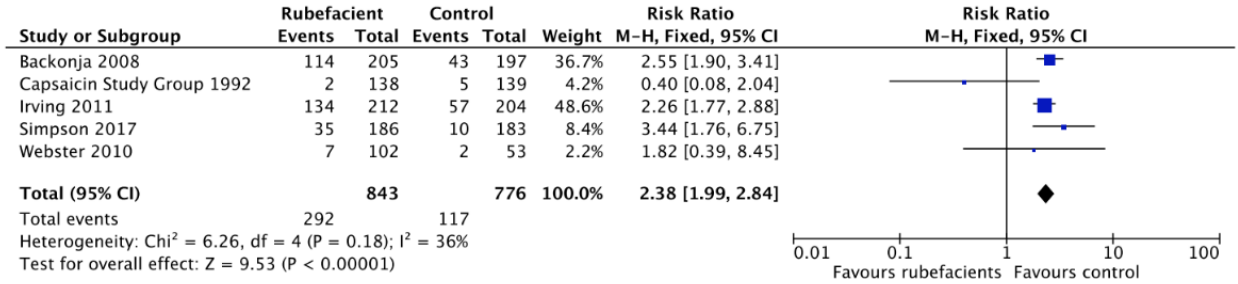


Figure 17.11 Rubefacients versus control; Adverse Event: Papules at Application Site

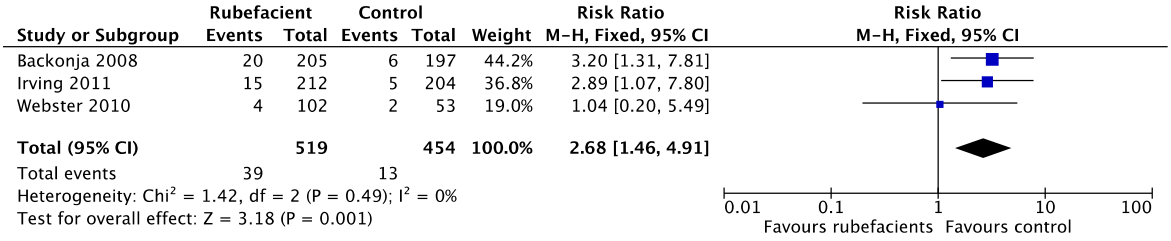


Figure 17.12 Rubefacients versus control; Adverse Event: Pruritus at Application Site

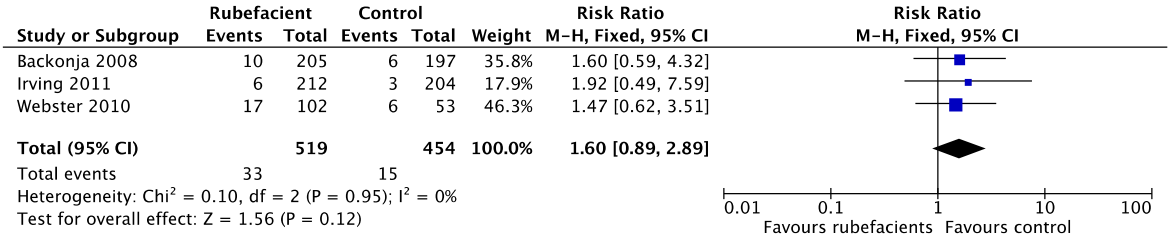


Figure 17.13 Rubefacients versus control; Adverse Event: Serious Adverse Events

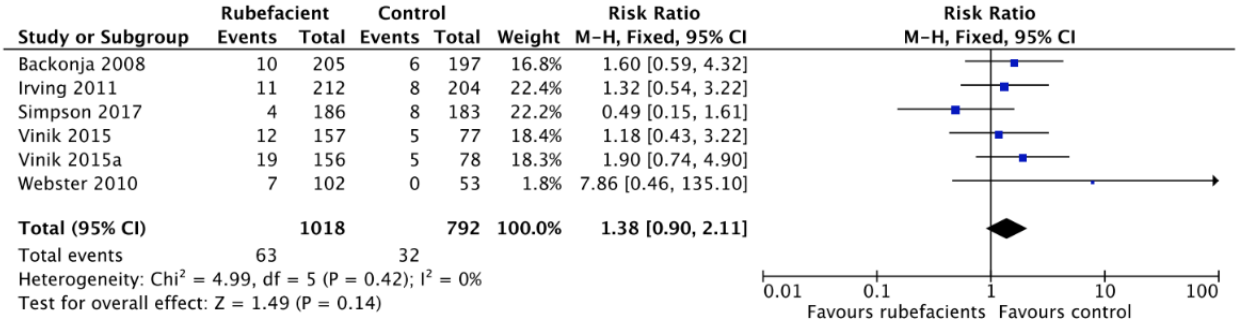


Figure 17.14 Rubefacients versus control; Adverse Event: Sinusitis

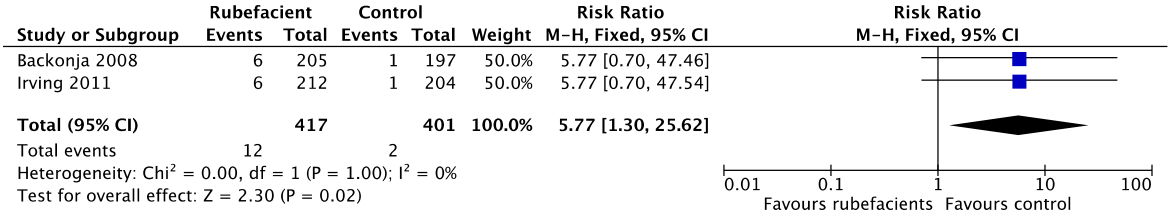


Figure 17.15 Rubefacients versus control; Adverse Event: Swelling at Application Site

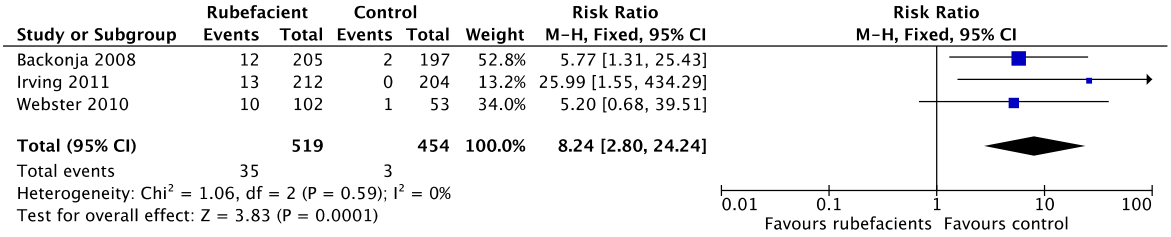


Figure 17.16 Rubefacients versus control; Adverse Event: Unspecific Application Site Reaction

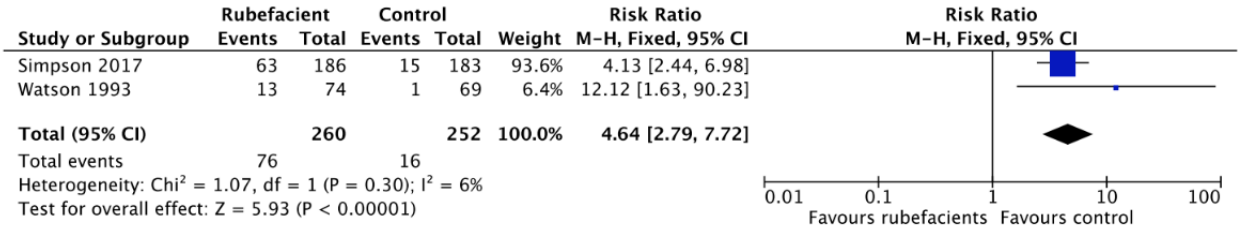


Figure 17.17 Rubefacients versus control; Adverse Event: Upper Respiratory Tract Infection

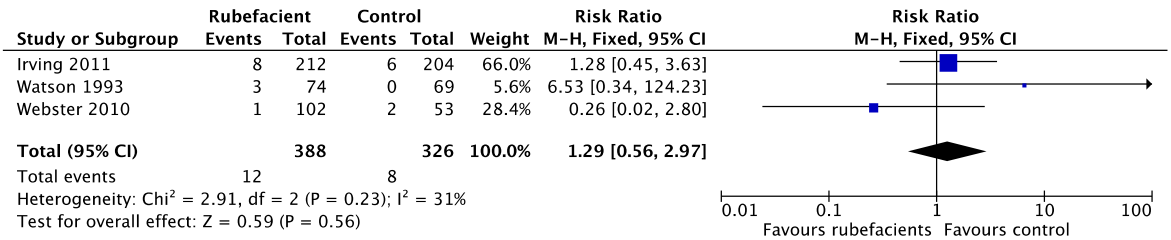
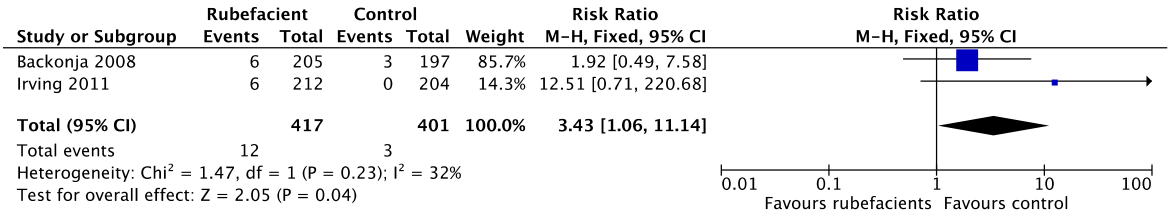


Figure 17.18 Rubefacients versus control; Adverse Event: Vomiting



SNRIs

Figure 18.1 SNRIs versus control; Withdrawals due to Adverse Events

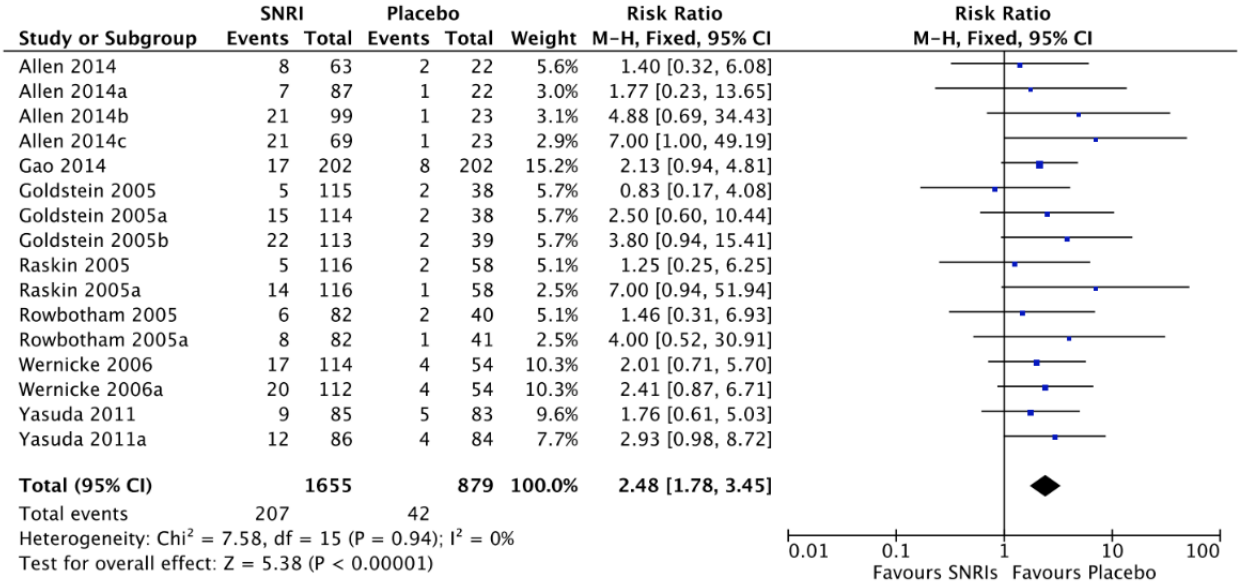


Figure 18.2 SNRIs versus control; Adverse Event: Anorexia

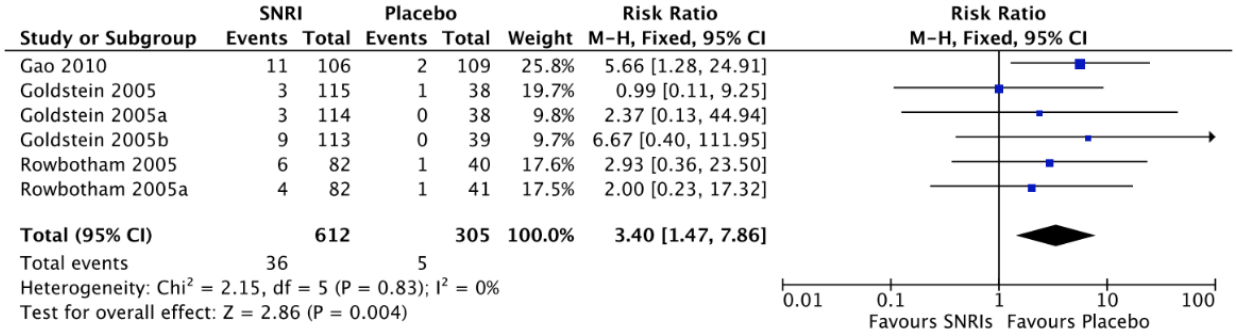


Figure 18.3 SNRIs versus control; Adverse Event: Asthenia

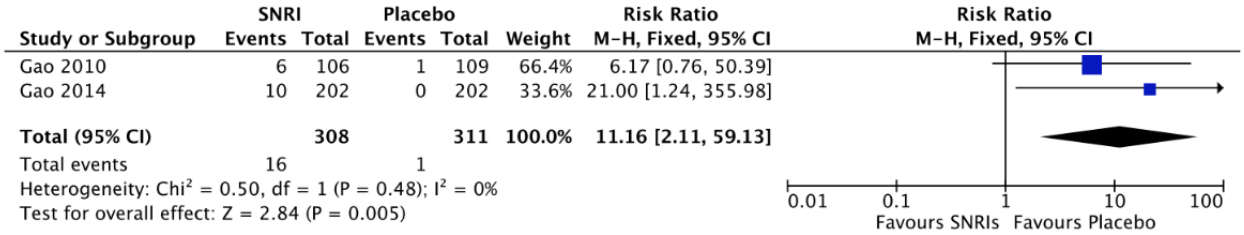


Figure 18.4 SNRIs versus control; Adverse Event: Constipation

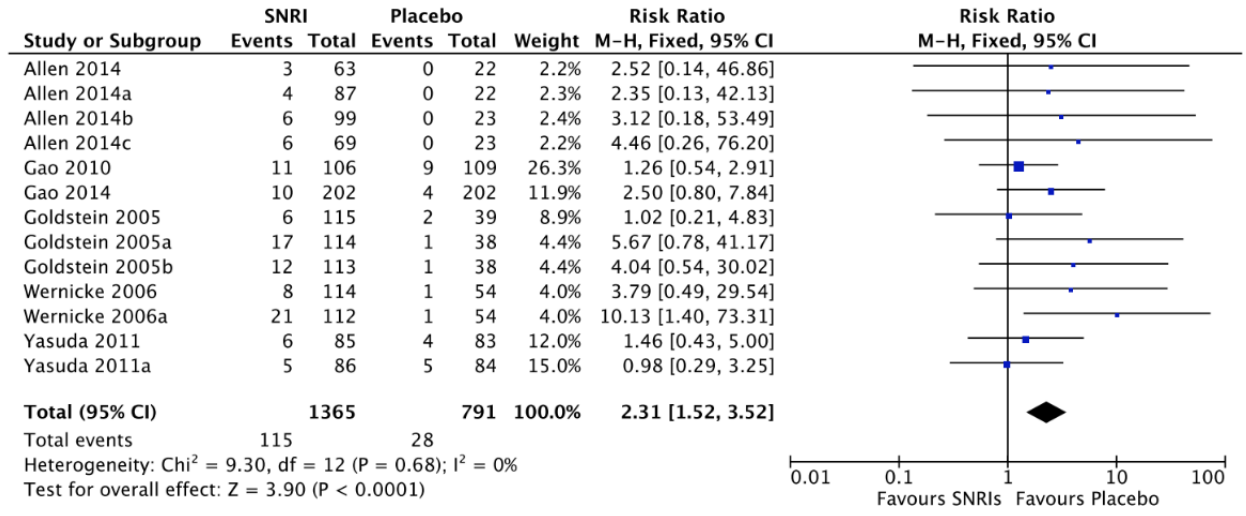


Figure 18.5 SNRIs versus control; Adverse Event: Decreased Appetite

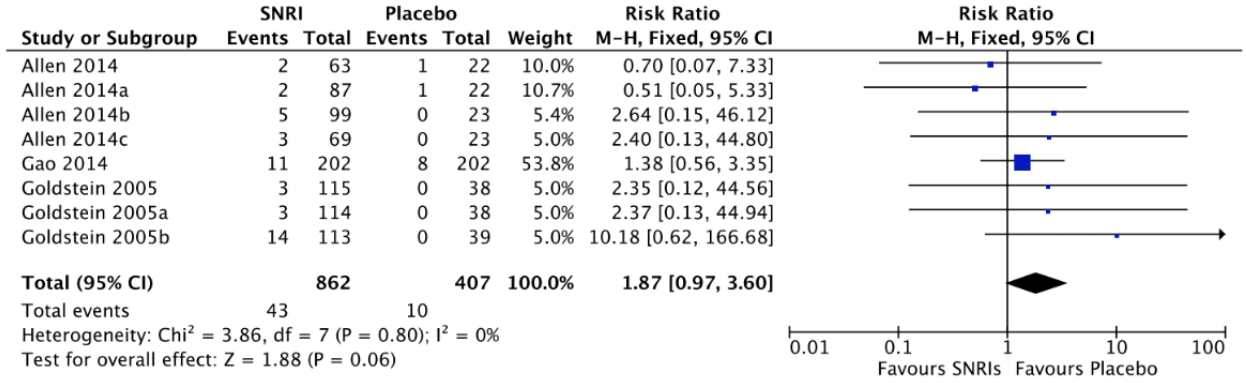


Figure 18.6 SNRIs versus control; Adverse Event: Diarrhea

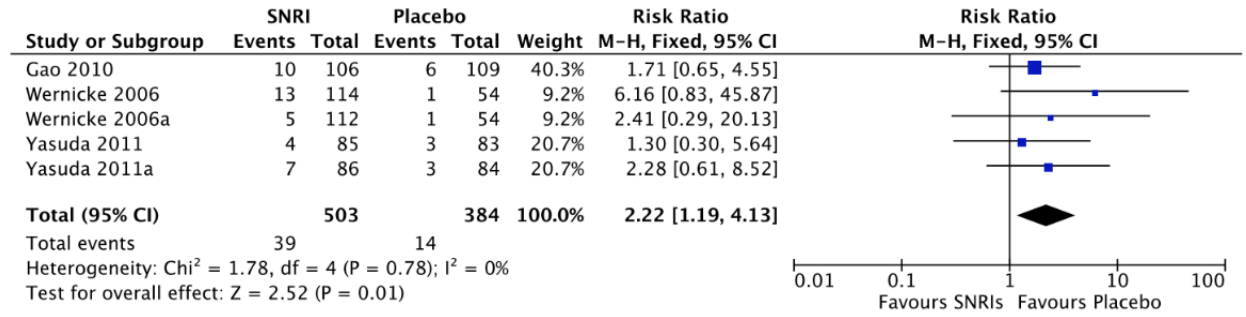


Figure 18.7 SNRIs versus control; Adverse Event: Dizziness

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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]
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: $Chi^2 = 10.59$, df = 12 (P = 0.56); $I^2 = 0\%$
Test for overall effect: Z = 3.90 (P < 0.0001)

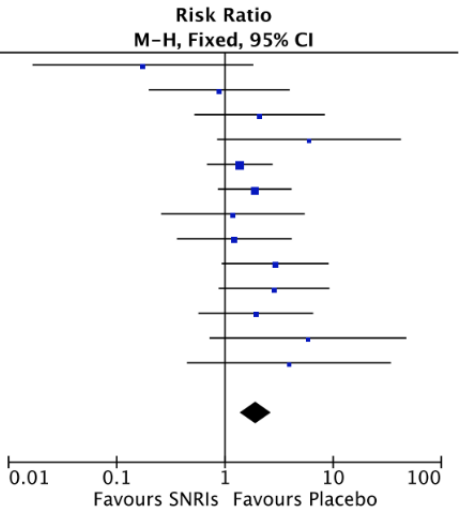


Figure 18.8 SNRIs versus control; Adverse Event: Dry Mouth

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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]
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: $Chi^2 = 1.09$, df = 7 (P = 0.99); $I^2 = 0\%$
Test for overall effect: Z = 1.87 (P = 0.06)

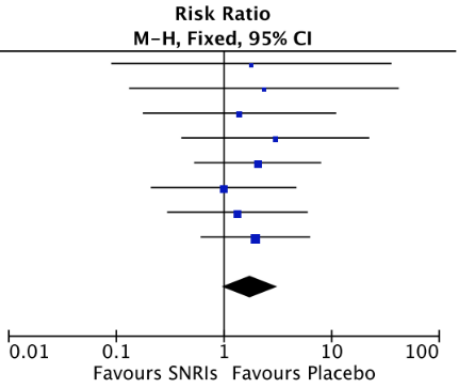


Figure 18.9 SNRIs versus control; Adverse Event: Fatigue

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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]
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: $Chi^2 = 4.35$, df = 7 (P = 0.74); $I^2 = 0\%$
Test for overall effect: Z = 2.90 (P = 0.004)

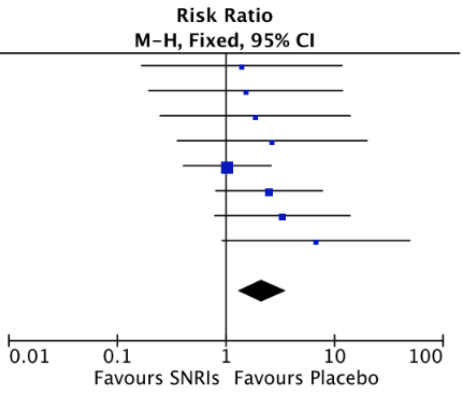


Figure 18.10 SNRIs versus control; Adverse Event: Headache

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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: $Chi^2 = 1.07$, df = 2 (P = 0.58); $I^2 = 0\%$
Test for overall effect: Z = 1.30 (P = 0.19)

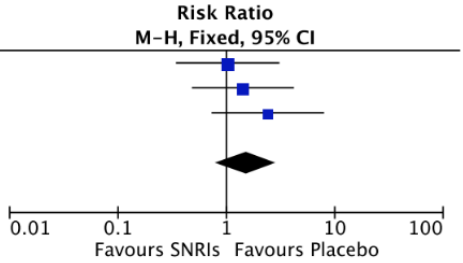


Figure 18.11 SNRIs versus control; Adverse Event: Increased Sweating

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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]
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: $Chi^2 = 3.11$, df = 7 (P = 0.87); $I^2 = 0\%$
Test for overall effect: Z = 3.25 (P = 0.001)

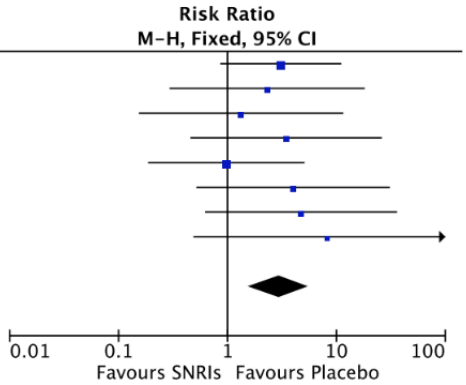


Figure 18.12 SNRIs versus control; Adverse Event: Insomnia

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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: $Chi^2 = 1.32$, df = 7 (P = 0.99); $I^2 = 0\%$
Test for overall effect: Z = 2.30 (P = 0.02)

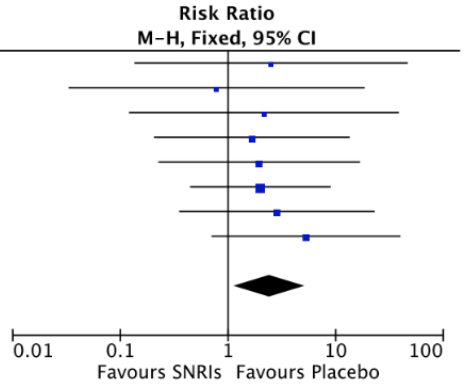


Figure 18.13 SNRIs versus control; Adverse Event: Lethargy

Study or Subgroup	SNRI Events	SNRI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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]
Total (95% CI)		**424**		**199**	**100.0%**	**2.33 [0.96, 5.66]**
Total events	21		4			

Heterogeneity: $Chi^2 = 0.53$, df = 4 (P = 0.97); $I^2 = 0\%$
Test for overall effect: Z = 1.87 (P = 0.06)

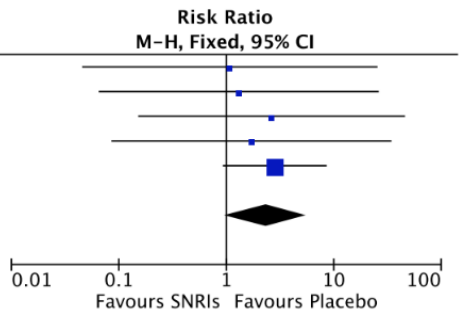


Figure 18.14 SNRIs versus control; Adverse Event: Nasopharyngitis

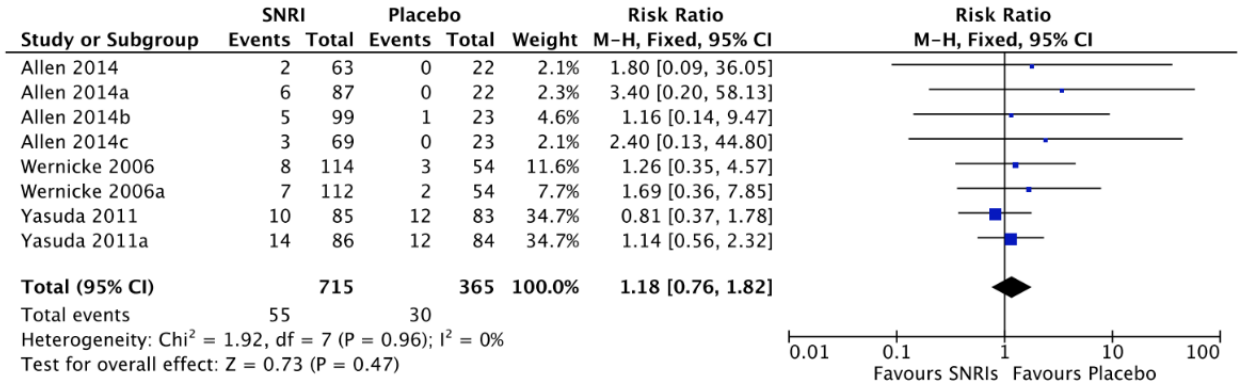


Figure 18.15 SNRIs versus control; Adverse Event: Nausea

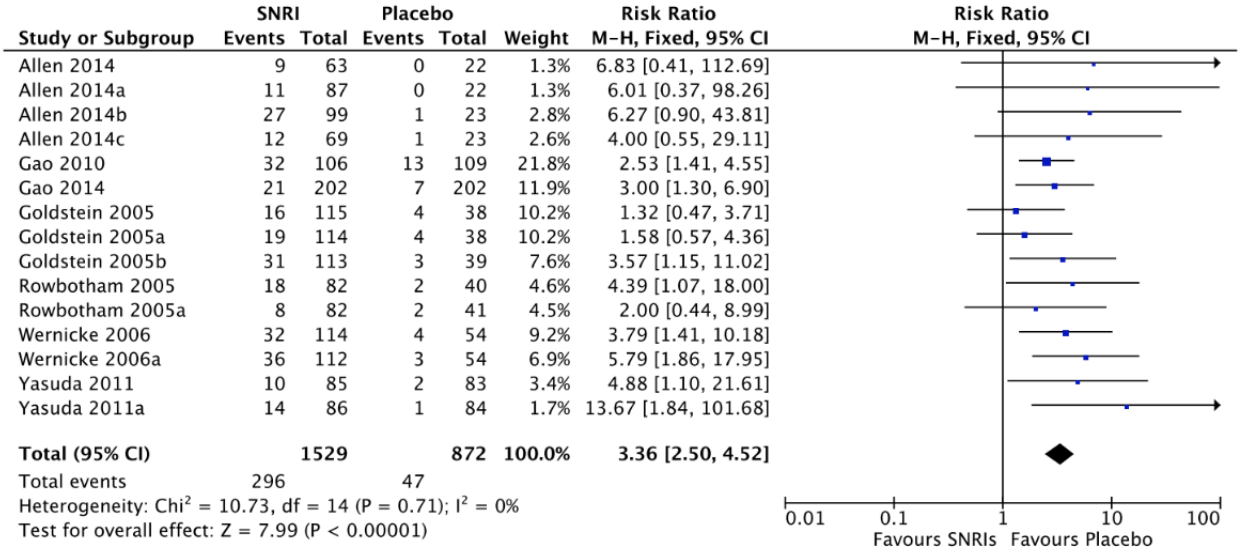


Figure 18.16 SNRIs versus control; Adverse Event: Serious Adverse Events

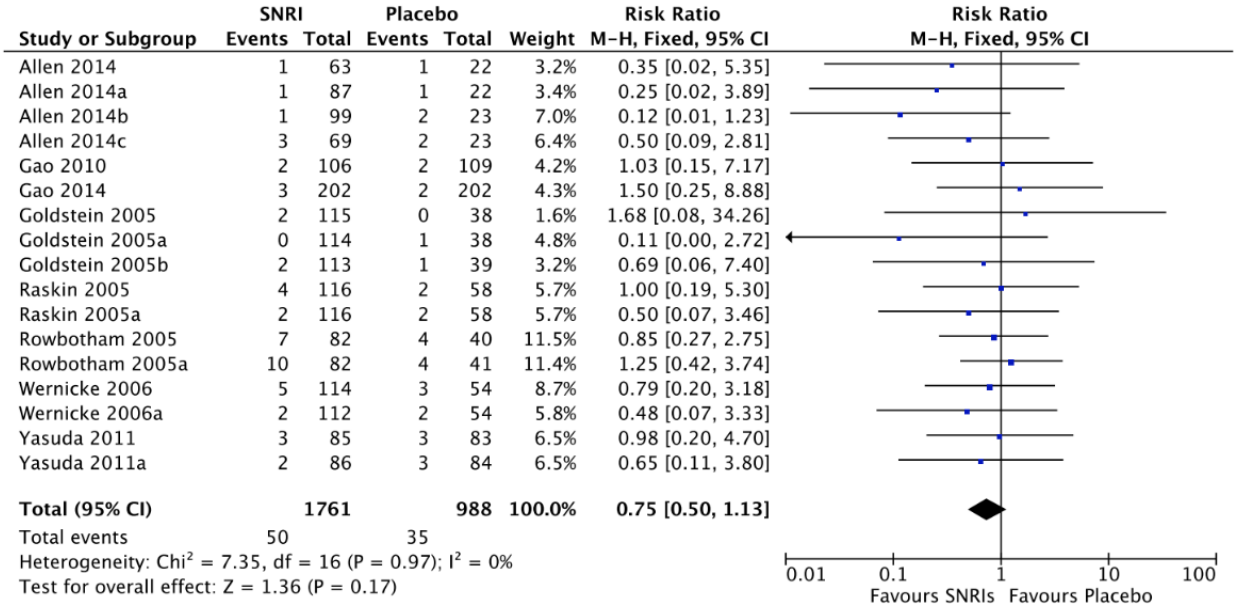


Figure 18.17 SNRIs versus control; Adverse Event: Somnolence and Fatigue

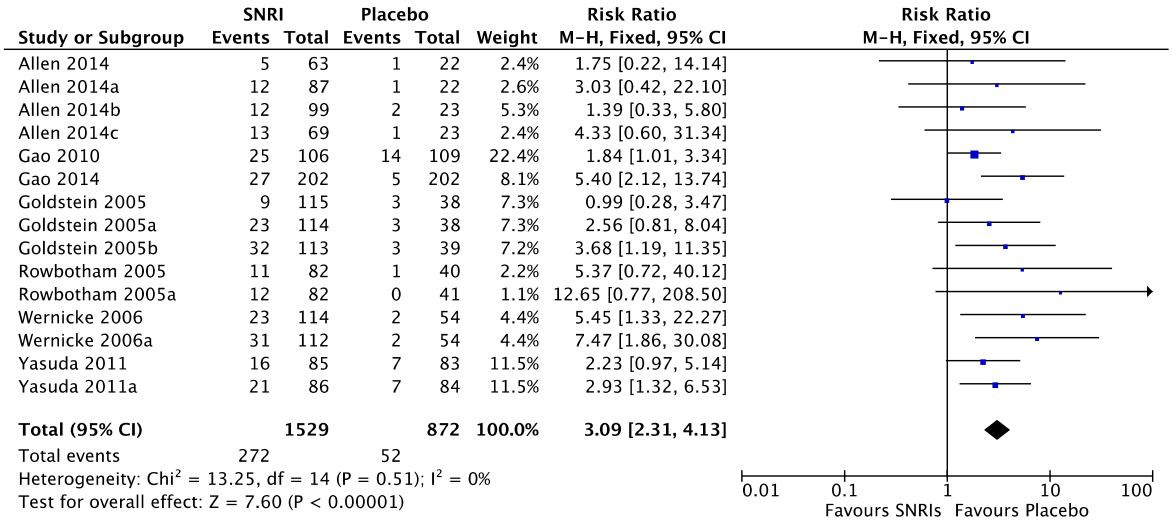


Figure 18.18 SNRIs versus control; Adverse Event: Sustained Hypertension

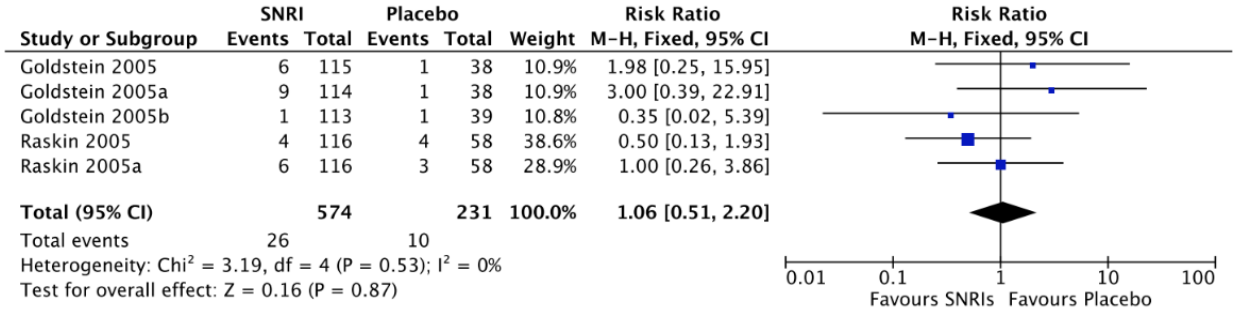
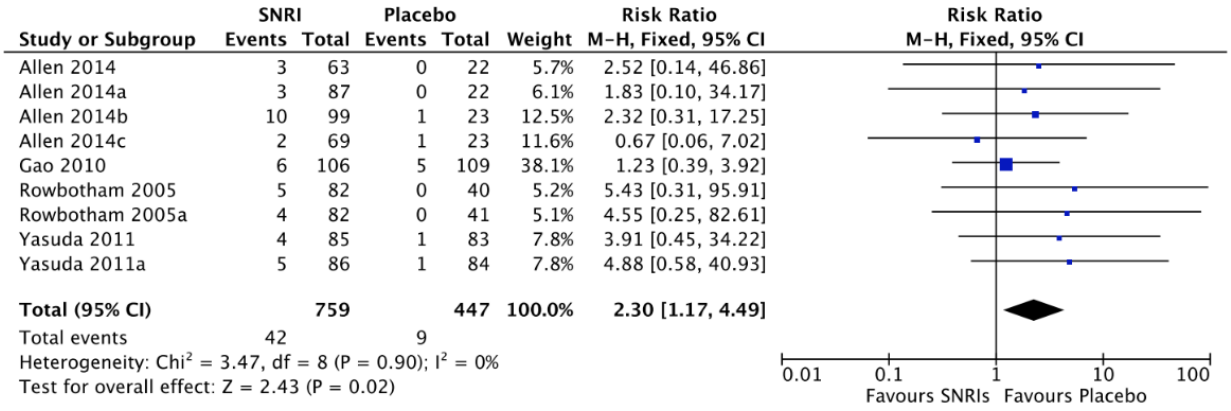


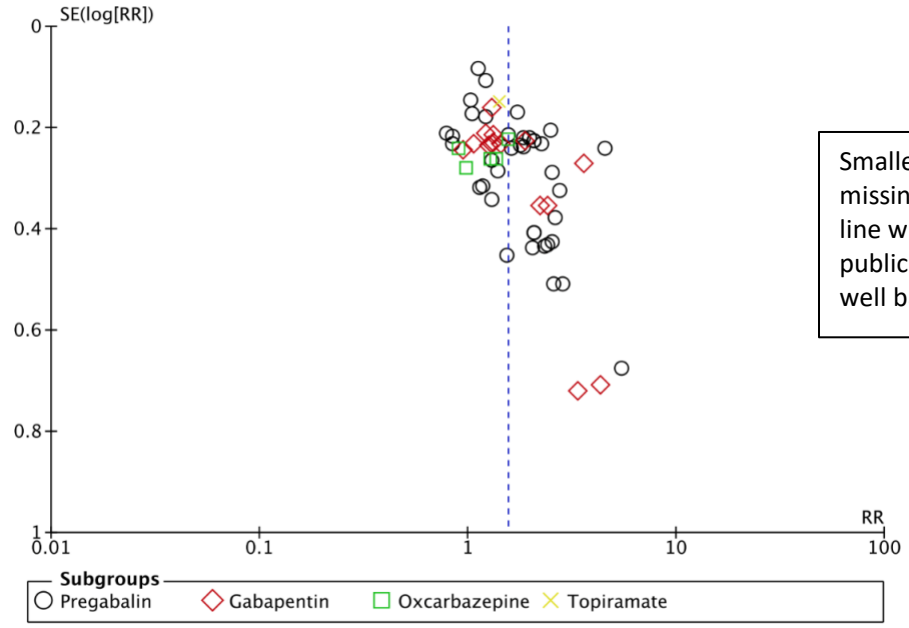
Figure 18.19 SNRIs versus control; Adverse Event: Vomiting



Funnel Plots

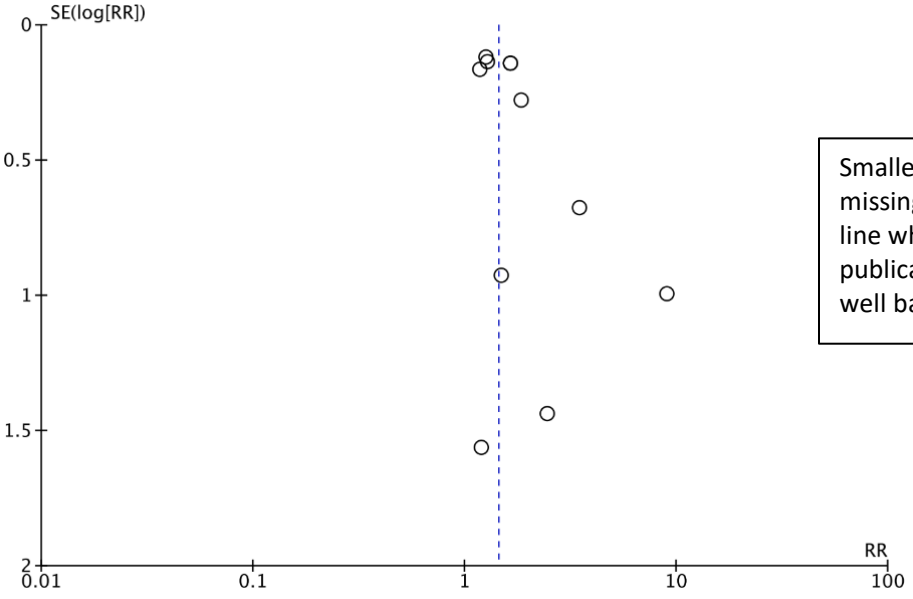
Funnel plots were generated via RevMan for interventions with ≥8 studies. This information was used in the GRADE process to assess potential publication bias.

Figure 19.1 Anticonvulsants



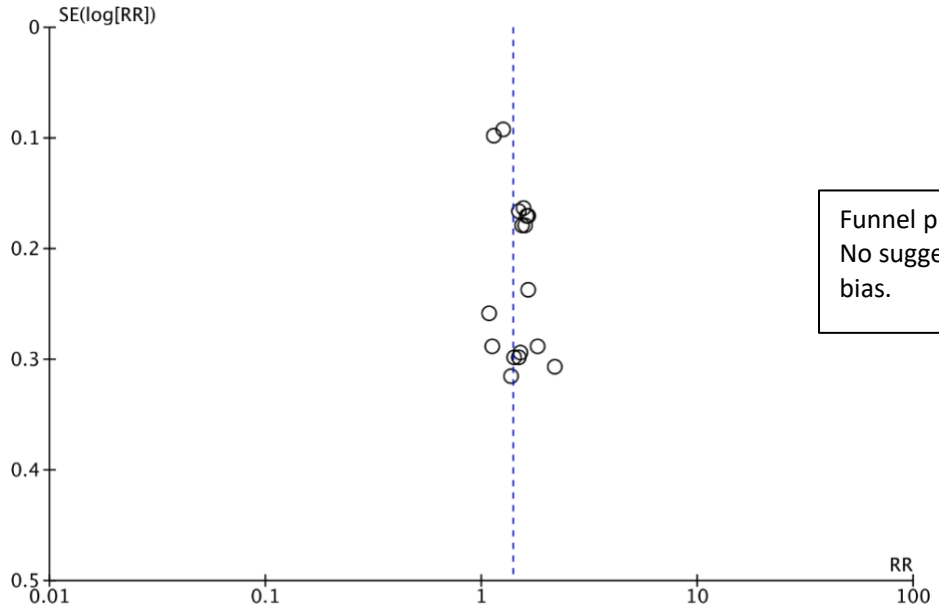
Smaller studies appear to be missing to the left of the effect line which may suggest some publication bias, but otherwise well balanced.

Figure 19.2 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



Funnel plot appears balanced. No suggestion of publication bias.

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

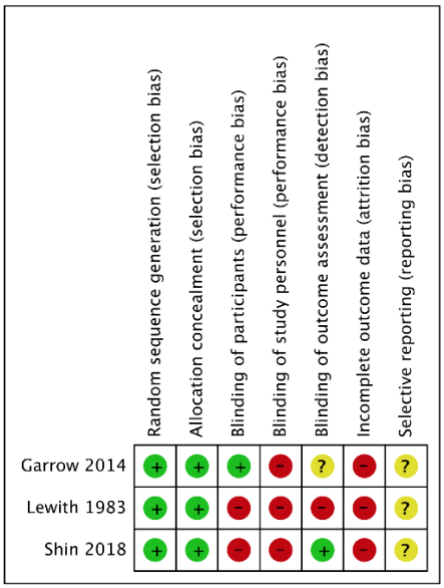


Figure 20.1b Acupuncture Risk of Bias Graph

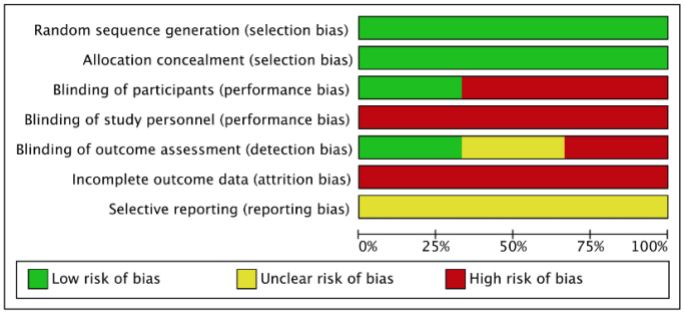
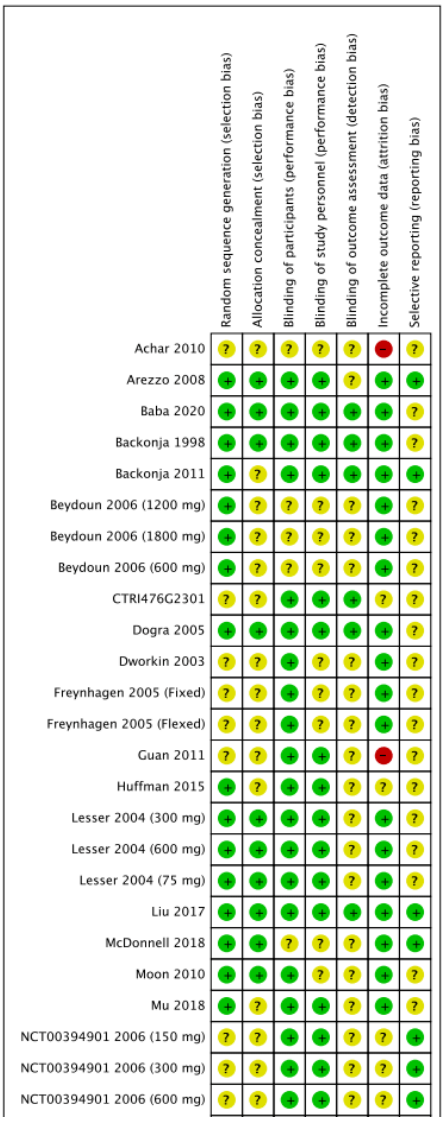


Figure 20.2a Anticonvulsants Risk of Bias Summary



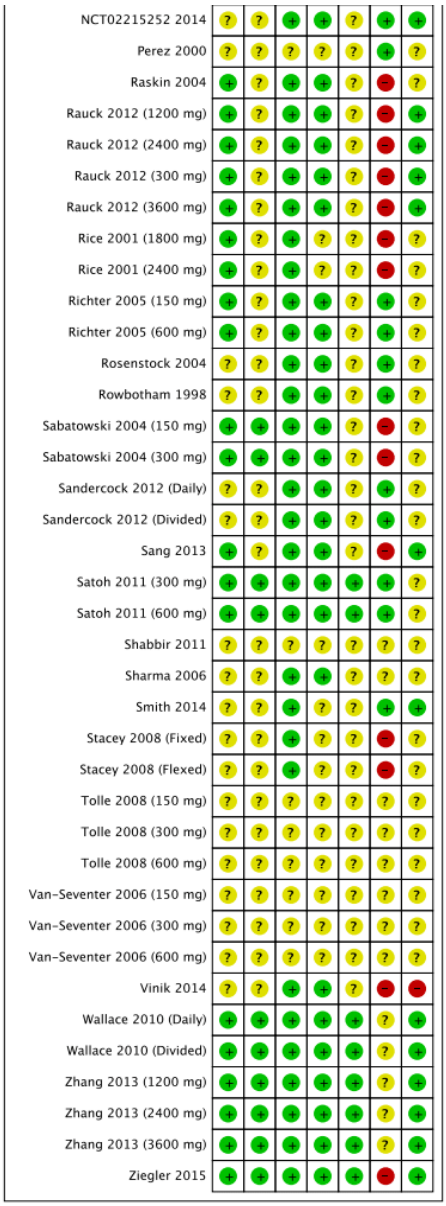


Figure 20.2b Anticonvulsants Risk of Bias Graph

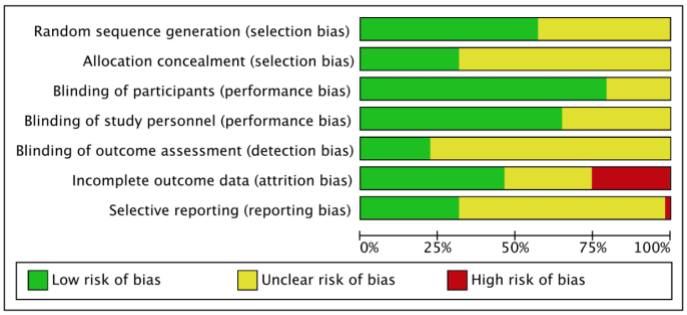


Figure 20.3a Opioids Risk of Bias Summary

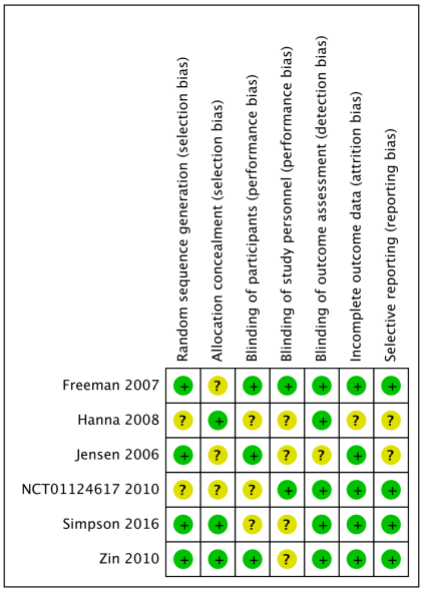


Figure 20.3b Opioids Risk of Bias Graph

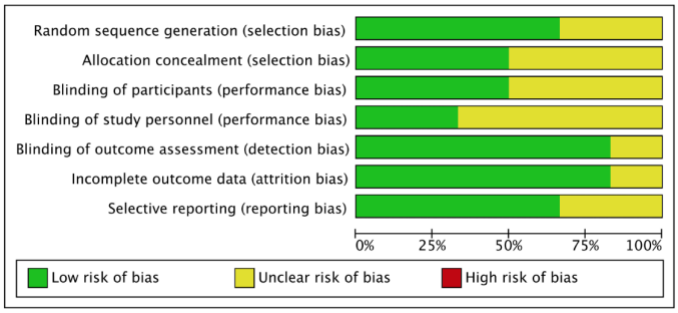


Figure 20.4a Rubefacients Risk of Bias Summary

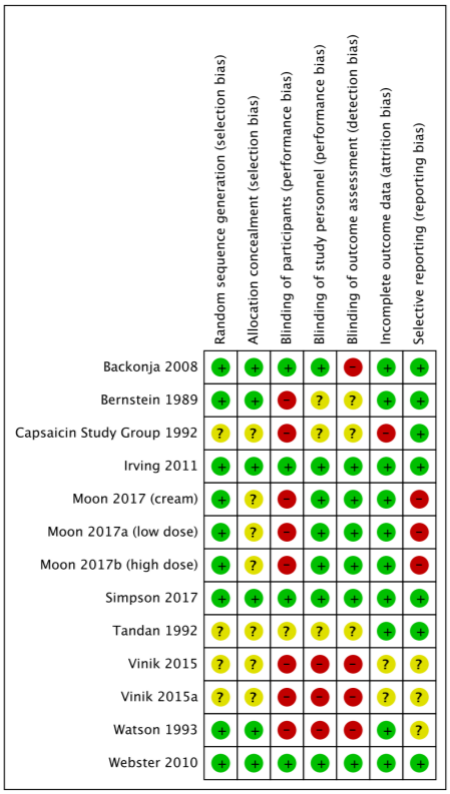


Figure 20.4b Rubefacients Risk of Bias Graph

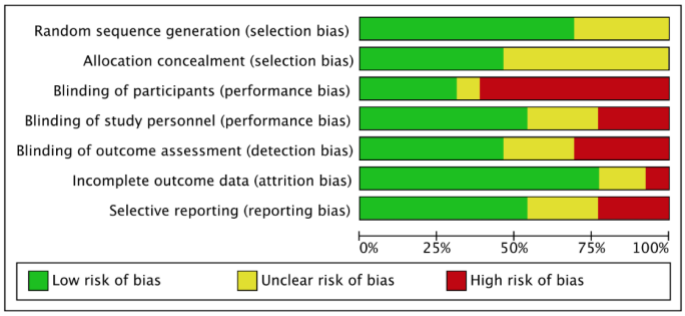


Figure 20.5a SNRIs Risk of Bias Summary

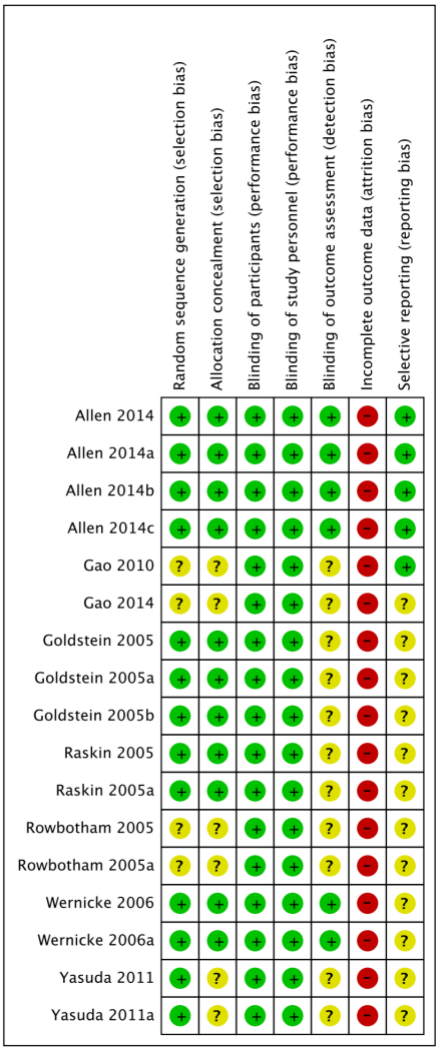


Figure 20.5b SNRIs Risk of Bias Graph

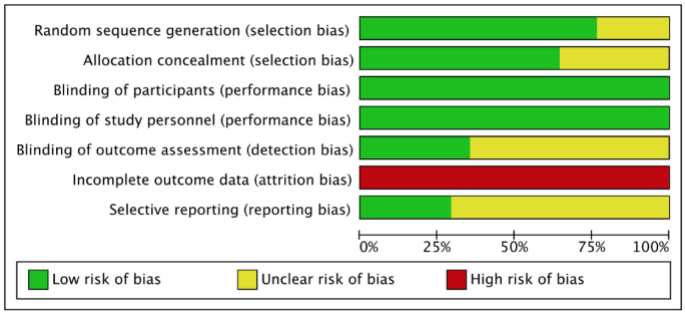


Figure 20.6a TCAs Risk of Bias Summary

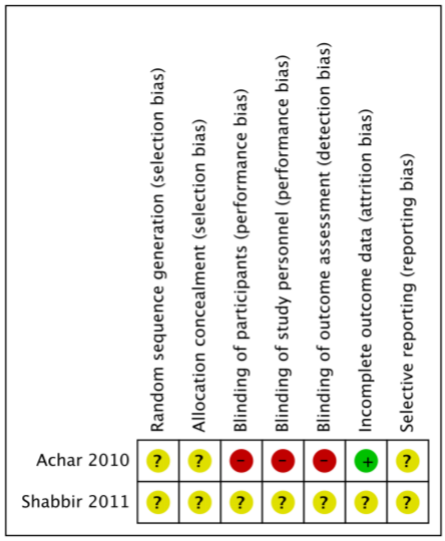


Figure 20.6b TCAs Risk of Bias Graph

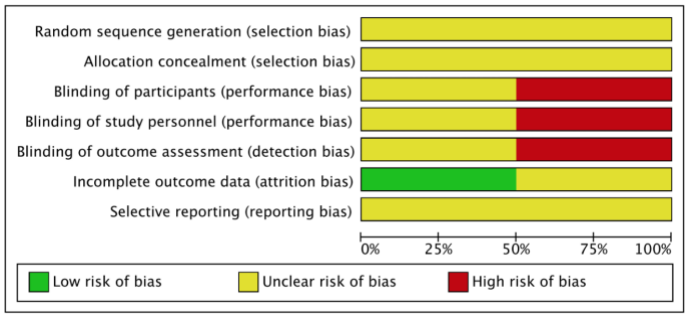


Table 15: GRADE Evaluation of Evidence Quality

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% CI 1.45, 1.63)	Publication Bias (-1)	Moderate
Opioids	6	RR 1.37 (95% CI 1.19, 1.57)	Indirect (-1) Publication Bias (-1)	Low
Rubefacients	10	RR 1.40 (95% CI 1.26, 1.55)	Risk of Bias (-1) Publication Bias (-1)	Low
SNRIs	8	RR 1.45 (95% CI 1.33, 1.59)	Publication Bias (-1)	Moderate
TCAs	2	RR 3.00 (95% CI 2.05, 4.38)	Risk of Bias (-1) Inconsistency (-1) Indirectness (-1) Imprecision (-1) Publication Bias (-1)	Very Low

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

GRADE Criteria for Quality Assessment Sections

Risk of Bias	Consider allocation concealment, blinding, large losses to follow-up, ITT analysis, stopping early for benefit, etc. Failure to report outcomes/selective reporting of outcomes
Inconsistency	Do the estimates of the treatment effect vary widely across studies? Statistical heterogeneity, variability in results Unexplained inconsistency/heterogeneity → decreased quality
Indirectness	Differences in population (i.e. patients or animal studies) 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 bias	Small number of trials Only industry funded trials included Funnel plot
Magnitude of effect	Large and consistent estimates of the magnitude of a treatment effect Large effect: RR >2 or <0.5; very large effect: RR >5 or <0.2
Dose response gradient	Presence of this gradient increases the confidence.
Plausible confounding	If residual confounding would be expected to bias the treatment effect in the opposite direction as observed - increases confidence in results.
Reference: Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 20 The GRADE Working Group, 20 Available from guidelinedevelopment.org/handbook.	

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 included...all types?	Addressed. See above.
Overall solid paper. A few suggestions:	
Introduction	
• 1st paragraph could be simplified – line 2: by removing "symptom based"; line 3 by removing "is typically both persistent and paroxysmal in nature"	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 interventions?	Addressed. See above.
• Search strategy – specify whether only publications in English were considered and provide the clinical trial registries that were used	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 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^2, 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^2 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	
• Lines 228-229. Consider removing topiramate and oxcarbazepine are typically not prescribed for neuropathic pain (especially not in primary care)	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.
• Consider including the typical placebo response and general NNT (5-10)	Refer to PEER Simplified Decision Aid for Neuropathic Pain
• 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	Manuscript revised.
• 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?	Requires further study to answer.
• It would also be interesting to know whether tramadol is any different than the other opioids as it is currently being marketed as the opioid to use for neuropathic pain	Manuscript revised.
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 intervals were reasonably similar between fixed and random effect analyses, we concluded that it was unlikely that *small studies were disproportionately influencing the result and chose fixed effects for the primary analysis*". ???	Addressed above (added a reference to the Cochrane handbook).
This sentence does not make sense. The size of the study is not the only factor affecting the fixed or random effect model. Perhaps delete it or provide more explanation	Added a reference to the Cochrane handbook.
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 quality of trials, the inclusion of a number of neuropathic pain types or different patient populations, and variance in the 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.	Heterogeneity may also be due to other things, not only those that were examined in subgroup analyses.
Additional comments:	
Are any of these studies conducted in primary care setting? As the systematic review claims that these results are appropriate for primary care providers, it is worth mentioning if they have been done in the primacy care setting.	A very small percentage (1%) of studies were clearly conducted in primary care, however 66% of trials did not clearly state the setting where the study was conducted.
Defining outcomes of interest--"While only a proportion of RCTs report a responder analysis, focusing on dichotomous outcomes allowed us to combine trials utilizing different pain measures, by 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.	We did report the limitations of only reporting responder analyses within the discussion section.

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Anticonvulsants

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