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

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Table 1: Low Back 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, eg. 25% and 35% improvement, we would use the higher number.
2. Clinically meaningful change on any low back pain scale (e.g. Minimally Clinical Important Change on a Roland Morris 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 (eg. 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

Interventions are listed in alphabetical order.

Intervention Type	Author, Year	Sample Size	Duration of Back Pain (weeks)	Mean Age	Outcome Measured At	Intervention(s), Comparator(s)	Outcome used in Meta-Analysis
Acupuncture	Brinkhaus 2006	219	764 weeks	59	8 weeks	Acupuncture; 12, 30-minute sessions Minimal Acupuncture; 12, 30-minute sessions	At least 50% reduction in pain intensity
Acupuncture	Cherkin 2009	638	Not reported	47	8 weeks	Individualized acupuncture; 10 sessions Standardized Acupuncture; 10 sessions Simulated Acupuncture; 10 sessions Usual Care including self-help book	Proportion of patients with MCID in pain (decrease in symptom bothersome scale by 2 or greater)
Acupuncture	Coan 1980	50	468 weeks	47	10 weeks	Acupuncture Waitlist	PGIC rated "improved" (decrease in $\geq$2 on 10-point scale)
Acupuncture	Haake 2007	1162	395 weeks	49	24 weeks	Verum Acupuncture; 10, 30-minute sessions Sham Acupuncture; 10, 30-minute sessions	33% or greater improvement on 3 pain-related items on the Von Korff Chronic Pain Grade Scale or 12% improvement or greater on back-specific functional status measured by the Hanover Functional Ability Questionnaire
Acupuncture	Hunter 2011	51	515 weeks	43	24 weeks	Auricular Acupuncture; provided prior to each exercise class and to be removed in 48 hours + Exercise (see below) Exercise; physiotherapy-delivered for 6 weeks followed by 6 weeks of unsupervised exercise	Proportion of patients achieving a MCID (8% change on Oswestry Disability Questionnaire)
Acupuncture	Kerr 2003	60	303 weeks	41	24 weeks	Acupuncture; 6, 30-minute sessions Placebo-TENS (no elec); 6, 30-minute sessions	Proportion of patients who experienced pain relief

Acupuncture	Meng 2003	51	624 weeks	71	6 weeks	Acupuncture + Standard Therapy; 10 sessions Standard Therapy	PGIC rated "much better"
Acupuncture	Molsberger 1998	186	515 weeks	50	4 weeks	Verum Acupuncture + Conventional Orthopedic Therapy (see below) Sham + Conventional Orthopedic Therapy; 12, 30-minute sessions	50% reduction in VAS
Acupuncture	Qin 2019	80	Not reported	62	8 weeks	Acupuncture; 24, 30-minute sessions Sham Acupuncture; 24, 30-minute sessions	Proportion of patients with a 30% or more improvement in Roland Morris Disability Questionnaire
Acupuncture	Witt 2006	2841	374 weeks	53	12 weeks	Acupuncture; maximum 15 sessions Waitlist	Proportion of patients who improved ≥20% in "back function loss")
Anticonvulsants	Atkinson 2016	108	910 weeks	56	12 weeks	Gabapentin (mean 3265 mg) Placebo	30% Improvement in Pain
Corticosteroid Injections	Arden 2005	228	NR	44	52 weeks	Corticosteroid Injections (Weeks 0,3,6) Saline Injections (Weeks 0,3,6)	≥75% improvement in Oswestry Disability Questionnaire
Corticosteroid Injections	Carette 1997	158	13 weeks	40	12 weeks	Epidural Corticosteroid (methylprednisolone) Injections (Up to 3) – Could be at 0,3,6 weeks and depended if no marked improvement or Oswestry Disability Questionnaire >20 seen. Saline Injections - Could be at 0,3,6 weeks	Oswestry Disability Questionaire ≤20 points
Corticosteroid Injections	Ghahreman 2010	23	67 weeks	45	4 weeks	Bupivacine 0.5% followed with Corticosteroi Injection (Triamcinolone) – (Up to 3 injections, repeat injections offered if 1st thought to be beneficial) Bupivacaine 0.5% (Up to 3 injections, repeat injections offered if 1st thought to be beneficial)	≥50% improvement 1 month after treatment

Corticosteroid Injections	Ghai 2015	69	82 weeks	45	52 weeks	Lidocaine 0.5% mixed with Corticosteroid Injection (Methylprednisolone) – Multiple Injections Offered if deterioration of pain relief was <50% - Need to be spaced at least 15 days apart Lidocaine 0.5% Only - Multiple Injections Offered if deterioration of pain relief was <50% - Need to be spaced at least 15 days apart	≥50% improvement from baseline
Corticosteroid Injections	Manchikanti 2012	100	399 weeks	56	52 weeks	Epidural Injections (Lidocaine 0.5% mixed with Betamethasone) – multiple injections offered Lidocaine 0.5% Only – multiple injections offered	≥50 pain relief and functional status improvement
Corticosteroid Injections	Manchikanti 2012a	120	384 weeks	46	104 weeks	Lidocaine 0.5% mixed with Corticosteroid Injection (Methylprednisolone or betamethasaone) – Multiple Injections Offered if deterioration of pain relief was <50% Lidocaine 0.5% Only - Multiple Injections Offered if deterioration of pain relief was <50%	≥50 pain relief and functional status improvement
Corticosteroid Injections	Manchikanti 2014	120	405 weeks	43	104 weeks	Injection of local anesthetic and Corticosteroid (betamethasone) – Around 6 procedures in 104 weeks Injection of local anesthetic only – Around 6 procedures in 104 weeks	≥50% reduction in pain and Oswestry disability index
Corticosteroid Injections	Ng 2005	86	58 weeks	51	12 weeks	Single Injection Corticosteroid (Methylprednisolone) and Bupivacaine Single Injection Bupivacaine	At least a 10% reduction in Oswestry Disability Index

Corticosteroid Injections	Nguyen 2017	135	330 weeks	47	4 weeks	Single Injection Contrast and Corticosteroid (Prednisolone) Single Injection Contrast Dye Only	Low back pain intensity <40 on 11 Numerical Rating Scale (0-100 in 10point increments)
Corticosteroid Injections	Saqib 2016	109	60 weeks	NR	4 weeks	Single Injection Corticosteroid (Methylprednisolone) and Bupivacaine Single Injection Bupivacaine	Achieved a moderate disability score (Oswestry Disability Index of 21-40%)
Exercise	Albaladejo 2010	348	Not Reported	52	12 weeks	Four, 1-hour group exercise sessions with physical therapist + Back Book Back Book + 15-minute group talk	Evolution of low back pain: Disappeared or Improved
Exercise	Brandt 2015	13	208 weeks	30	12 weeks	Physical Therapy-delivered core strengthening for 4 days/week Usual activity	MCID in numerical pain scale (Change of 2 or more)
Exercise	Brodsky 2019	69	Not reported	49	12 weeks	Group stretching program, once weekly for 15-30 minutes Self-care book with weekly emails for follow-up	At least 50% reduction in Roland Morris Disability Questionnaire
Exercise	Chan 2017	96	14 weeks	42	10 weeks	Physiotherapy-delivered individualized functional restoration, one weekly for 30 minutes Physiotherapy advice delivered in two, 30-minute sessions	Reduced pain at least 50% on numerical pain scale
Exercise	Costa 2009	154	332 weeks	54	52 weeks	Physiotherapy-delivered motor control exercises, 12, 30-minute sessions Detuned shortwave diathermy and ultrasound delivered over 12, 30-minute sessions	Pain Free (Recovered)
Exercise	Cox 2010	20	588 weeks	45	12 weeks	Yoga classes delivered once weekly for 75 minutes + Back Book + Usual Care Back Book + Usual Care	Roland Disability Questionnaire: At least 2 point improvement
Exercise	Ford 2016	300	15 weeks	44	10 weeks	Individualized physiotherapy delivered once weekly for 30 minute sessions + Advice Advice delivered in two, 30 minute sessions	Reduced pain by $\geq$50% on numerical pain scale

Exercise	Frost 2004	286	Not Reported	41	8 weeks	Physiotherapy-delivered exercise; patients received a median of 5 sessions (range 1-12) averaging 30 minutes in length Advice to stay active delivered in one, 30-minute session	Patient perceived benefit (benefit versus no benefit)
Exercise	Groessl 2017	150	780 weeks	53	12 weeks	Yoga delivered twice a week for 60-minutes a session + Usual Care Delayed Yoga + Usual Care	30% decrease in Roland Morris Disability Questionnaire
Exercise	Hall 2011	160	Not reported	44	10 weeks	Tai Chi; 18, 40-minute sessions + Usual Care Waitlist + Usual Care	At least 30% improvement in pain
Exercise	Hartvigsen 2010	136	Not reported	47	10 weeks	Supervised Nordic Walking; 16, 45-minute sessions Unsupervised Nordic Walking Advice Only	Proportion of patients achieving an MCID on low back pain rating scale (LBPRS)
Exercise	Highland 2018	68	Not reported	44	8 weeks	Therapeutic Yoga; 12, 60-minute sessions Treatment as usual	Proportion of patients reporting MCID (2 point on 11-point scale or 30% reduction)
Exercise	Jensen 2012	100	Not reported	46	10 weeks	Physiotherapy-delivered group exercise; once weekly for 10, 60-minute sessions Rest (avoid physical activity and to rest twice daily for one hour)	Achieved a MCID in pain
Exercise	Moffett 1999	187	Not reported	42	6 weeks	Physiotherapy-delivered exercise; 8, 60-minute sessions Usual Care	Minimum 3 point improvement on Roland Morris Disability Questionnaire
Exercise	Natour 2015	60	Not reported	48	12 weeks	Pilates; 24, 50-minute sessions, delivered twice weekly Waitlist	PGIC rated “much better”
Exercise	Saper 2009	29	Not reported	44	12 weeks	Yoga; once weekly for 75 minutes + Routine Care + Education Book Routine Care + Education Book	Proportion of patients with MCID in pain ($\geq$2 point decrease in pain and $\geq$)
Exercise	Saper 2017	320	Not reported	46	12 weeks	Yoga; once weekly for 75 minutes	At least 30% reduction in back pain

						Physical Therapist-led aerobic exercise; 15, 60-minute sessions Back Pain Help Book	
Exercise	Sherman 2005	101	Not reported	44	12 weeks	Yoga; once weekly for 75 minutes Physical Therapist-led aerobic and strength exercise; once weekly for 75 minutes Back Pain Help Book	At least 50% reduction in Roland Morris Disability Questionnaire
Exercise	Sherman 2011	228	558 weeks	48	12 weeks	Yoga; once weekly for 75 minutes Physiotherapy-led aerobic and stretching exercise; once weekly for 75 minutes Back Pain Help Book	PGIC rated "better", "much better", or "completely gone"
Opioids	Buynak 2010	965	Not reported	50	12 weeks	Oxycodone CR 20-50mg BID Tapentadol ER 100-250mg BID Placebo	≥30% pain relief
Opioids	Cristoph 2017	637	562 weeks	58	12 weeks	Tapentadol PR 200mg BID Cebranopadol 200-600mg QD Placebo	≥30% pain relief
Opioids	Lee 2013	245	Not reported	60	4 weeks	Tramadol/Acetaminopen ER 37.5/325mg 1-2tabs BID Placebo	≥30% pain relief
Opioids	Uberall 2012	236	296 weeks	58	4 weeks	Tramadol ER 200mg QD Placebo	≥30% pain relief
Opioids	Peloso 2004	336	Not reported	58	12 weeks	Tramadol/Acetaminopen ER 37.5/325mg 3-8 tabs per day Placebo	≥30% pain relief
Opioids	Ruoff 2003	318	Not reported	54	12 weeks	Tramadol/Acetaminopen ER 37.5/325mg 1-8 tabs per day Placebo	≥30% pain relief
Oral NSAIDs	Coats 2004	293	585 weeks	49	4 weeks	Valdecoxib 40 mg daily Placebo	50% reduction in pain

Oral NSAIDs	Katz 2011	129	621 weeks	52	12 weeks	Naproxen 1000 mg daily + Single IV infusion of tanezumab placebo Oral placebo + Single IV infusion of tanezumab placebo	30% reduction in low back pain
Oral NSAIDs	Katz 2003	690	629 weeks	53	4 weeks	Rofecoxib 25 mg daily Rofecoxib 50 mg daily Placebo	PGIC rated- "good" or "excellent"
Oral NSAIDs	Katz 2004 (second publication to Katz 2003)	""	""	""	""	""	Change in VAS only
Oral NSAIDs	Kivitz 2013	525	585 weeks	52	16 weeks	Naproxen 500 mg twice daily Placebo	30% reduction in pain
Rubefacients	Chrubasik 2010	142	Not reported	48	3 weeks	Capsaicin 0.05% Cream Placebo Cream	≥30% improvement
Rubefacients	Frerick 2003	319	Not reported	NR	3 weeks	Capsaicin Plaster applied once daily for 4-8 hours Placebo Plaster	≥30% improvement
Rubefacients	Keitel 2001	150	Not reported	NR	3 weeks	Capsaicin Plaster 11 mg applied once daily for 4-12 hours Placebo Plaster	≥30% improvement
SNRI (Duloxetine)	Konno 2016	458	520 weeks	59	12 weeks	Duloxetine 60mg/day Placebo	≥30% reduction in pain
SNRI (Duloxetine)	Skljarevski 2009	404	608 weeks	54	13 weeks	Duloxetine 20, 60 or 120mg/day Placebo	≥30% reduction in pain
SNRI (Duloxetine)	Skljarevski 2010	401	442 weeks	54	12 weeks	Duloxetine 60mg/day Placebo	≥30% reduction in pain
SNRI (Duloxetine)	Skljarevski 2010a	236	476 weeks	52	13 weeks	Duloxetine 60-120mg/day Placebo	≥30% reduction brief pain index average pain from baseline

Spinal Manipulation	Bialosky 2014	55	18 weeks	33	2 weeks	Spinal Manipulation; 6 sessions Sham Manipulation; 6 sessions	PGIC rated “good” or “excellent”
Spinal Manipulation	Bond 2020	29	176 weeks	24	3 weeks	Spinal Manipulation; 7 sessions Sham Manipulation; 7 sessions	Proportion of patients who met MCID (reduction of ≥1.25 on 11-point VAS pain scale)
Spinal Manipulation	Ford 2019	64	16 weeks	45	10 weeks	Spinal Manipulation; 10, 30-minute sessions Guidance-based Advice; 2, 30-minute sessions	50% or greater reduction in pain
Spinal Manipulation	Goertz 2017	83	Not reported	73	12 weeks	Spinal Manipulation (median 17.5 visits) + Medical Care Medical Care; median 2 visits	PGIC rated “completely gone”, “much better” or “moderately better”
Spinal Manipulation	Licciardone 2013	455	Not reported	41	12 weeks	Spinal Manipulation; 6, 15-minute sessions Sham Manipulation; 6, 15-minute sessions	30% or greater reduction in pain
Topical NSAIDs	Song 2008	127	Not Reported	52	1 week	Flurbiprofen Tape 63 mg/day worn 12 or 24 hours Placebo Tape, worn 12 or 24 hours	PGIC rated “very much improved, much improved or improved”

Table 3: Overall proportion of patients with meaningful response and proportion at less than or equal to four weeks, four to twelve weeks and at greater than twelve weeks.
Interventions are Ordered by Highest to Lowest Risk Ratio of Overall Efficacy.

Intervention Type	Number of RCTs	Subgroup	Intervention Event Rate	Control Event Rate	Risk Ratio (95% CI)	NNT
Exercise	**18**	**Overall Efficacy**	**50% (734/1472)**	**35% (386/1089)**	**RR 1.71 (95% CI 1.37, 2.15)**	**7**
	1	Assessed at: ≤4 weeks	40% (4/10)	30% (3/10)	RR 1.33 (95% CI 0.40, 4.49)	NSS
	11	Assessed at: >4 weeks to <12 weeks	47% (446/939)	27% (210/790)	RR 2.04 (95% CI 1.66, 2.51)	5
	10	Assessed at: ≥12 weeks	49% (383/779)	44% (199/449)	RR 1.64 (95% CI 1.16, 2.32)	21
Acupuncture	**8**	**Overall Efficacy**	**54% (1320/2457)**	**35% (754/2161)**	**RR 1.58 (95% CI 1.13, 2.21)**	**6**
	1	Assessed at: ≤4 weeks	60% (39/65)	33% (20/61)	RR 1.83 (95% CI 1.21, 2.76)	4
	6	Assessed at: >4 weeks to <12 weeks	53% (501/941)	50% (352/710)	RR 1.26 (0.99, 1.62)	NSS
	2	Assessed at: ≥12 weeks	55% (1015/1838)	34% (611/1777)	RR 1.49 (95% CI 0.75, 2.98)	NSS
Corticosteroid Injections	**10**	**Overall Efficacy**	**48% (276/581)**	**45% (257/571)**	**RR 1.07 (95% CI 0.87, 1.30)**	**NSS**
	5	Assessed at: ≤4 weeks	30% (99/333)	22% (70/324)	RR 1.55 (95% CI 0.93, 2.59)	NSS
	-	Assessed at: >4 weeks to <12 weeks	-	-	-	-
	7	Assessed at: ≥12 weeks	50% (221/446)	50% (217/435)	RR 1.01 (95% CI 0.82, 1.24)	NSS

RCTs: Randomized Controlled Trials; RR: Risk Ratio; CI: Confidence Interval; RR: Risk Ratio; NNT: Number Needed to Treat; NSS: Not statistically significant

Table 4: Overall proportion of patients with meaningful response at longest follow-up point after intervention
Interventions ordered by Highest to Lowest Risk Ratio (RR)

Intervention Type	Number of RCTs	Follow-up (range in weeks)	Intervention Event Rate	Control Event Rate	Risk Ratio (95% CI)	NNT
Exercise	11	12-48 Weeks After Intervention	53% (526/987)	37% (322/881)	RR 1.58 (95% CI 1.32, 1.89)	6
Acupuncture	4	8-45 Weeks After Intervention	49% (213/437)	40% (111/277)	RR 1.42 (0.87, 2.32)	NSS
Spinal Manipulation	1	42 Weeks After Intervention	61% (20/33)	45% (14/31)	RR 1.34 (0.83, 2.16)	NSS

RCTs: Randomized Controlled Trials; RR: Risk Ratio; CI: Confidence Interval; RR: Risk Ratio; NNT: Number Needed to Treat; NSS: Not statistically significant

Table 5: Proportion of patients with clinically meaningful response based on funding source (clearly publicly or industry funding)
Interventions ordered by Highest to Lowest Risk Ratio (RR)

Intervention Type	Number of RCTs	Subgroup	Intervention Event Rate	Control Event Rate	Risk Ratio (95% CI)	NNT	p-value Between Subgroups
Exercise	17	Public Funding	52% (714/1381)	36% (378/1044)	RR 1.76 (95% CI 1.38, 2.23)	7	NA
	0	Industry Funding	-	-	-	-	
Acupuncture	7	Public Funding	54% (1302/2417)	35% (745/2121)	RR 1.54 (95% CI 1.08, 2.20)	6	NA
	0	Industry Funding	-	-	-	-	
Corticosteroid Injections	7	Public Funding	44% (212/478)	44% (205/469)	RR 1.01 (95% CI 0.82, 1.24)	-	NA
	0	Industry Funding	-	-	-	-	

RCTs: Randomized Controlled Trials; RR: Risk Ratio; CI: Confidence Interval; RR: Risk Ratio; NNT: Number Needed to Treat; NA: Not Applicable

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

Ordered by Highest to Lowest Risk Ratio (RR).

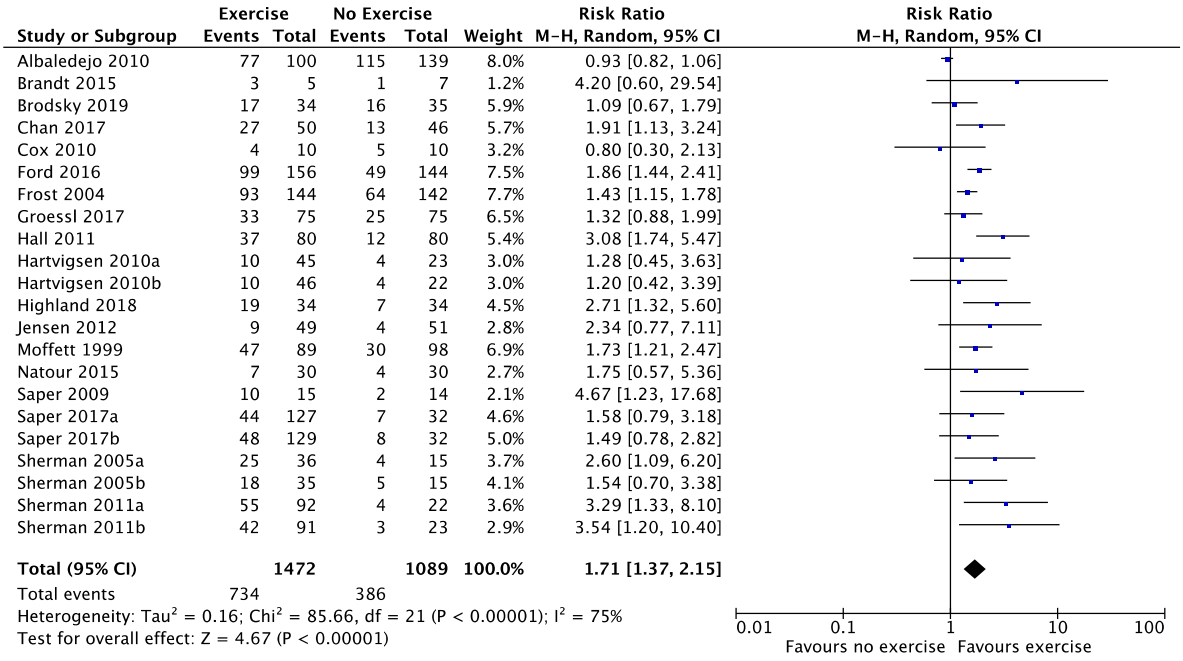
Intervention Type	Number of RCTs	Subgroup	Intervention Event Rate	Control Event Rate	Risk Ratio (95% CI)	NNT	p-value
Exercise	**7**	**Less than the median risk of bias score**	**57% (326/569)**	**42% (253/596)**	**RR 1.55 (95% CI 1.03, 2.32)**	**7**	P=0.66
	11	Greater than or equal to the median risk of bias score	45% (408/903)	27% (133/493)	RR 1.71 (95% CI 1.42, 2.05)	6	
Acupuncture	**4**	**Less than the median risk of bias score**	**63% (511/807)**	**59% (386/650)**	**RR 1.22 (95% CI 0.97, 1.55)**	**NSS**	P=0.02
	4	Greater than or equal to the median risk of bias score	49% (809/1650)	24% (368/1511)	RR 1.89 (95% CI 1.42, 2.51)	5	
Corticosteroid Injections	**5**	**Less than the median risk of bias score**	**56% 113/202**	**51% 102/200**	**RR 1.11 (95% CI 0.78, 1.59)**	**NSS**	P=0.73
	5	Greater than or equal to the median risk of bias score	43% 163/379	42% 155/371	RR 1.03 (95% CI 0.81, 1.32)	NSS	

RCTs: Randomized Controlled Trials; NNT: Number Needed to Treat; NSS: Not Statistically Significant; CI: Confidence Interval; RR: Risk Ratio

Data Analysis

Exercise

Figure 1.1: Exercise versus no exercise; Outcome: Proportion of patients with a meaningful response to treatment.



Study or Subgroup	Exercise Events	Exercise Total	No Exercise Events	No Exercise Total	Weight	Risk Ratio M-H, Random, 95% CI
Albaledejo 2010	77	100	115	139	8.0%	0.93 [0.82, 1.06]
Brandt 2015	3	5	1	7	1.2%	4.20 [0.60, 29.54]
Brodsky 2019	17	34	16	35	5.9%	1.09 [0.67, 1.79]
Chan 2017	27	50	13	46	5.7%	1.91 [1.13, 3.24]
Cox 2010	4	10	5	10	3.2%	0.80 [0.30, 2.13]
Ford 2016	99	156	49	144	7.5%	1.86 [1.44, 2.41]
Frost 2004	93	144	64	142	7.7%	1.43 [1.15, 1.78]
Groessl 2017	33	75	25	75	6.5%	1.32 [0.88, 1.99]
Hall 2011	37	80	12	80	5.4%	3.08 [1.74, 5.47]
Hartvigsen 2010a	10	45	4	23	3.0%	1.28 [0.45, 3.63]
Hartvigsen 2010b	10	46	4	22	3.0%	1.20 [0.42, 3.39]
Highland 2018	19	34	7	34	4.5%	2.71 [1.32, 5.60]
Jensen 2012	9	49	4	51	2.8%	2.34 [0.77, 7.11]
Moffett 1999	47	89	30	98	6.9%	1.73 [1.21, 2.47]
Natour 2015	7	30	4	30	2.7%	1.75 [0.57, 5.36]
Saper 2009	10	15	2	14	2.1%	4.67 [1.23, 17.68]
Saper 2017a	44	127	7	32	4.6%	1.58 [0.79, 3.18]
Saper 2017b	48	129	8	32	5.0%	1.49 [0.78, 2.82]
Sherman 2005a	25	36	4	15	3.7%	2.60 [1.09, 6.20]
Sherman 2005b	18	35	5	15	4.1%	1.54 [0.70, 3.38]
Sherman 2011a	55	92	4	22	3.6%	3.29 [1.33, 8.10]
Sherman 2011b	42	91	3	23	2.9%	3.54 [1.20, 10.40]
Total (95% CI)		**1472**		**1089**	**100.0%**	**1.71 [1.37, 2.15]**
Total events	734		386			

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 85.66$, df = 21 ($P < 0.00001$); $I^2 = 75\%$

Test for overall effect: $Z = 4.67$ ($P < 0.00001$)

Figure 1.2: Exercise versus no exercise; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less.

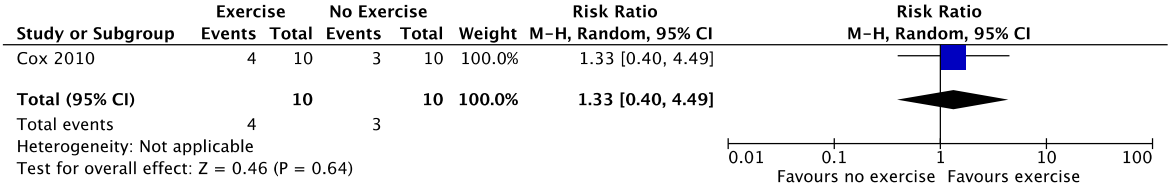


Figure 1.3: Exercise versus no exercise; Outcome: Proportion of patients with a meaningful response to treatment at greater than 4 weeks and less than 12 weeks.

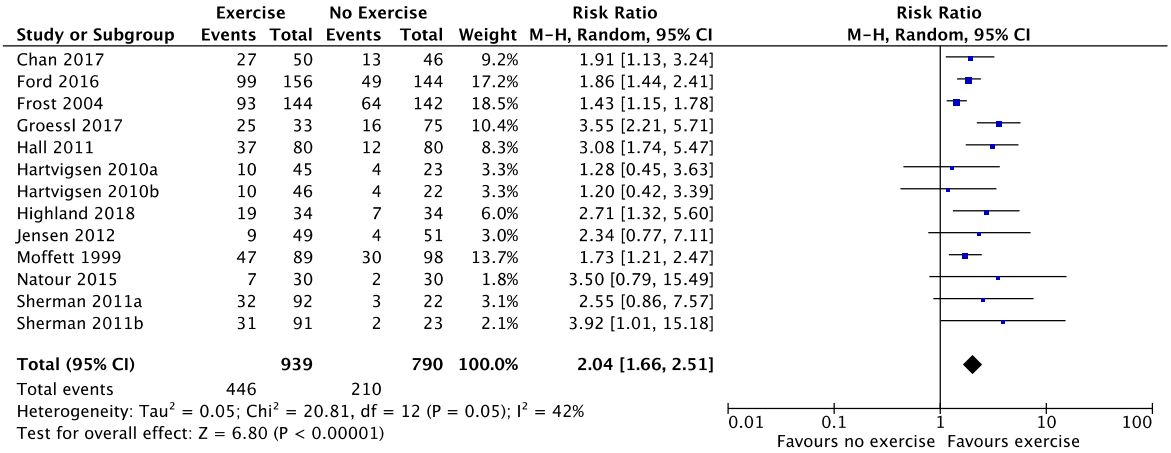
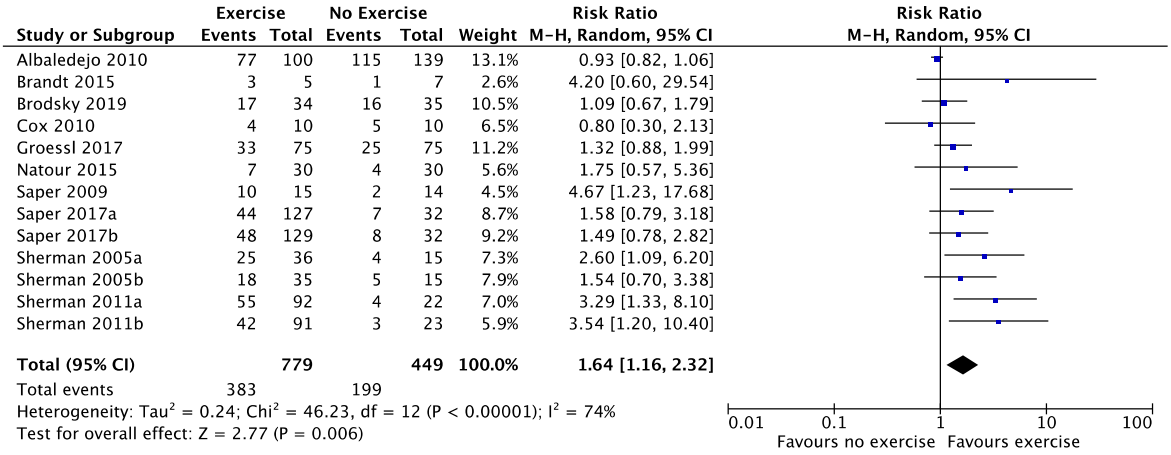
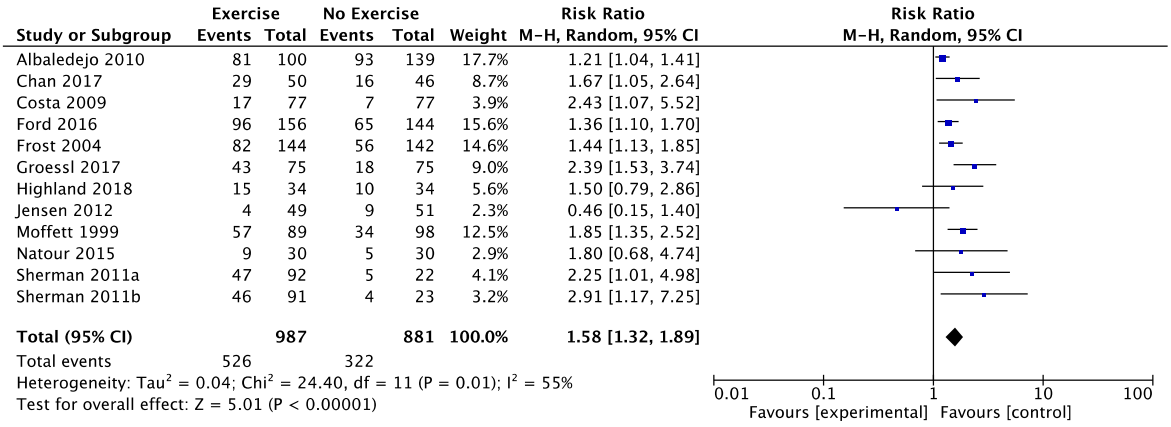


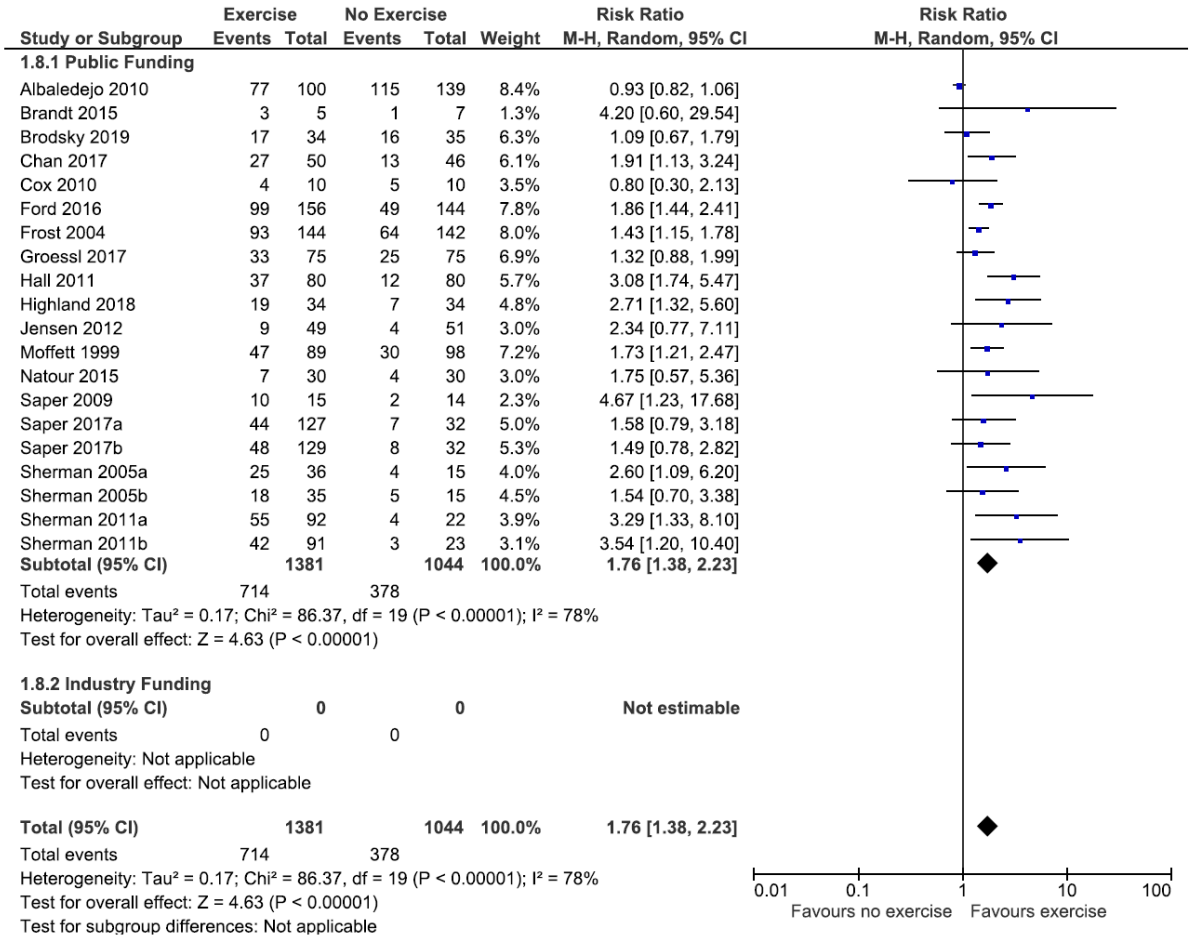
Figure 1.4: Exercise versus no exercise; Outcome: Proportion of patients with a meaningful response to treatment at 12 weeks or greater.



Figures 1.5: Exercise versus no exercise; Outcome: Proportion of patients with a meaningful response at longest follow up time.

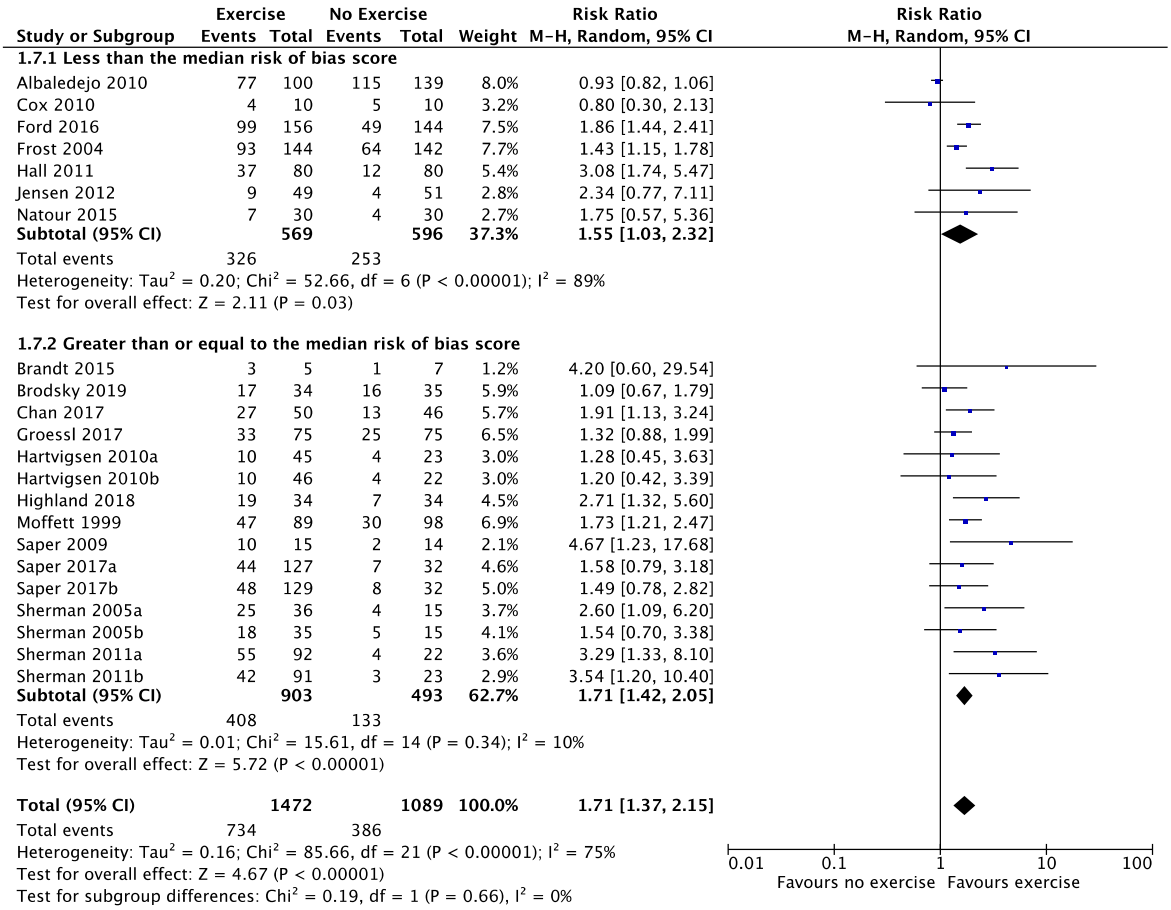


Figures 1.6: Exercise versus no exercise; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source (public or industry funding)



Figures 1.7: Exercise versus no exercise; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by median risk of bias (less than the median risk of bias score or greater than or equal to the median risk of bias score)

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)



Acupuncture

Figure 2.1: Acupuncture versus control; Outcome: Proportion of patients with a meaningful response to treatment.

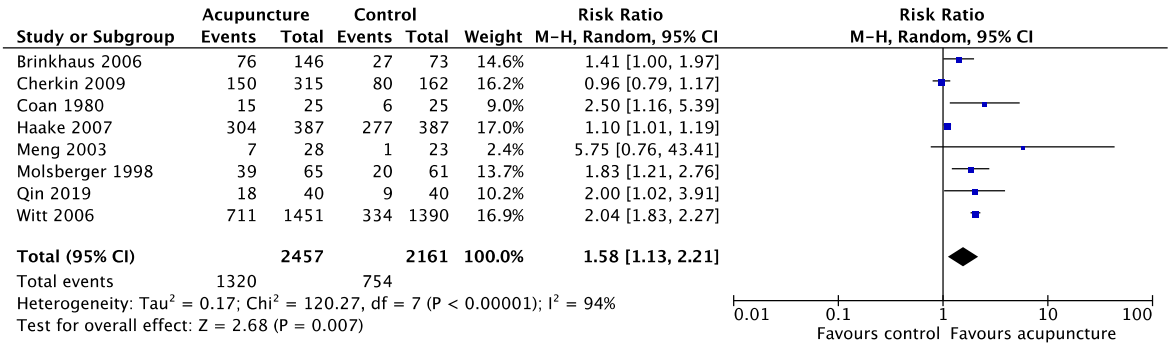


Figure 2.2: Acupuncture versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less.

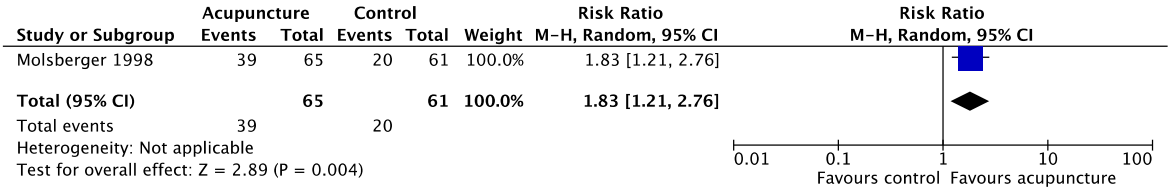


Figure 2.3: Acupuncture versus control; Outcome: Proportion of patients with a meaningful response to treatment at greater than 4 weeks and less than 12 weeks.

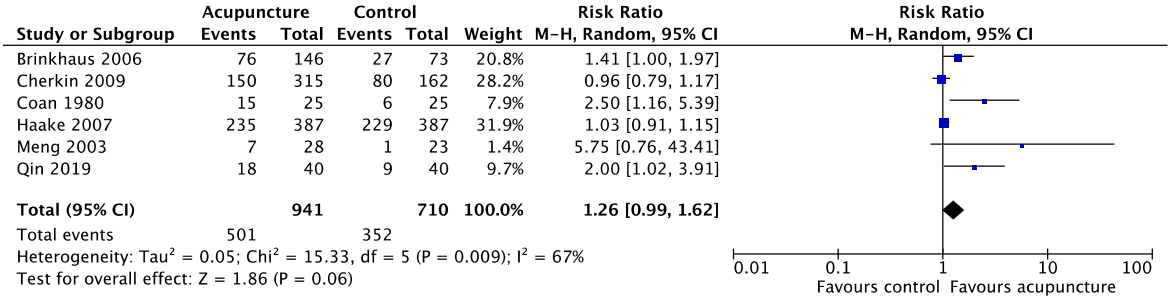


Figure 2.4: Acupuncture versus control; Outcome: Proportion of patients with a meaningful response to treatment at 12 weeks or greater.

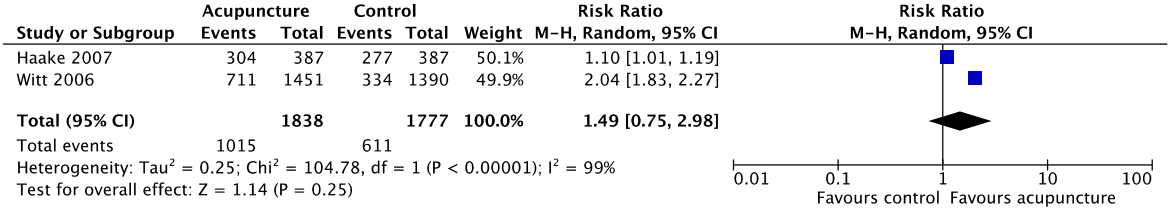


Figure 2.5: Acupuncture versus control; Outcome: Proportion of patients with a meaningful response at longest follow up time

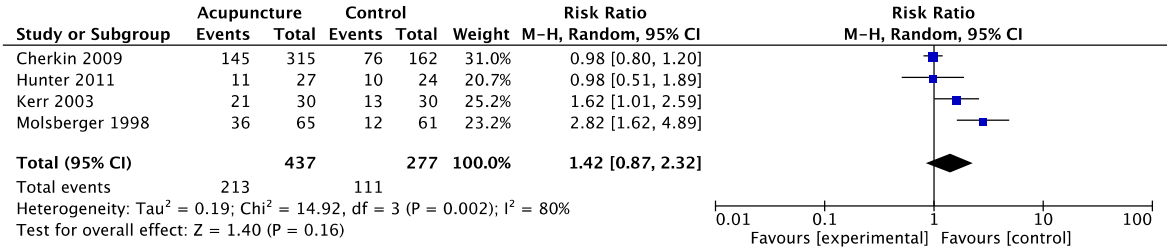


Figure 2.6: Acupuncture versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source (public or industry funding)

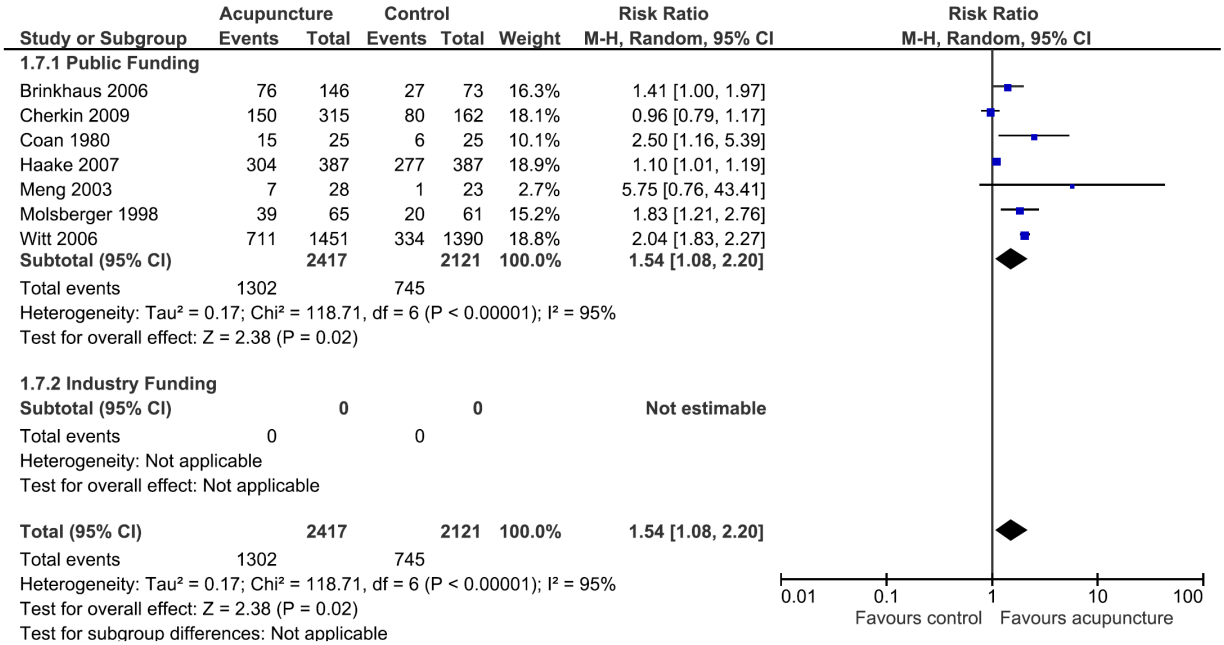


Figure 2.7: Acupuncture versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by median risk of bias (less than the median risk of bias score or greater than or equal to the median risk of bias score)

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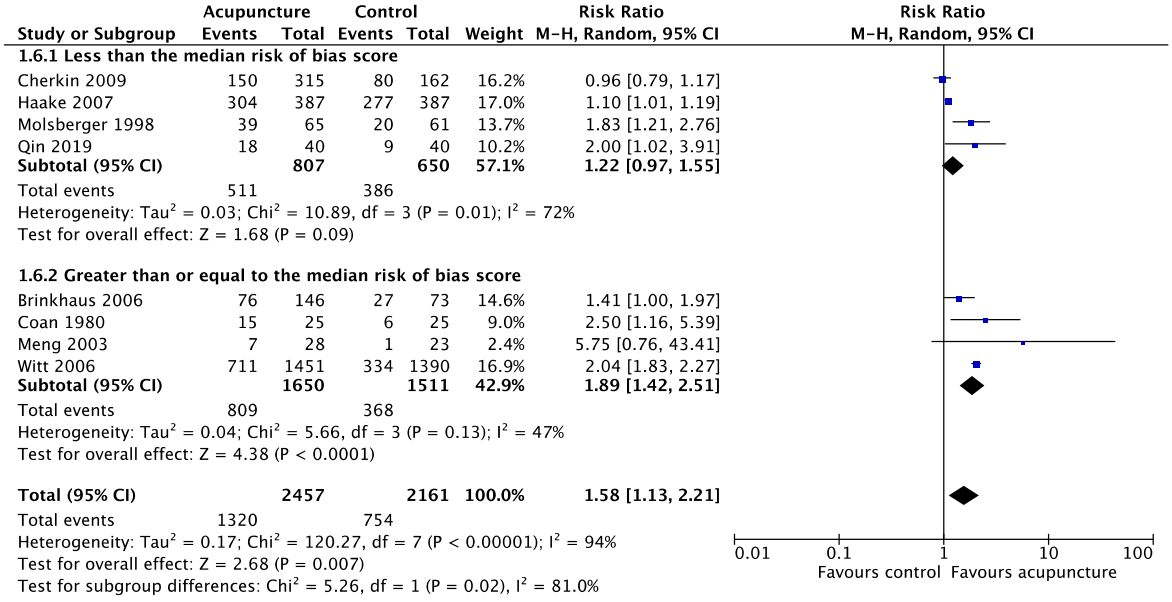

Spinal Manipulation

Figure 3.1: Spinal Manipulation versus control; Outcome: Proportion of patients with a meaningful response to treatment

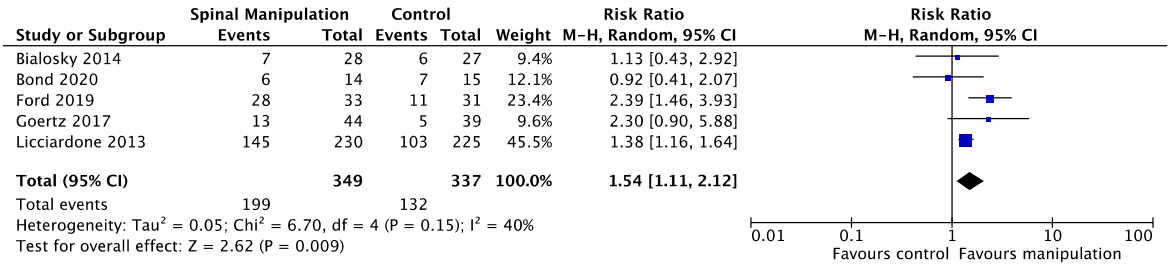

Figure 3.2: Spinal Manipulation versus control; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less. (Post hoc analysis)

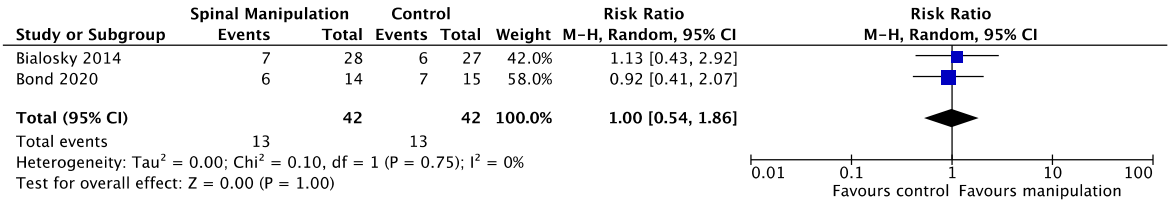

Figure 3.3: Spinal Manipulation versus control; Outcome: Proportion of patients with a meaningful response to treatment at greater than 4 weeks and less than 12 weeks. (Post hoc analysis)

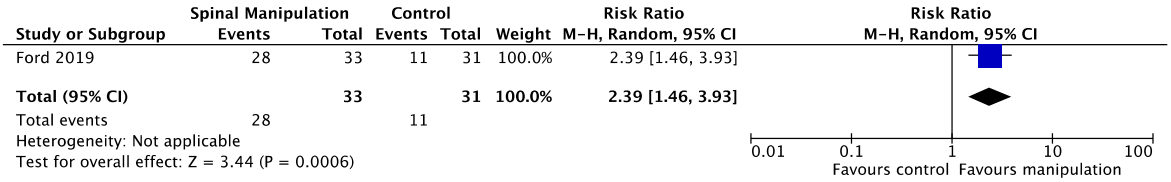

Figure 3.4: Spinal Manipulation versus control; Outcome: Proportion of patients with a meaningful response to treatment at 12 weeks or greater. (Post hoc analysis)

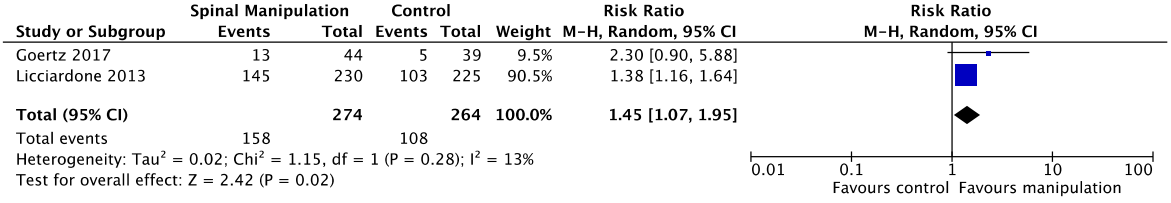

Figure 3.5: Spinal Manipulation versus control; Outcome: Proportion of patients with a meaningful response at longest follow up time.

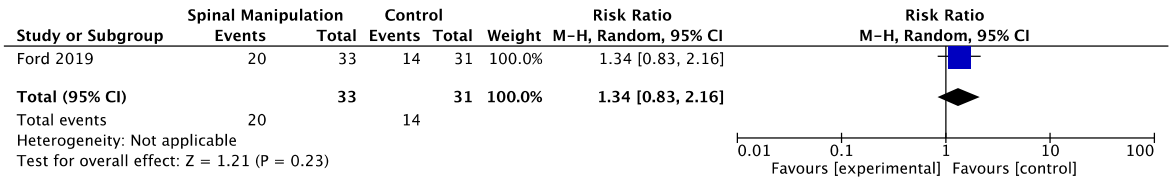

Figure 3.6: Spinal Manipulation versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source (public or industry funding) (Post hoc analysis)

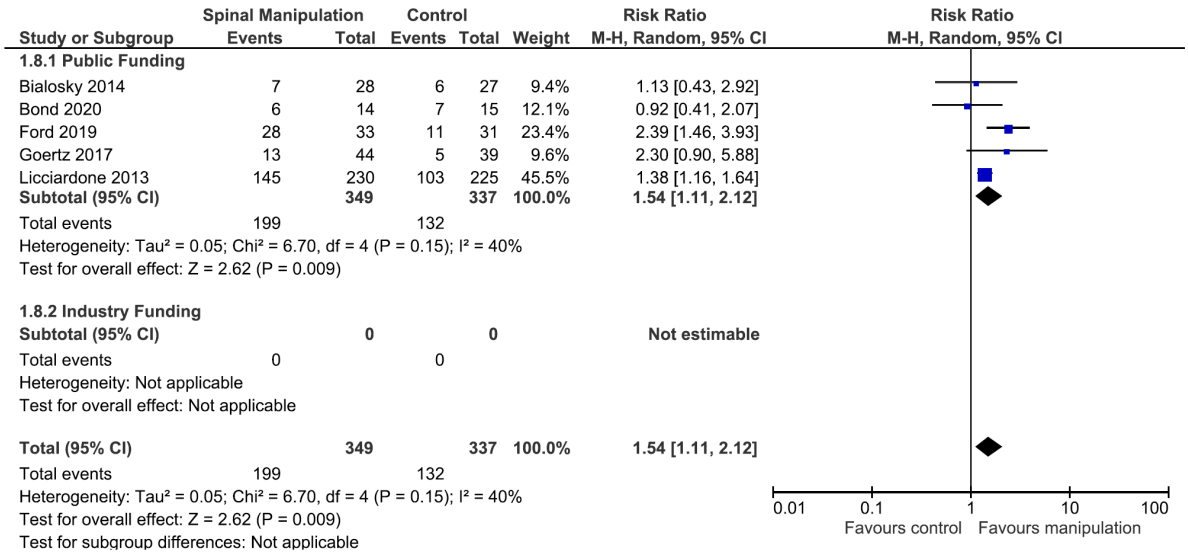

Figure 3.7: Spinal Manipulation versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by median risk of bias (less than the median risk of bias score or greater than or equal to the median risk of bias score) (post hoc analysis)

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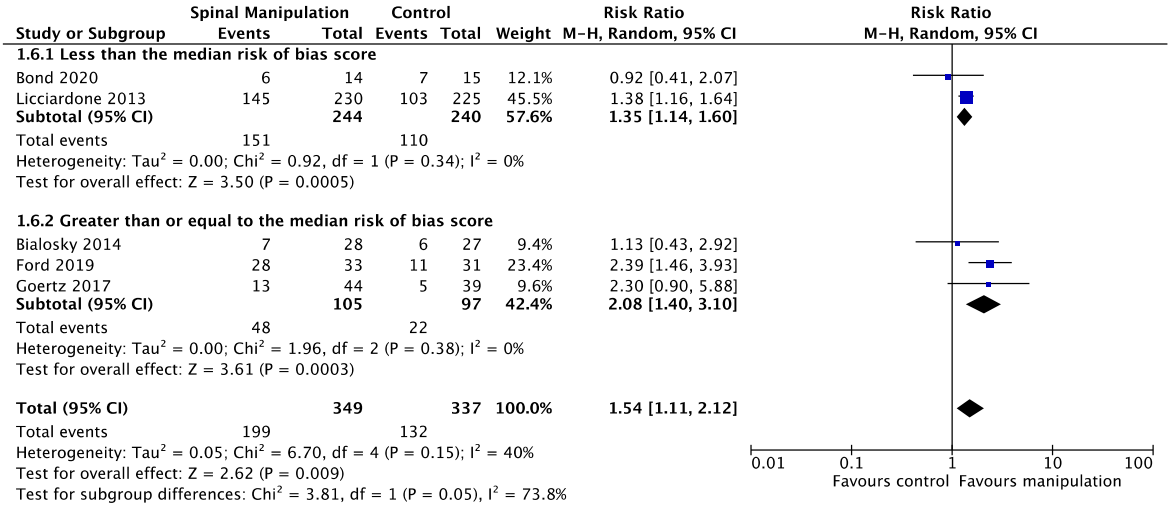

Oral NSAIDs

Figure 4.1: Oral NSAIDs versus placebo; Outcome: Proportion of patients with a meaningful response to treatment.

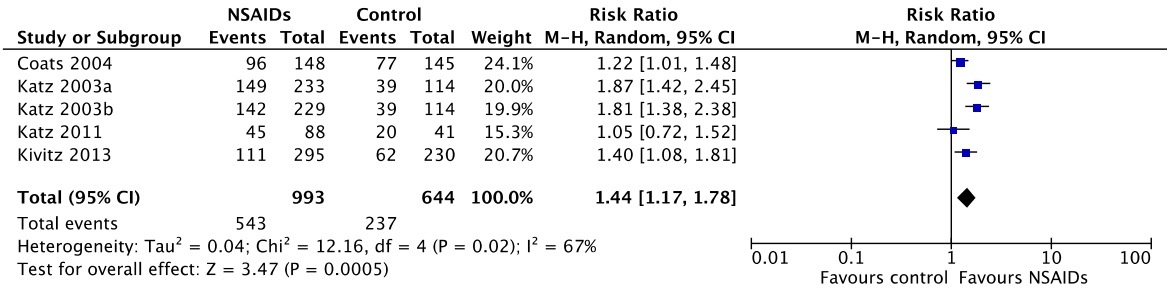

Figure 4.2: Oral NSAIDs versus placebo; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less. (Post hoc analysis)

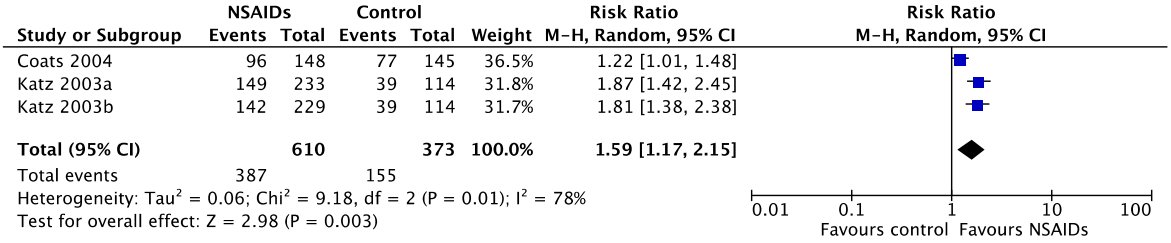

Figure 4.3: Oral NSAIDs versus placebo; Outcome: Proportion of patients with a meaningful response to treatment at greater than 4 weeks and less than 12 weeks. (Post hoc analysis)

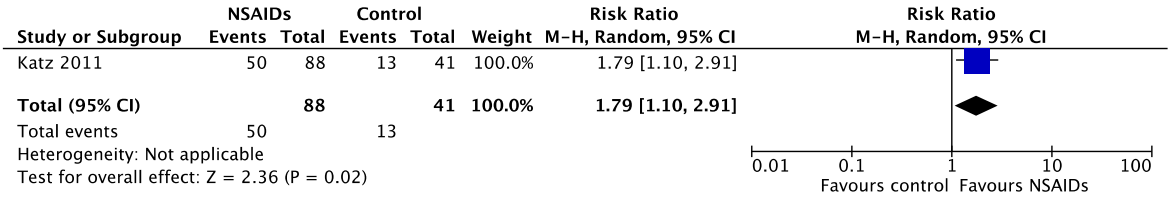

Figure 4.4: Oral NSAIDs versus placebo; Outcome: Proportion of patients with a meaningful response to treatment at 12 weeks or greater. (Post hoc analysis)

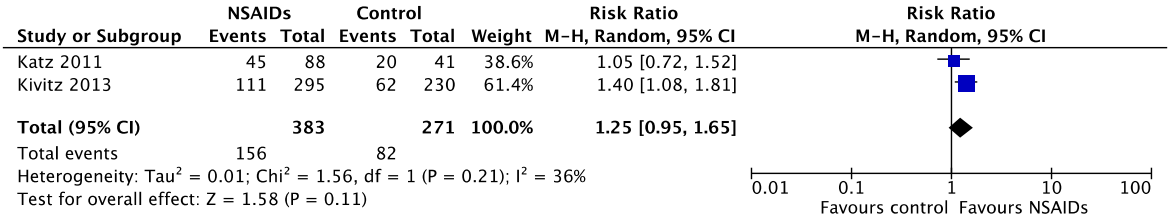

Figure 4.5: Oral NSAIDs versus placebo; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source (public or industry funding) (Post hoc analysis)

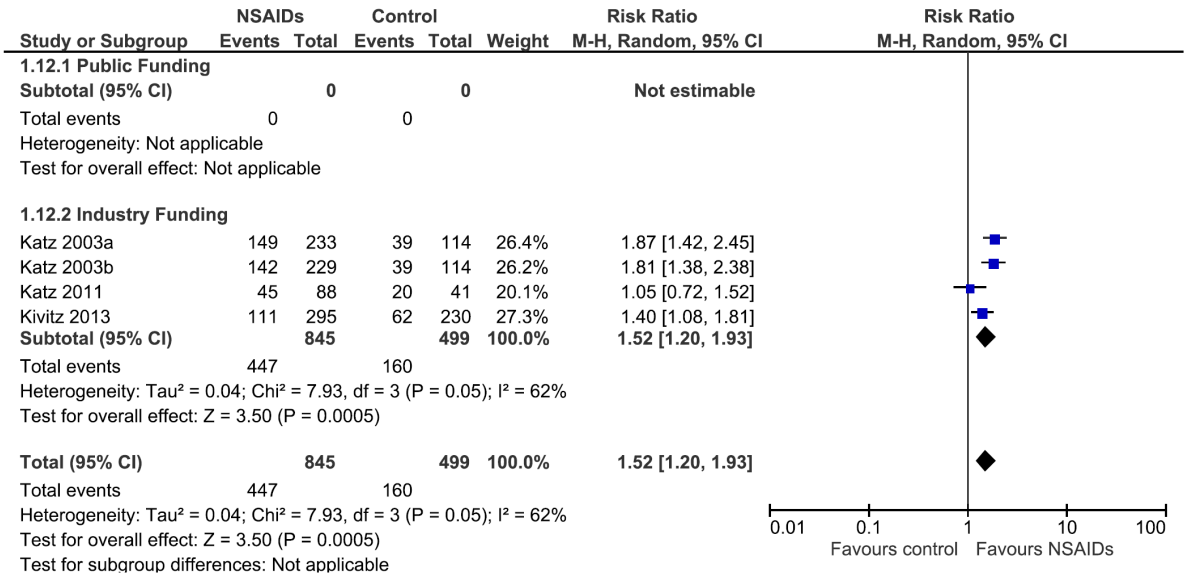

Figure 4.6: Oral NSAIDs versus placebo; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by median risk of bias (less than the median risk of bias score or greater than or equal to the median risk of bias score) (post hoc analysis)

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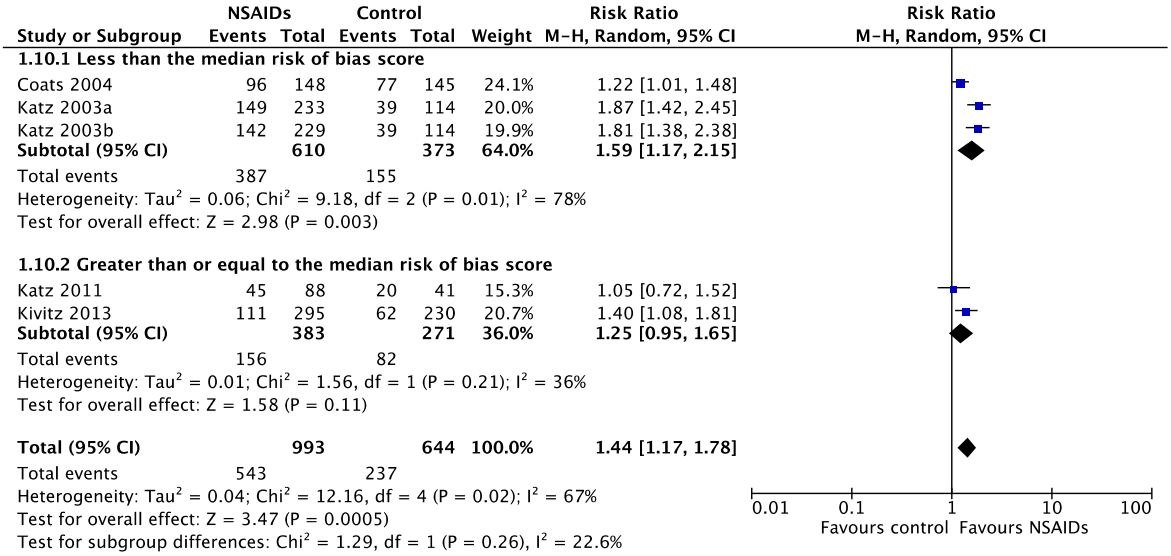

Rubefacients

Figure 5.1: Rubefacients versus placebo; Outcome: Proportion of patients with a meaningful response to treatment.

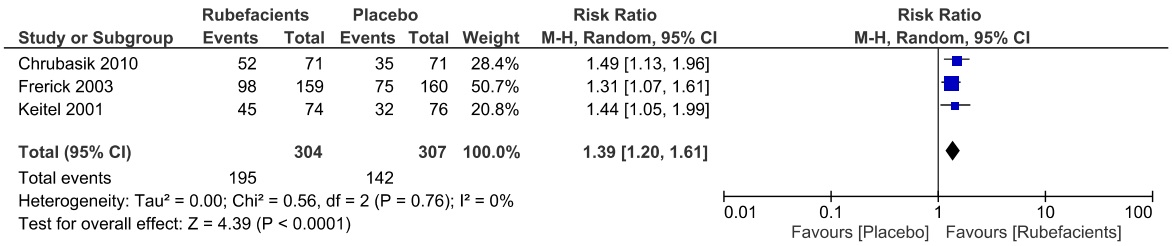

Figure 5.2: Rubefacients versus placebo; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less. (Post hoc analysis)

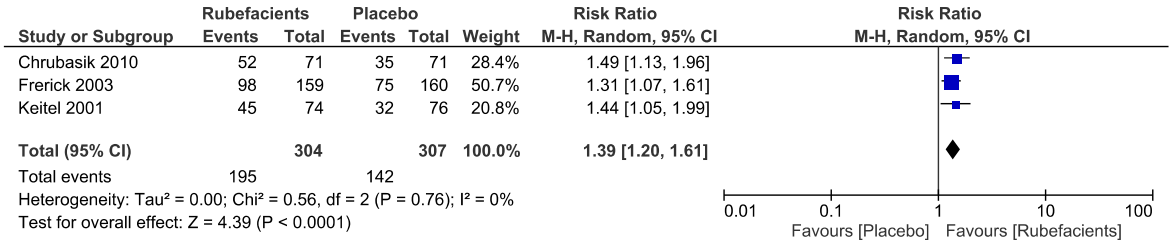

Figure 5.3: Rubefacients versus placebo; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source (public or industry funding) (Post hoc analysis)

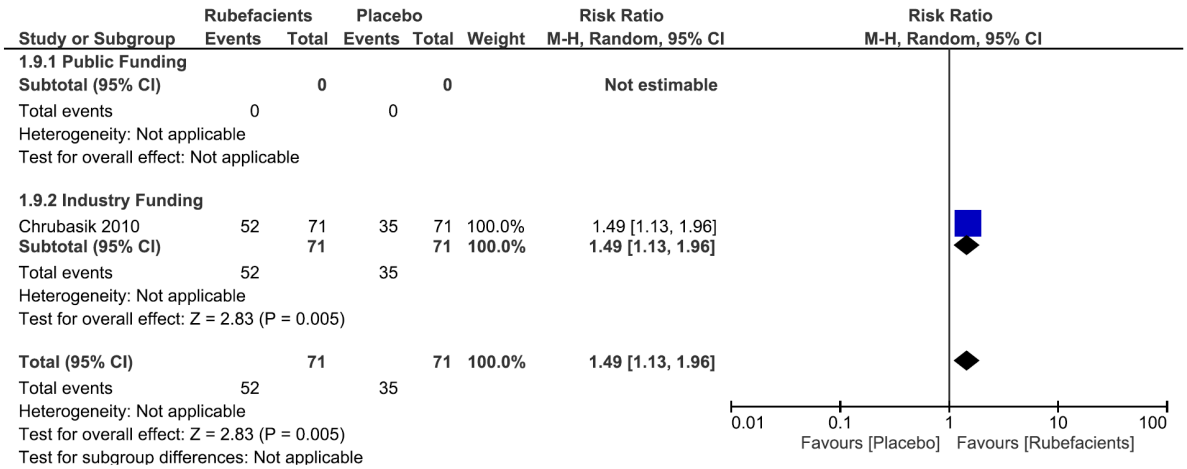

Figure 5.4: Rubefacients versus placebo; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by median risk of bias (less than the median risk of bias score or greater than or equal to the median risk of bias score) (post hoc analysis)

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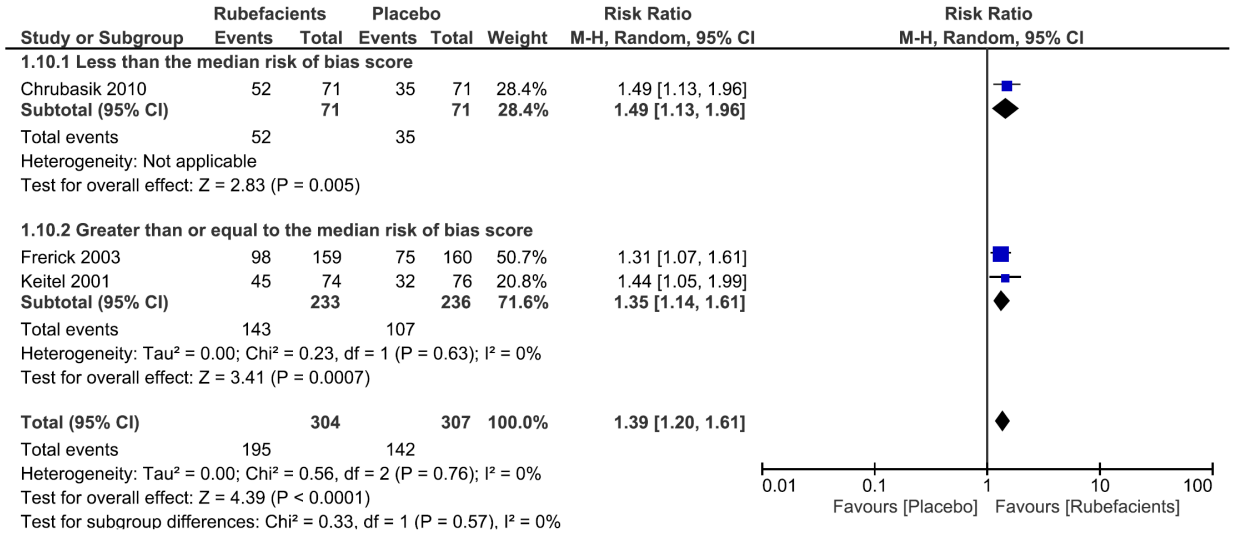


Opioids

Figure 6.1: Opioids versus placebo; Outcome: Proportion of patients with a meaningful response to treatment.

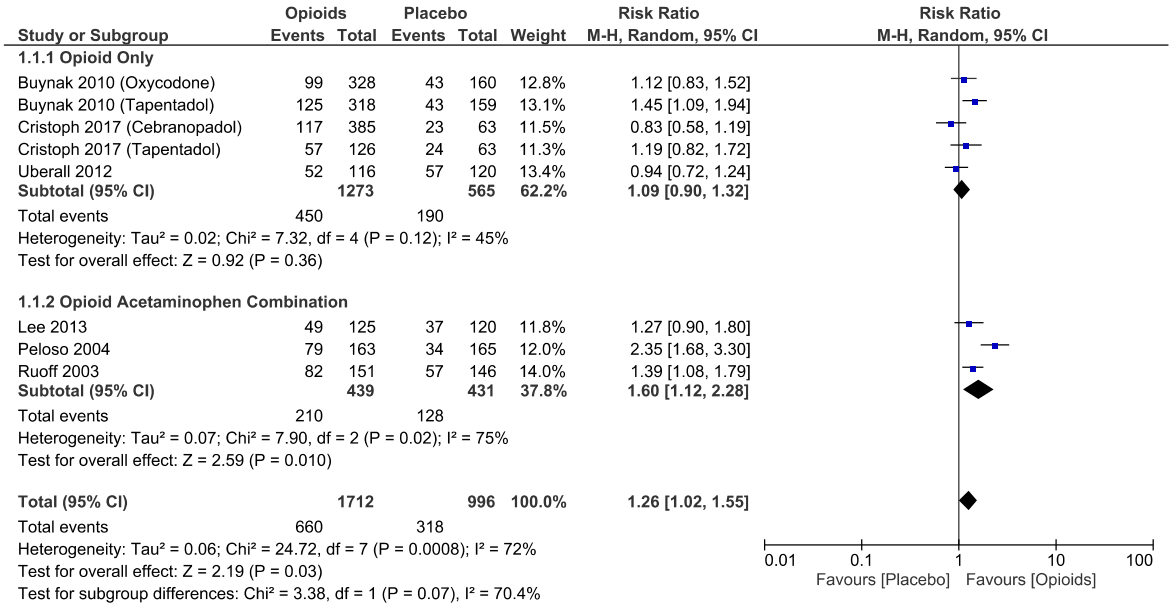


Figure 6.2: Opioids versus placebo; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less. (Post hoc analysis)

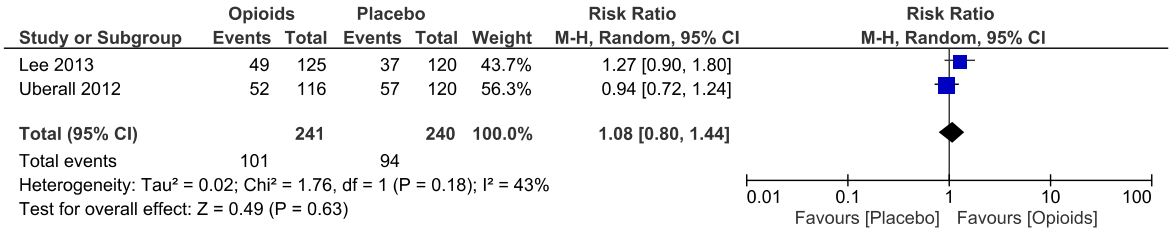
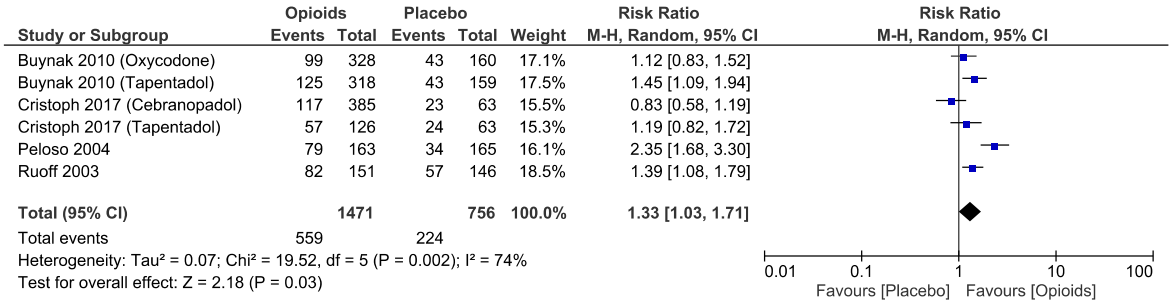


Figure 6.3: Opioids versus placebo; Outcome: Outcome: Proportion of patients with a meaningful response to treatment at 12 weeks or greater. (Post hoc analysis)



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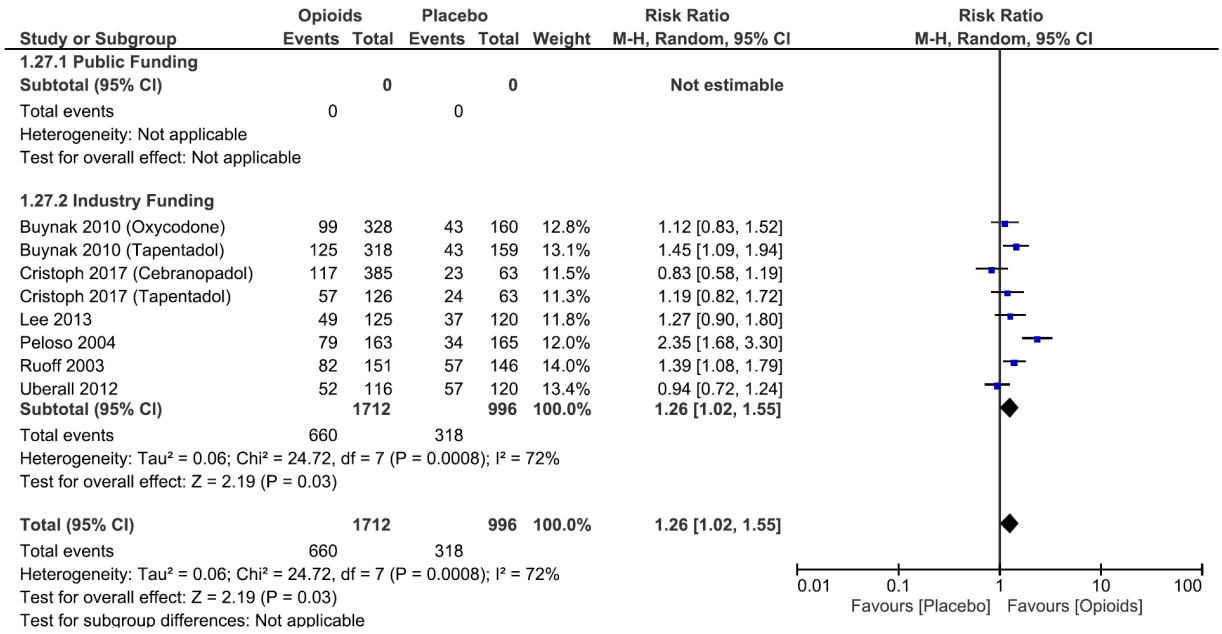

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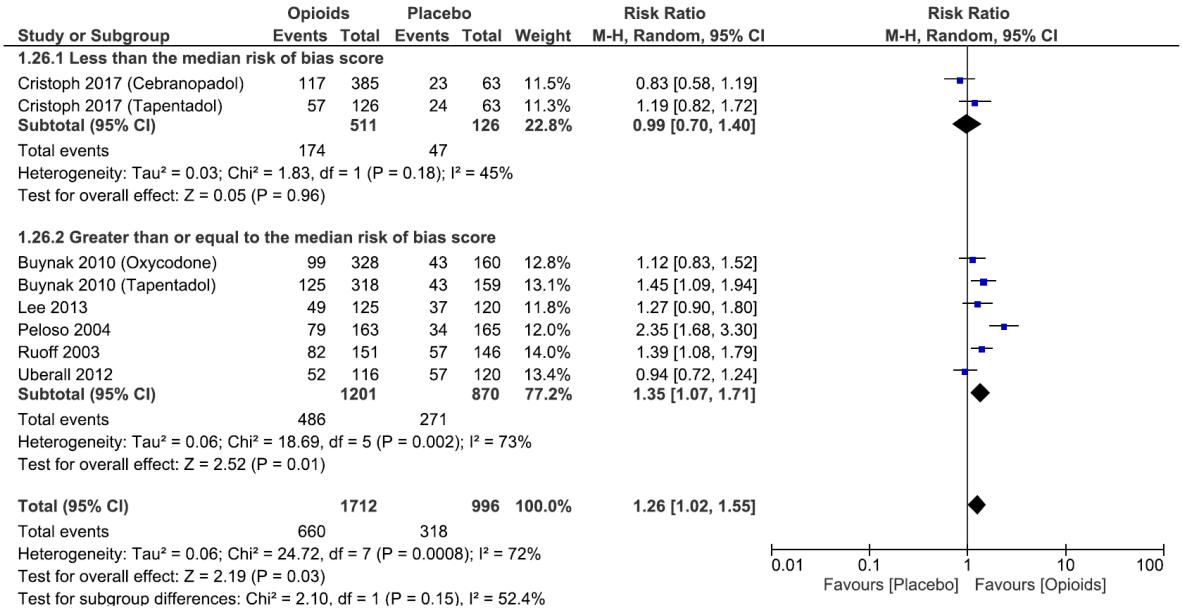

SNRIs

Figure 7.1: SNRIs (duloxetine) versus placebo; Outcome: Proportion of patients with a meaningful response to treatment.

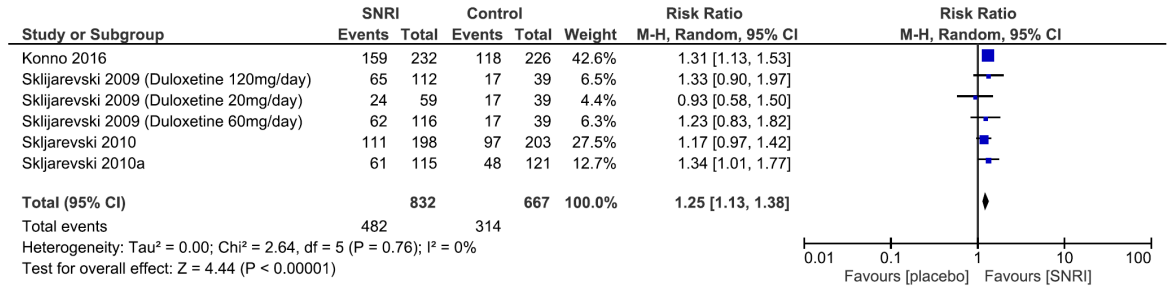

Figure 7.2: SNRIs (duloxetine) versus placebo; Outcome: Proportion of patients with a meaningful response to treatment at 12 weeks or greater. (Post hoc analysis)

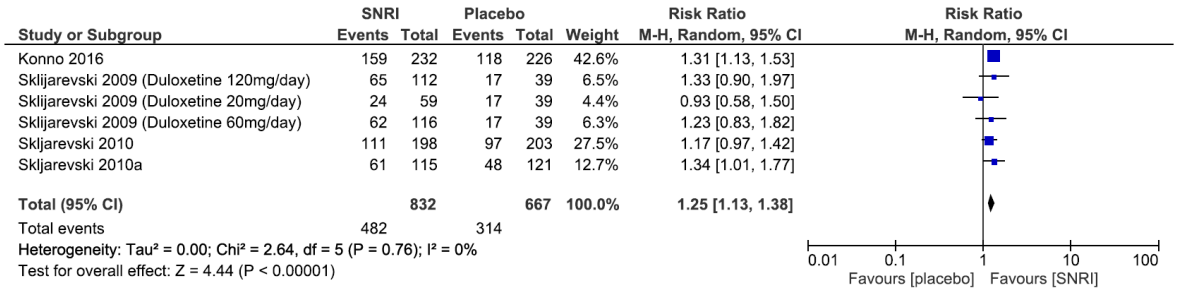

Figure 7.3: SNRIs (duloxetine) versus placebo; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source (public or industry funding) (Post hoc analysis)

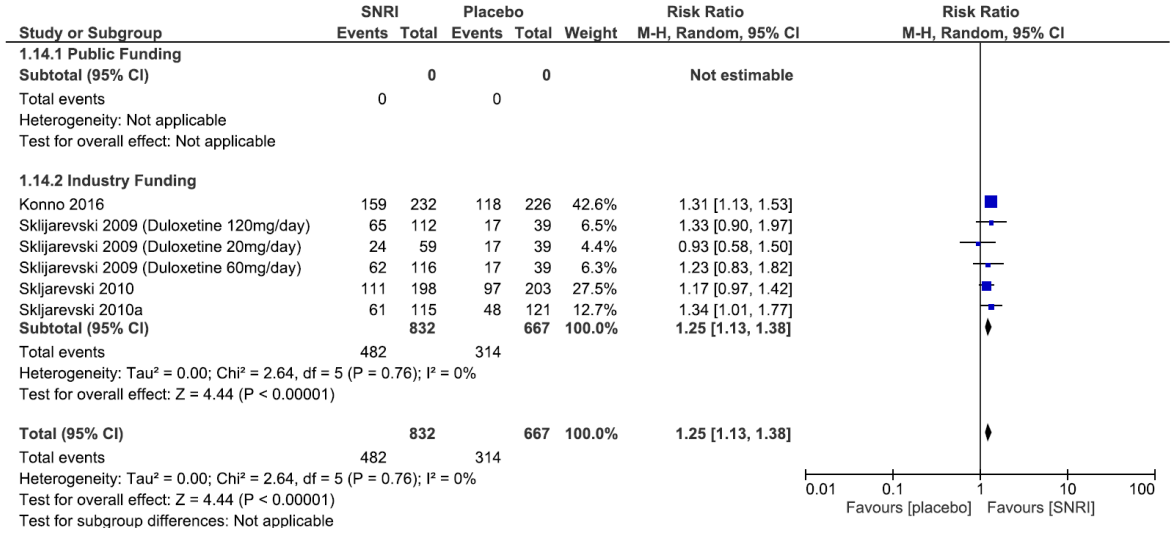

Figure 7.4: SNRIs (duloxetine) versus placebo; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by median risk of bias (less than the median risk of bias score or greater than or equal to the median risk of bias score) (post hoc analysis)

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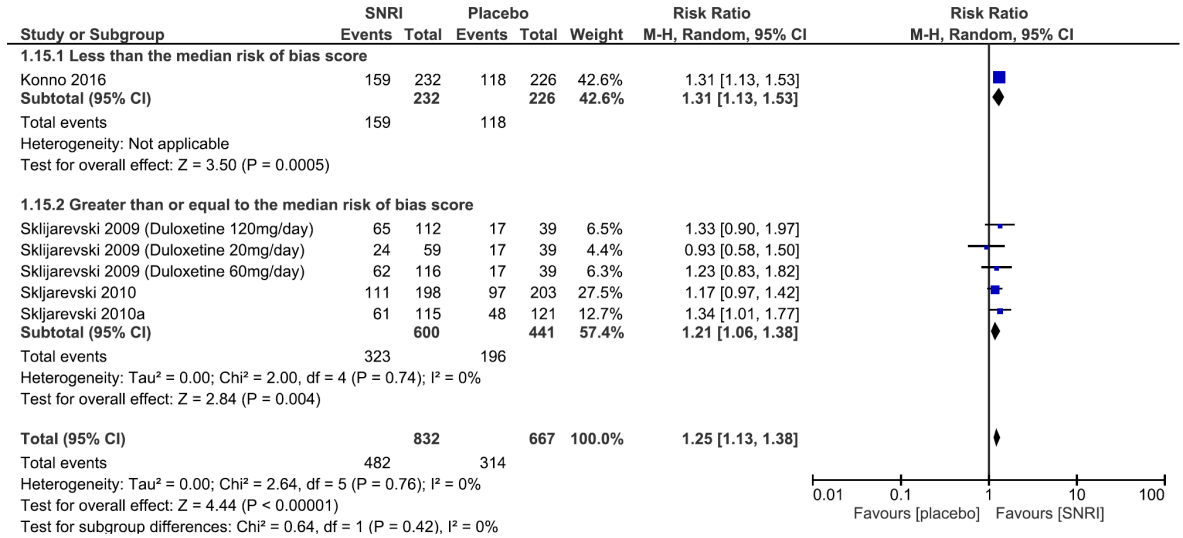

Corticosteroid Injections

Figure 8.1: Corticosteroid injections versus saline injections; Outcome: Proportion of patients with a meaningful response to treatment.

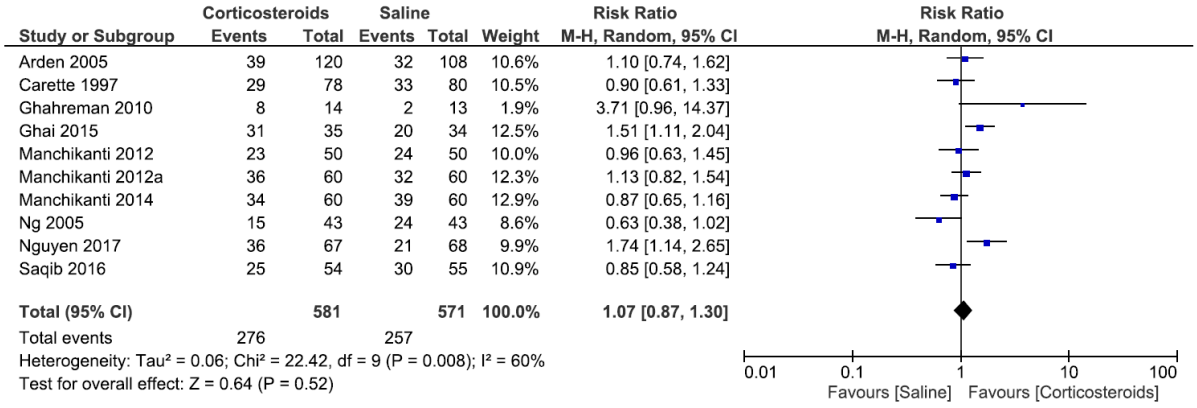

Figure 8.2: Corticosteroid injections versus saline injections; Outcome: Proportion of patients with a meaningful response to treatment at 4 weeks or less

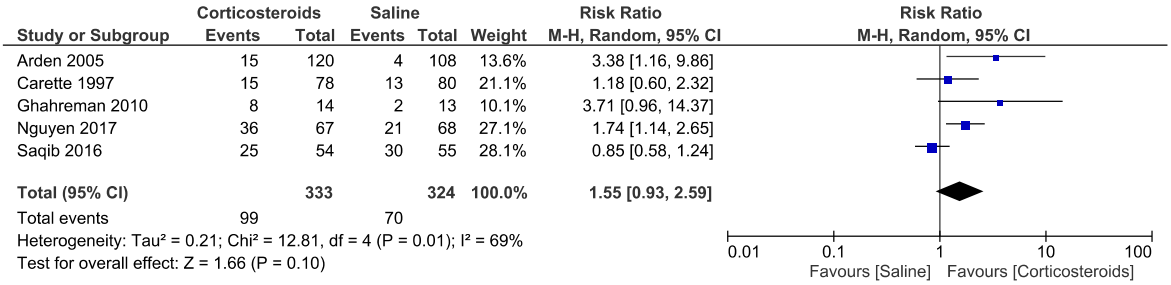

Figure 8.3: Corticosteroid injections versus saline injections; Outcome: Outcome: Proportion of patients with a meaningful response to treatment at 12 weeks or greater.

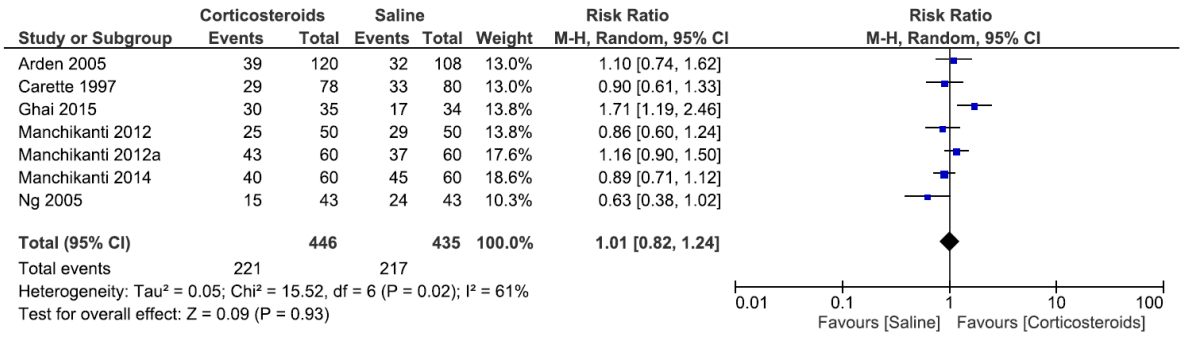

Figure 8.4: Corticosteroid injections versus saline injections; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study funding source (public or industry funding)

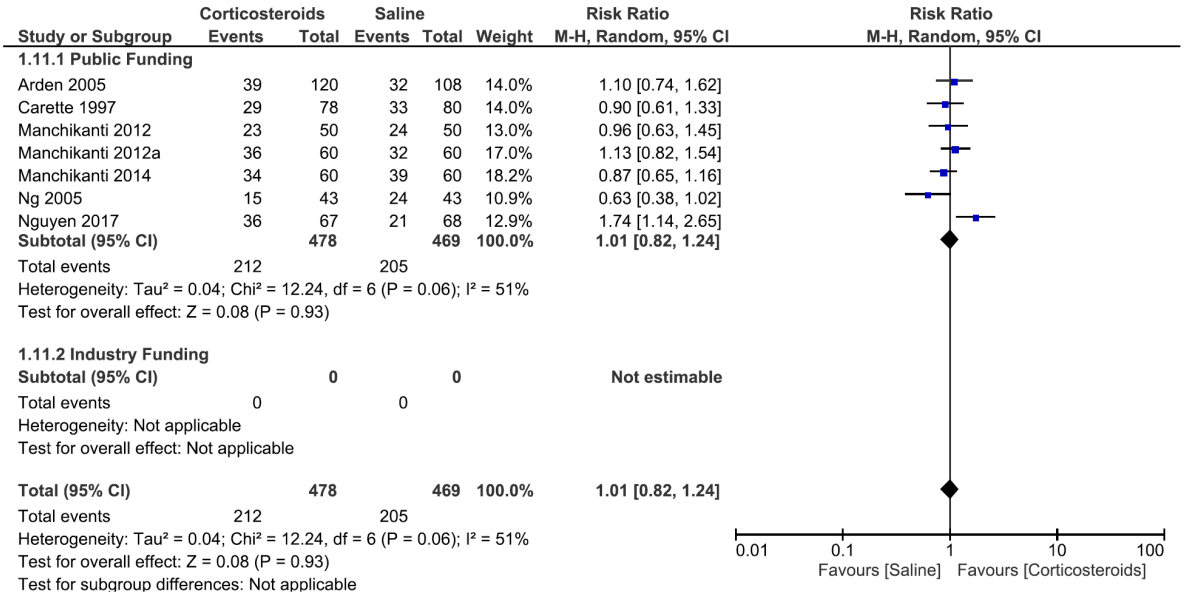

Figure 8.5: Corticosteroid injections versus saline injections; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by median risk of bias (less than the median risk of bias score or greater than or equal to the median risk of bias score)

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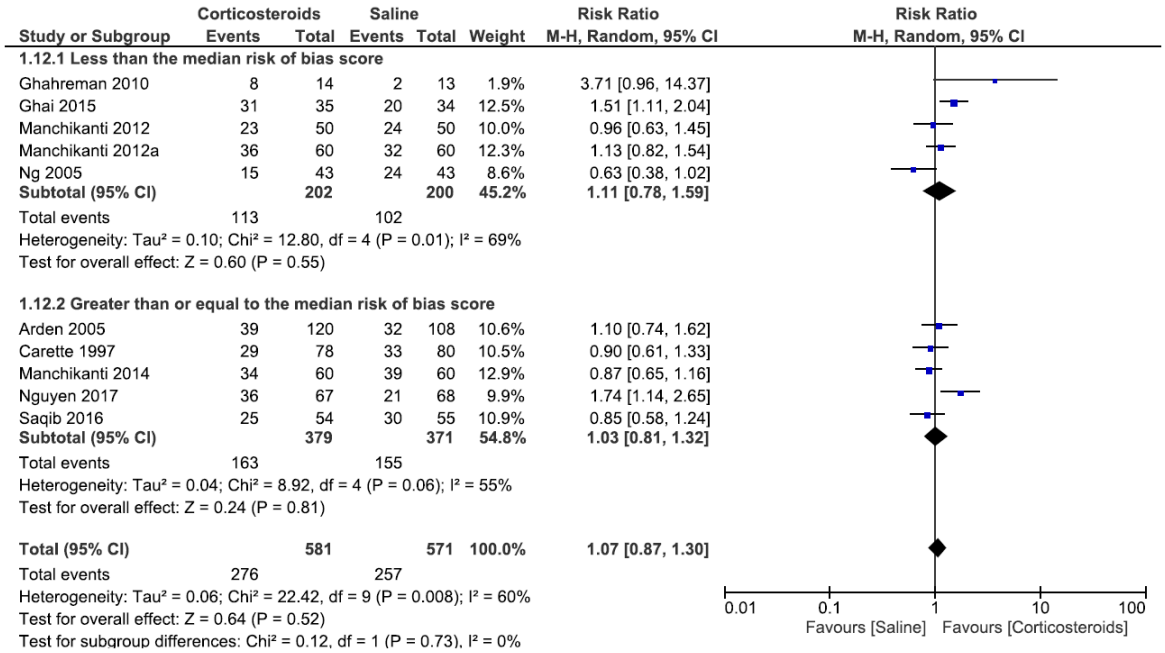


Post Hoc Analysis

I. Fixed Effects Analysis

Figure 9.1: Exercise versus no exercise; Outcome: Proportion of patients with a meaningful response to treatment (fixed effects analysis)

Study or Subgroup	Exercise Events	Exercise Total	No Exercise Events	No Exercise Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Albaledejo 2010	77	100	115	139	24.8%	0.93 [0.82, 1.06]
Brandt 2015	3	5	1	7	0.2%	4.20 [0.60, 29.54]
Brodsky 2019	17	34	16	35	4.1%	1.09 [0.67, 1.79]
Chan 2017	27	50	13	46	3.5%	1.91 [1.13, 3.24]
Cox 2010	4	10	5	10	1.3%	0.80 [0.30, 2.13]
Ford 2016	99	156	49	144	13.1%	1.86 [1.44, 2.41]
Frost 2004	93	144	64	142	16.6%	1.43 [1.15, 1.78]
Groessl 2017	33	75	25	75	6.4%	1.32 [0.88, 1.99]
Hall 2011	37	80	12	80	3.1%	3.08 [1.74, 5.47]
Hartvigsen 2010a	10	45	4	23	1.4%	1.28 [0.45, 3.63]
Hartvigsen 2010b	10	46	4	22	1.4%	1.20 [0.42, 3.39]
Highland 2018	19	34	7	34	1.8%	2.71 [1.32, 5.60]
Jensen 2012	9	49	4	51	1.0%	2.34 [0.77, 7.11]
Moffett 1999	47	89	30	98	7.4%	1.73 [1.21, 2.47]
Natour 2015	7	30	4	30	1.0%	1.75 [0.57, 5.36]
Saper 2009	10	15	2	14	0.5%	4.67 [1.23, 17.68]
Saper 2017a	44	127	7	32	2.9%	1.58 [0.79, 3.18]
Saper 2017b	48	129	8	32	3.3%	1.49 [0.78, 2.82]
Sherman 2005a	25	36	4	15	1.5%	2.60 [1.09, 6.20]
Sherman 2005b	18	35	5	15	1.8%	1.54 [0.70, 3.38]
Sherman 2011a	55	92	4	22	1.7%	3.29 [1.33, 8.10]
Sherman 2011b	42	91	3	23	1.2%	3.54 [1.20, 10.40]
Total (95% CI)		**1472**		**1089**	**100.0%**	**1.56 [1.42, 1.72]**
Total events	734		386			

Heterogeneity: $Chi^2 = 85.66$, df = 21 ($P < 0.00001$); $I^2 = 75\%$
Test for overall effect: $Z = 9.05$ ($P < 0.00001$)

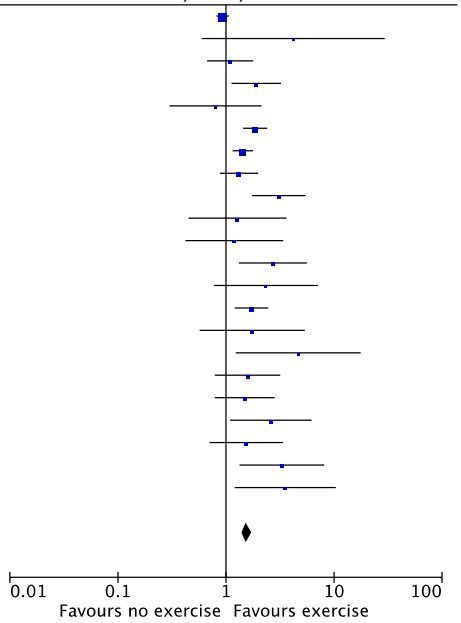


Figure 9.2: Acupuncture versus control; Outcome: Proportion of patients with a meaningful response to treatment (fixed effects analysis)

Study or Subgroup	Acupuncture Events	Acupuncture Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brinkhaus 2006	76	146	27	73	4.5%	1.41 [1.00, 1.97]
Cherkin 2009	150	315	80	162	13.3%	0.96 [0.79, 1.17]
Coan 1980	15	25	6	25	0.8%	2.50 [1.16, 5.39]
Haake 2007	304	387	277	387	34.8%	1.10 [1.01, 1.19]
Meng 2003	7	28	1	23	0.1%	5.75 [0.76, 43.41]
Molsberger 1998	39	65	20	61	2.6%	1.83 [1.21, 2.76]
Qin 2019	18	40	9	40	1.1%	2.00 [1.02, 3.91]
Witt 2006	711	1451	334	1390	42.8%	2.04 [1.83, 2.27]
Total (95% CI)		**2457**		**2161**	**100.0%**	**1.54 [1.45, 1.65]**
Total events	1320		754			

Heterogeneity: $Chi^2 = 120.27$, df = 7 ($P < 0.00001$); $I^2 = 94\%$
Test for overall effect: $Z = 13.01$ ($P < 0.00001$)

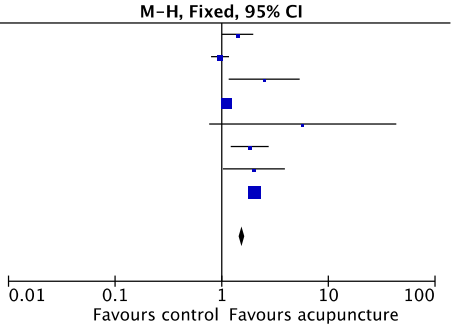


Figure 9.3: Spinal Manipulation versus control; Outcome: Proportion of patients with a meaningful response to treatment Oral NSAIDs (fixed effects analysis)

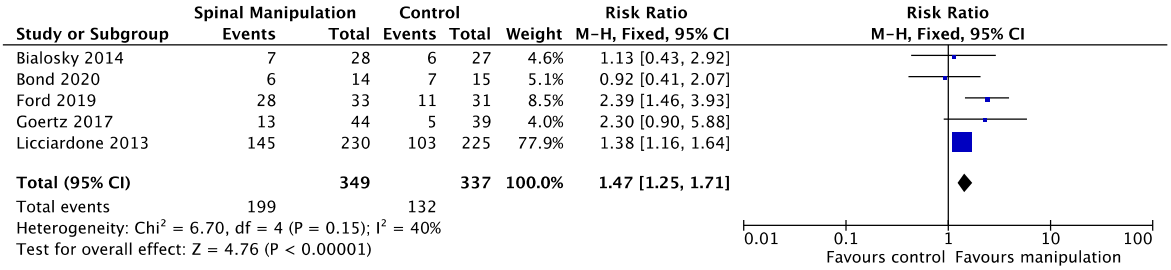


Figure 9.4: Oral NSAIDs versus placebo; Outcome: Proportion of patients with a meaningful response to treatment (fixed effects analysis)

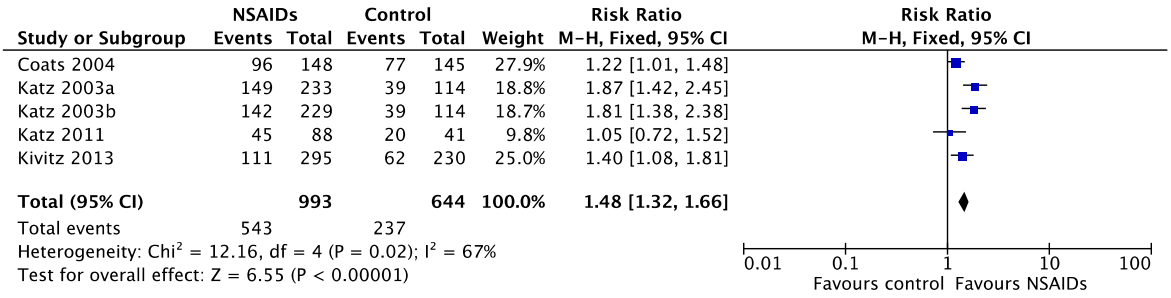


Figure 9.5: Rubefacients versus placebo; Outcome: Proportion of patients with a meaningful response to treatment (fixed effects analysis)

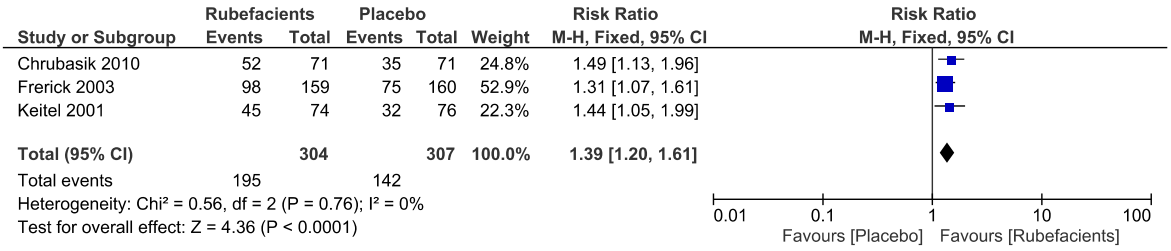


Figure 9.6: Opioids versus placebo; Outcome: Proportion of patients with a meaningful response to treatment (fixed effects analysis)

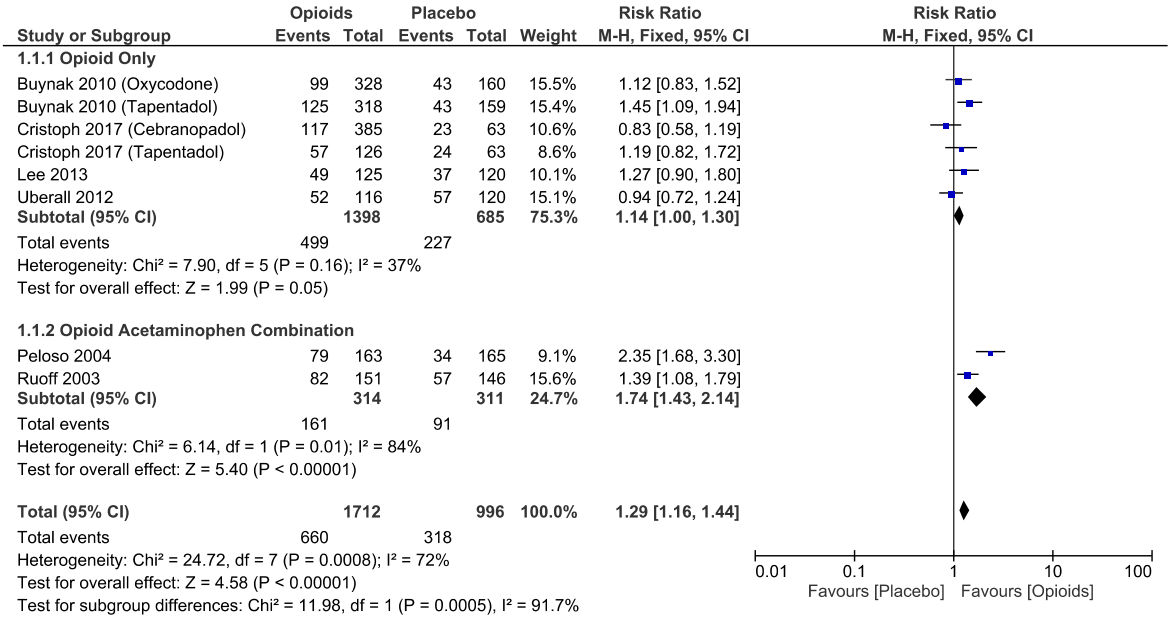


Figure 9.7: SNRIs (duloxetine) versus placebo; Outcome: Proportion of patients with a meaningful response to treatment (fixed effects analysis)

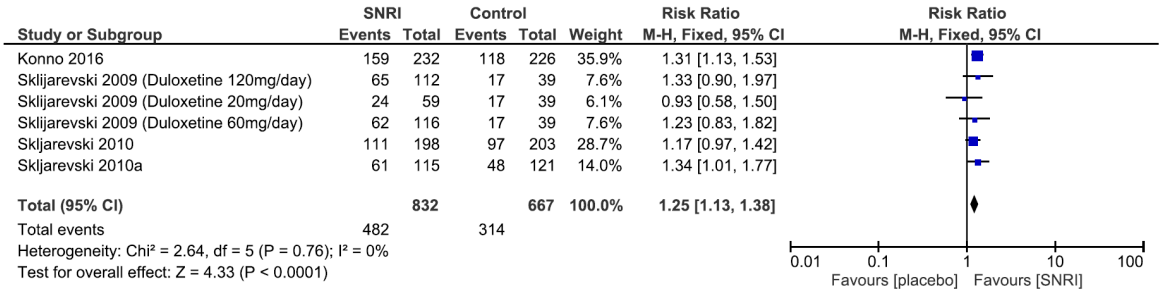
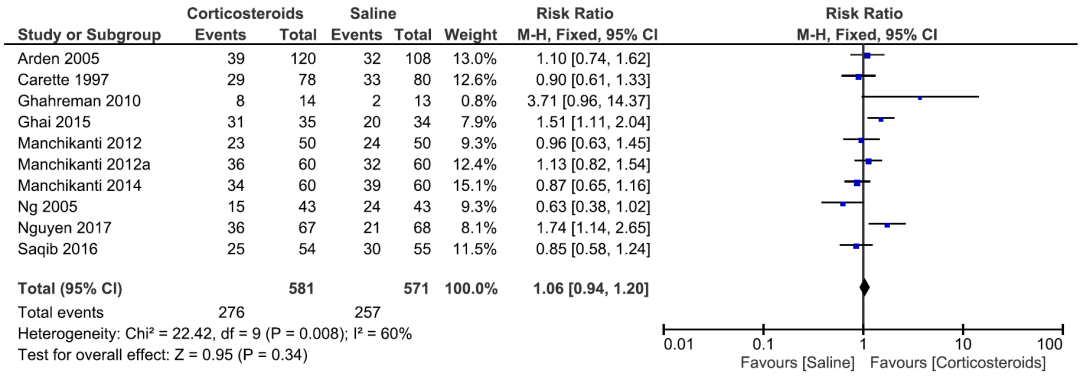


Figure 9.8: Corticosteroid injections versus saline injections; Outcome: Proportion of patients with a meaningful response to treatment (fixed effects analysis)



II. Subgroup analysis by control group characteristics (sham versus non-sham procedures or prescribed versus passive exercise controls)

Figures 10.1: Exercise versus no exercise; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by control group characteristics (prescribed versus passive exercise controls)

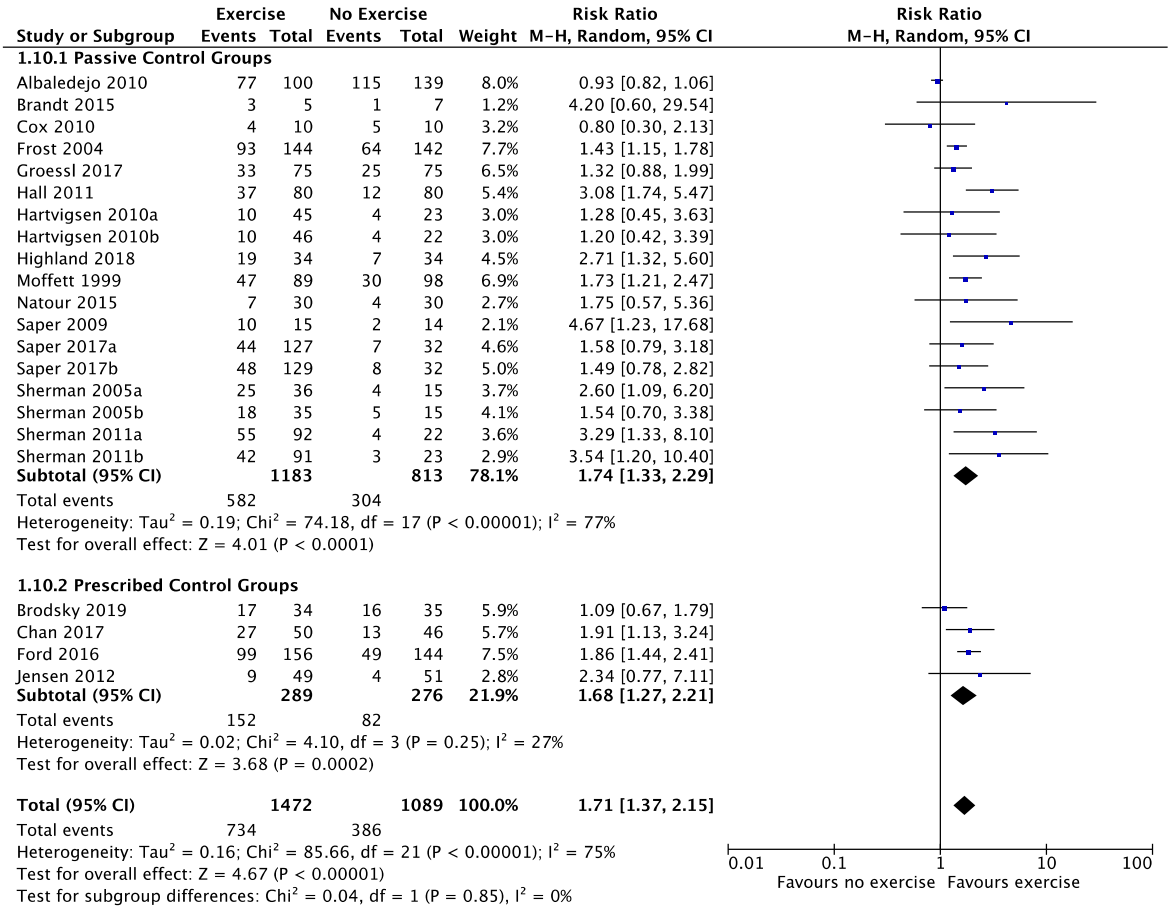


Figure 10.2: Acupuncture versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by control group characteristics (sham versus non-sham procedures)

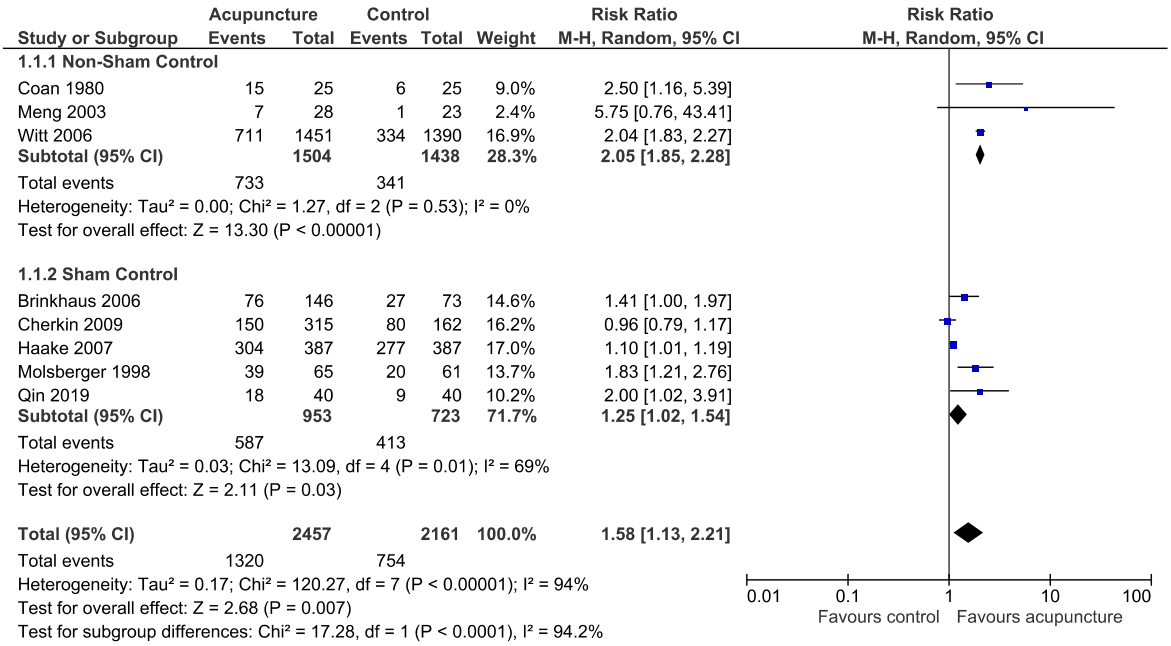
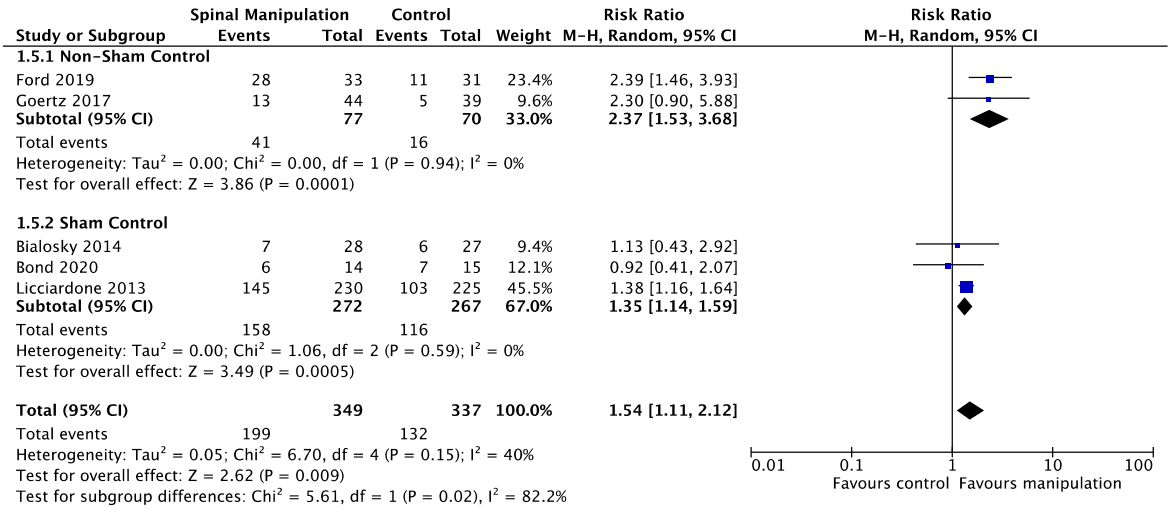
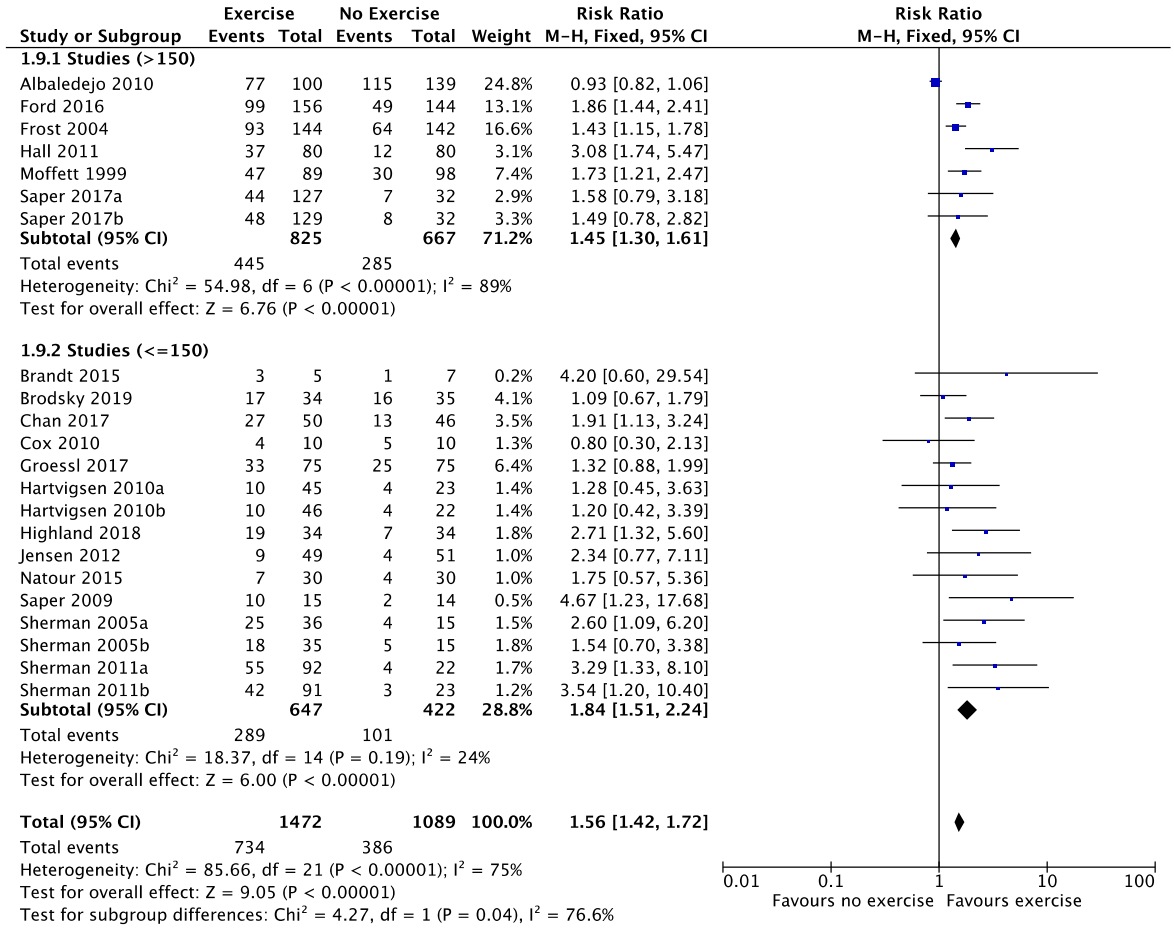


Figure 10.3: Spinal Manipulation versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by control group characteristics (sham versus non-sham procedures)

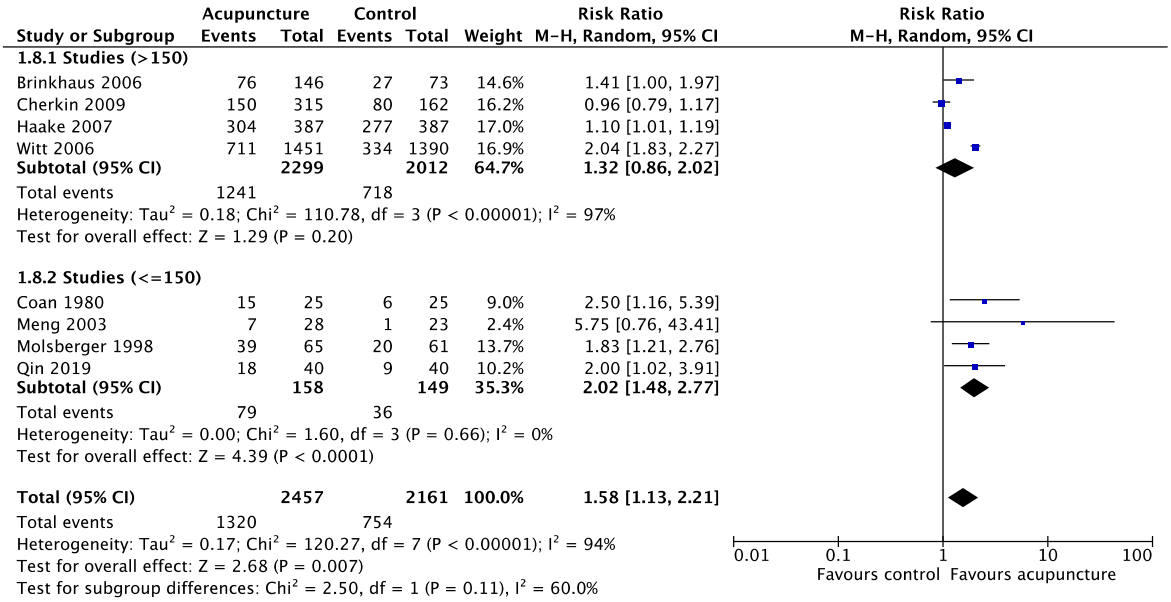


III. Subgroup analysis by trial size

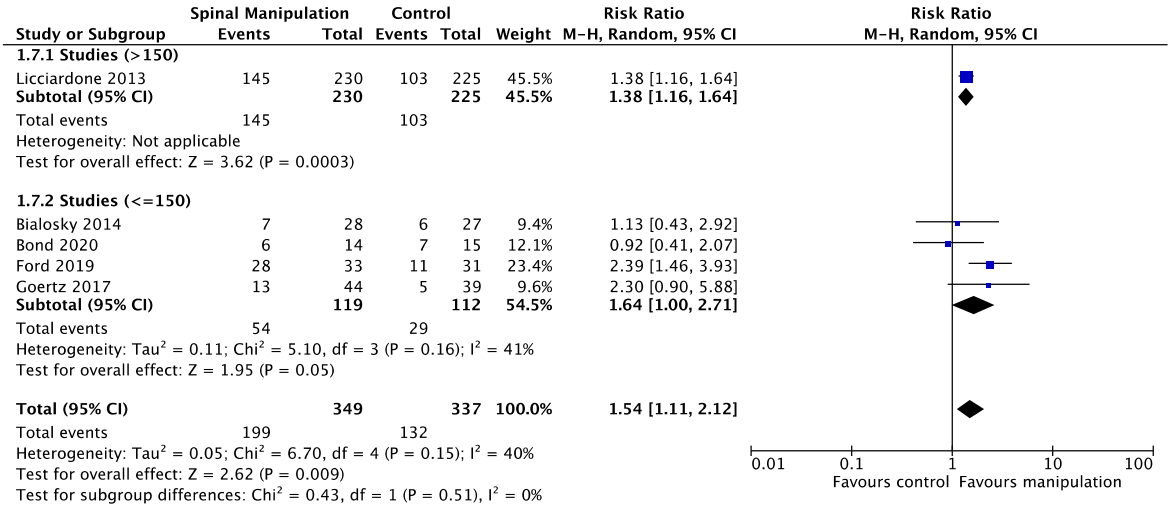
Figures 11.1: Exercise versus no exercise; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study size (<150 participants compared to ≥150 participants)



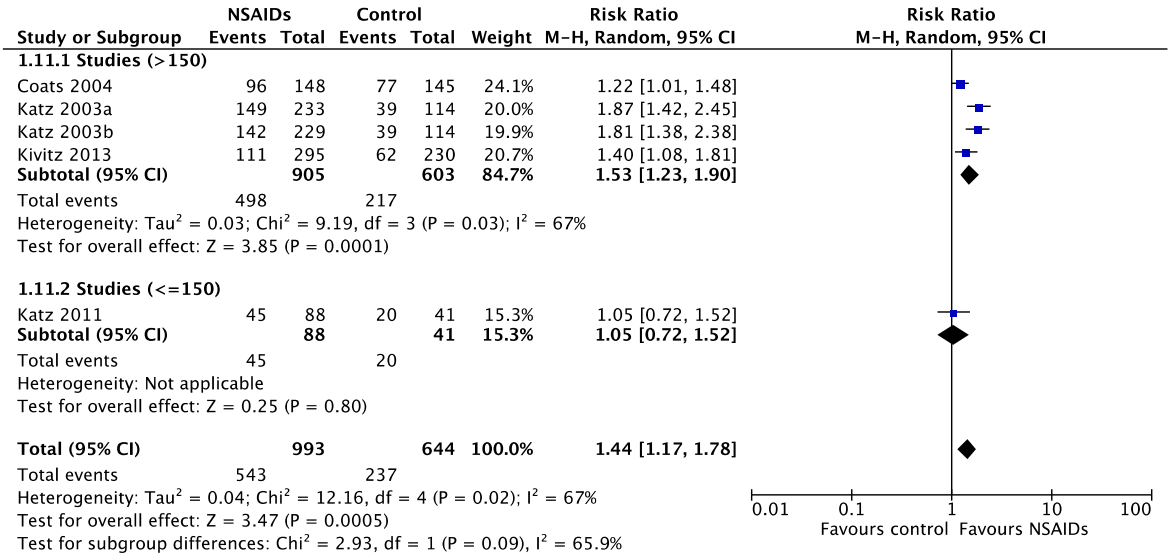
Figures 11.2: Acupuncture versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study size (<150 participants compared to ≥150 participants)



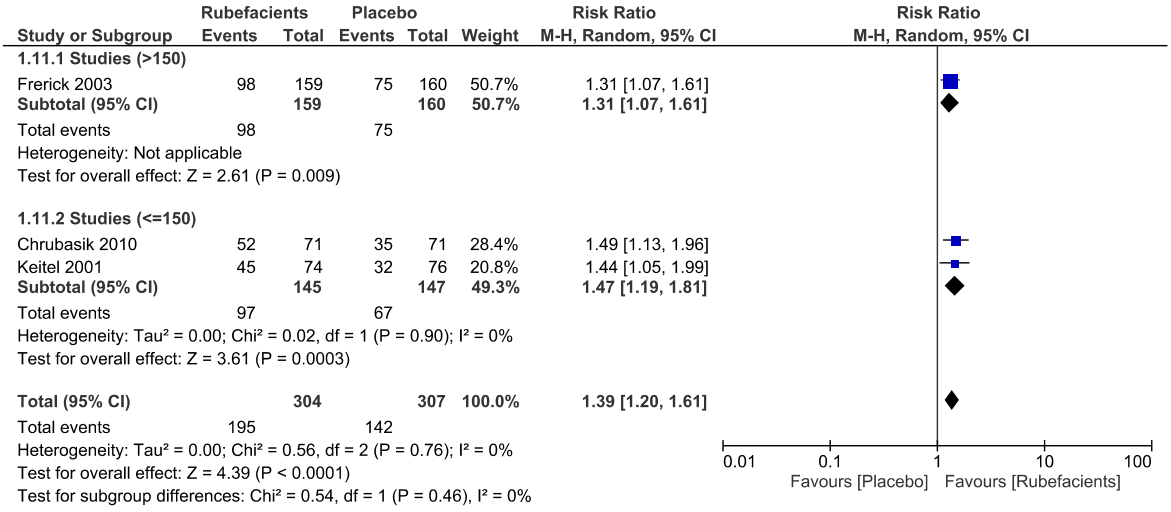
Figures 11.3: Spinal Manipulation versus control; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study size (<150 participants compared to ≥150 participants)



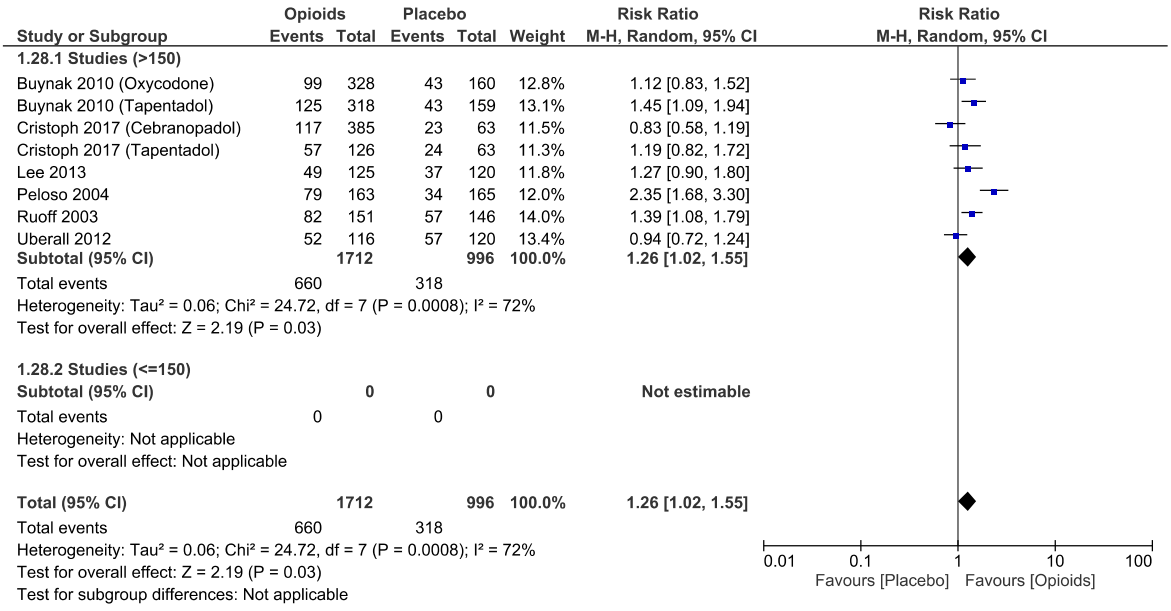
Figures 11.4: Oral NSAIDs versus placebo; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study size (<150 participants compared to ≥150 participants)



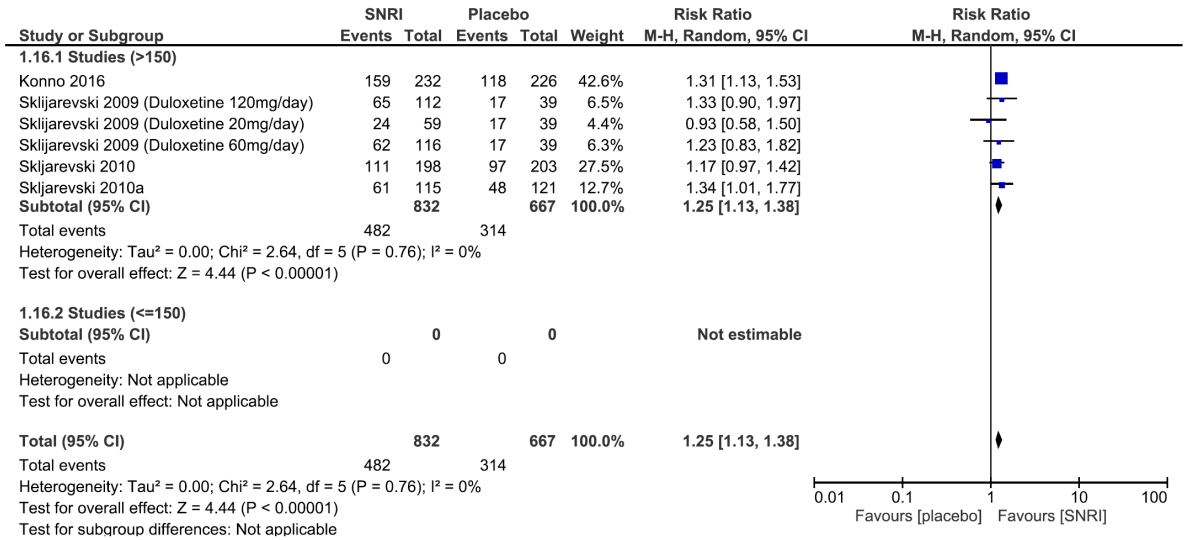
Figures 11.5: Rubefacients versus placebo; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study size (<150 participants compared to ≥150 participants)



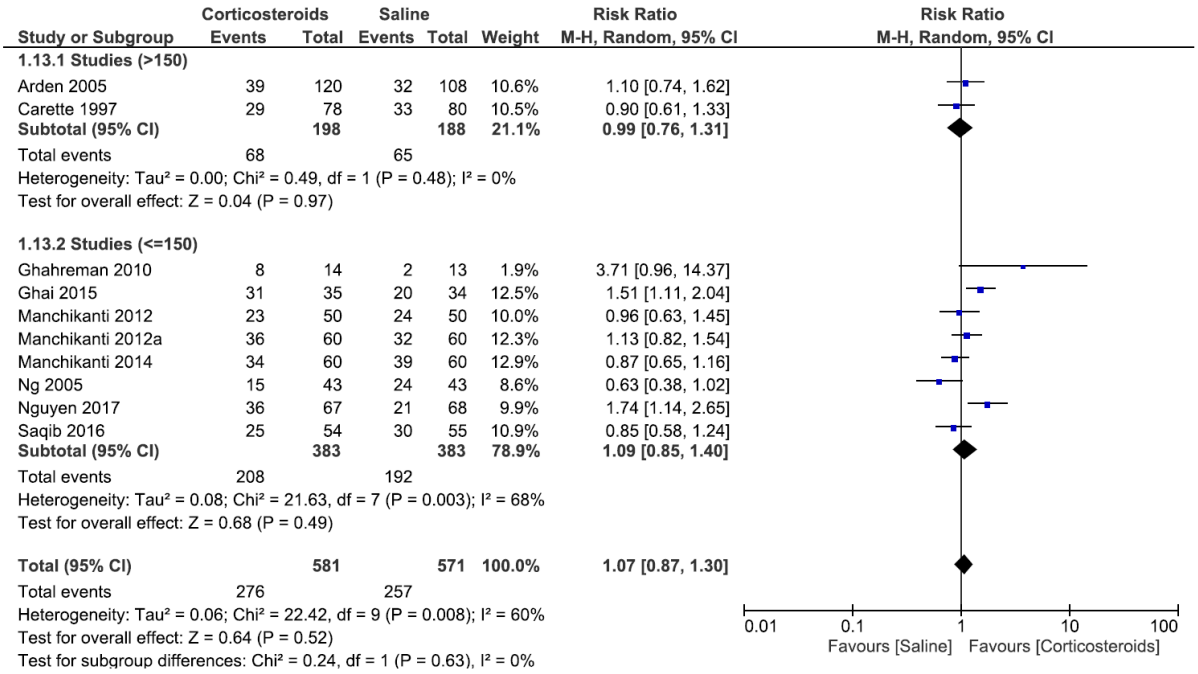
Figures 11.6: Opioids versus placebo; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study size (<150 participants compared to ≥150 participants)



Figures 11.7: SNRI (duloxetine) versus placebo; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study size (<150 participants compared to ≥150 participants)



Figures 11.8: Corticosteroid Injections versus saline injections; Subgroup analysis: Proportion of patients with a meaningful response to treatment, analyzed by study size (<150 participants compared to ≥150 participants)



Adverse Events

Table 7: Overall Adverse Events

Ordered Intervention by in Alphabetical Order

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	Adverse Events	Brinkhaus 2006	Acupuncture Minimal Acupuncture	1	219	10.3% (15/146)	16.4% (12/73)	RR 0.63 (95% CI 0.31, 1.27)*	NSS
Acupuncture	Adverse Events	Cherkin 2009	Standardized Acupuncture + Individualized Acupuncture Simulated Acupuncture	1	477	3.8% (12/315)	0% (0/162)	RR 12.90 (95% CI 0.77, 216.44)*	NSS
Acupuncture	Adverse Events	Kerr 2003	Acupuncture Placebo-TENS	1	60	6.7% (2/30)	6.7% (2/30)	RR 1.00 (95% CI 0.15, 6.64)*	NSS
Acupuncture	Adverse Events	Meng 2003	Acupuncture + Standard Therapy Standard Therapy	1	51	32.1% (9/28)	26.1% (6/23)	RR 1.23 (95% CI 0.51, 2.95)*	NSS
Acupuncture	Adverse Events	Qin 2019	Acupuncture Sham Acupuncture	1	80	7.5% (3/40)	12.5% (5/40)	RR 0.60 (95% CI 0.15, 2.34)*	NSS
Acupuncture	Serious Adverse Events	Haake 2007	Verum Acupuncture Sham Acupuncture	1	774	3.1% (12/387)	3.1% (12/387)	RR 1.00 (95% CI 0.45, 2.20)*	NSS

Acupuncture	Withdrawal due to Adverse Events	Qin 2019	Acupuncture Sham Acupuncture	1	80	2.5% (1/40)	0% (0/40)	RR 3.00 (95% CI 0.13, 71.51)	NSS
Anticonvulsants	Loss of Balance	Atkinson 2016	Gabapentin (Mean 3265 mg)	1	108	33% (18/55)	4% (2/53)	RR 8.67 (95% CI 2.11, 35.57)*	**4**
Anticonvulsants	Decreased Concentration	Atkinson 2016	Gabapentin (Mean 3265 mg)	1	108	38% (21/55)	11% (6/53)	RR 3.37 (95% CI 1.48, 7.70)*	**4**
Anticonvulsants	Dry Mouth	Atkinson 2016	Gabapentin (Mean 3265 mg)	1	108	40% (22/55)	19% (10/53)	RR 2.12 (95% CI 1.11, 4.04)*	**5**
Anticonvulsants	Fatigue	Atkinson 2016	Gabapentin (Mean 3265 mg)	1	108	49% (27/55)	28% (15/53)	RR 1.73 (1.05, 2.88)*	**5**
Anticonvulsants	Dizziness	Atkinson 2016	Gabapentin (Mean 3265 mg) Placebo	1	108	43.6% (24/55)	26.4% (14/53)	RR 1.65 (95% CI 0.96, 2.84)*	NSS
Anticonvulsants	GI-Related (Nausea, Vomiting, Constipation, Diarrhea)	Atkinson 2016	Gabapentin (Mean 3265 mg) Placebo	1	108	36.4% (20/55)	45.3% (24/53)	RR 0.80 (95% CI 0.51, 1.27)*	NSS
Anticonvulsants	Sexual Side Effects (Erectile Dysfunction, Decreased Sexual Desire)	Atkinson 2016	Gabapentin (Mean 3265 mg) Placebo	1	108	20% (11/55)	7.5% (4/53)	RR 2.65 (95% CI 0.90, 7.81)*	NSS
Anticonvulsants	Sleep Disturbances	Atkinson 2016	Gabapentin (Mean 3265 mg) Placebo	1	108	50.9% (28/55)	39.6% (21/53)	RR 1.28 (95% CI	NSS

								0.84, 1.96)*	
Anticonvulsants	Weight Gain	Atkinson 2016	Gabapentin (Mean 3265 mg) Placebo	1	108	10.9% (6/55)	1.9% (1/53)	RR 5.78 (95% CI 0.72, 46.43)*	NSS
Anticonvulsants	Withdrawal Due to Adverse Events	Atkinson 2016	Gabapentin (Mean 3265 mg) Placebo	1	108	12.7% (7/55)	9.4% (5/53)	RR 1.35 (95% CI 0.46, 3.99)*	NSS
Exercise	Adverse Events	Saper 2017a	Yoga Back Pain Help Book	1	320	7.1% (9/127)	3.1% (1/32)	RR 2.27 (95% CI 0.30, 17.25)*	NSS
Exercise	Adverse Events	Saper 2017b	Physical Therapy Back Pain Help Book	1	320	10.9% (14/129)	0% (0/32)	RR 7.36 (95% CI 0.45, 120.24)*	NSS
Exercise	Increased Back Pain	Saper 2017a	Yoga Back Pain Help Book	1	320	3.1% (4/127)	3.1% (1/32)	RR 1.01 (95% CI 0.12, 8.71)*	NSS
Exercise	Increased Back Pain	Saper 2017b	Physical Therapy Back Pain Help Book	1	320	3.9% (5/129)	0% (0/32)	RR 2.79 (95% CI 0.16, 49.24)*	NSS
Exercise	Increased Pain	Jensen 2012	Physiotherapy-delivered exercise Prescribed rest	1	100	6.1% (3/49)	9.8% (5/51)	RR 0.62 (95% CI 0.16, 2.47)*	NSS
Exercise	Joint Pain	Saper 2017a	Yoga Back Pain Help Book	1	320	3.1% (4/127)	0% (0/32)	RR 2.32 (95% CI 0.13, 42.03)*	NSS

Exercise	Joint Pain	Saper 2017b	Physical Therapy Back Pain Help Book	1	320	6.2% (8/129)	0% (0/32)	RR 4.32 (95% CI 0.26, 72.87)*	NSS
Exercise	Mild Muscle Soreness	Brodsky 2019	Group Stretching Self-Care Book	1	69	11.8% (4/34)	8.6% (3/35)	RR 1.37 (95% CI 0.33, 5.68)*	NSS
Exercise	Mild Adverse Events	Costa 2009	Physiotherapy-delivered motor control exercises Sham detuned shortwave diathermy/ultrasound	1	144	3.9% (3/77)	2.6% (2/77)	RR 1.50 (95% CI 0.26, 8.73)*	NSS
Exercise	Serious Adverse Events	Saper 2017a	Yoga Back Pain Help Book	1	320	0.79% (1/127)	0% (0/32)	RR 0.77 (95% CI 0.03, 18.56)*	NSS
Corticosteroid Injections	Accidental Dural Puncture	Carette 1997	Corticosteroid Injections (0,3,6 weeks if no marked improvement) Saline Injections (0,3,6 weeks)	1	158	1.3% 1/78	1.3% 1/80	RR 1.03 (95% CI 0.07, 16.11)	NSS
Corticosteroid Injections	Death	Nguyen 2017	Single Corticosteroid Injection Single Injection of Contrast	1	135	1.5% (1/67)	0% (0/68)	RR 3.04 (95% CI 0.13, 73.43)	NSS
Corticosteroid Injections	Non-Specific Headache	Arden 2005	Corticosteroid Injections (0,3,6 weeks) Saline Injections (0,3,6 weeks)	1	228	3.3% (4/120)	3.7% (4/108)	RR 0.90 (95% CI 0.23, 3.51)	NSS
Corticosteroid Injections	Postdural Puncture Headache and Nausea	Arden 2005	Corticosteroid Injections (0,3,6 weeks) Saline Injections (0,3,6 weeks)	1	228	1.7% (2/120)	1.9% (2/108)	RR 0.90 (95% CI 0.13, 6.28)	NSS

Corticosteroid Injections	Serious Adverse Events	Nguyen 2017	Single Corticosteroid Injection Single Injection of Contrast	1	135	0% (0/67)	1.5% (1/68)	RR 0.34 (95% CI 0.01, 8.16)	NSS
Corticosteroid Injections	Transient Headache	Carette 1997	Corticosteroid Injections (0,3,6 weeks if no marked improvement) Saline Injections (0,3,6 weeks)	1	158	26.9% (21/78)	20.0% (16/80)	RR 1.35 (95% CI 0.76, 2.38)	NSS
Corticosteroid Injections	Vasovagal Response	Ghai 2015	Corticosteroid and Lidocaine Injection (Multiple if pain relief of ≤50% was deteriorated, spaced at least 15 days) Lidocaine Injection (Multiple if pain relief of ≤50% was deteriorated, spaced at least 15 days)	1	69	0% (0/35)	2.9% (1/34)	RR 0.32 (95% CI 0.01, 7.69)	NSS
Opioids	Hot Flushes	Peloso 2004	• Tramadol/Acetaminopen ER 37.5/325mg 3-8 tabs per day • Placebo	1	336	7% (11/167)	1% (1/169)	RR 11.13 (95% CI 1.45, 85.26)	**17**
Opioids	Hyperhidrosis	Buynak 2010, Cristoph 2017, Peloso 2004, Uberall 2012	• Oxycodone CR 20-50mg BID • Tapentadol ER 100-250mg BID • Tapentadol PR 200mg BID • Cebranopadol 200-600mg QD • Tramadol/Acetaminopen ER 37.5/325mg 3-8 tabs per day • Tramadol ER 200mg QD • Placebo	4	1874	9% (97/1140)	0.4% (3/734)	RR 9.36 (95% CI 3.64, 24.07)	**13**

Opioids	Pruritus	Buynak 2010, Ruoff 2003	• Oxycodone CR 20-50mg BID • Tapentadol ER 100-250mg BID • Tramadol/Acetaminopen ER 37.5/325mg 1-8 tabs per day • Placebo	2	1283	11% (89/807)	2% (8/476)	RR 5.80 (95% CI 2.82, 11.94)	**11**
Opioids	Vomiting	Buynak 2010, Cristoph 2017, Peloso 2004, Uberall 2012	• Oxycodone CR 20-50mg BID • Tapentadol ER 100-250mg BID • Tapentadol PR 200mg BID • Cebranopadol 200-600mg QD • Tramadol/Acetaminopen ER 37.5/325mg 3-8 tabs per day • Tramadol ER 200mg QD • Placebo	4	2174	14% (208/1440)	2% (15/734)	RR 5.50 (95% CI 3.25, 9.32)	**9**
Opioids	Somnolence	Buynak 2010, Cristoph 2017, Peloso 2004, Ruoff 2003	• Oxycodone CR 20-50mg BID • Tapentadol ER 100-250mg BID • Tapentadol PR 200mg BID • Cebranopadol 200-600mg QD • Tramadol/Acetaminopen ER 37.5/325mg 3-8 tabs per day • Tramadol/Acetaminopen ER 37.5/325mg 1-8 tabs per day • Placebo	4	2256	16% (231/1485)	3% (21/771)	RR 5.20 (95% CI 3.34, 8.08)	**8**
Opioids	Anorexia	Peloso 2004	• Tramadol/Acetaminopen ER 37.5/325mg 3-8 tabs per day • Placebo	1	336	7% (11/167)	2% (3/169)	RR 3.71 (95% CI 1.05, 13.06)	**21**
Opioids	Nausea	Buynak 2010, Cristoph 2017, Lee 2013, Peloso 2004,	• Oxycodone CR 20-50mg BID • Tapentadol ER 100-250mg BID	6	2737	26% (454/1726)	7% (67/1011)	RR 3.62 (95% CI 2.83, 4.63)	**6**

		Ruoff 2003, Uberall 2012	• Tapentadol PR 200mg BID • Cebranopadol 200-600mg QD • Tramadol/Acetaminopen ER 37.5/325mg 1-2tabs BID • Tramadol ER 200mg QD • Tramadol/Acetaminopen ER 37.5/325mg 3-8 tabs per day • Tramadol/Acetaminopen ER 37.5/325mg 1-8 tabs per day • Placebo						
Opioids	Dry Mouth	Buynak 2010, Peloso 2004, Ruoff 2003, Uberall 2012	• Oxycodone CR 20-50mg BID • Tapentadol ER 100-250mg BID • Tramadol ER 200mg QD • Tramadol/Acetaminopen ER 37.5/325mg 3-8 tabs per day • Tramadol/Acetaminopen ER 37.5/325mg 1-8 tabs per day • Placebo	4	1855	7% (77/1090)	2% (16/765)	RR 3.24 (95% CI 1.88, 5.61)	**21**
Opioids	Constipation	Buynak 2010, Cristoph 2017, Peloso 2004, Ruoff 2003, Uberall 2012	• Oxycodone CR 20-50mg BID • Tapentadol ER 100-250mg BID • Tapentadol PR 200mg BID • Cebranopadol 200-600mg QD • Tramadol ER 200mg QD • Tramadol/Acetaminopen ER 37.5/325mg 3-8 tabs per day • Tramadol/Acetaminopen ER 37.5/325mg 1-8 tabs per day • Placebo	5	2737	17% (276/1601)	5% (45/891)	RR 3.17 (95% CI 2.32, 4.35)	**9**

Opioids	Dizziness	Buynak 2010, Cristoph 2017, Lee 2013, Peloso 2004, Ruoff 2003, Uberall 2012	• Oxycodone CR 20-50mg BID • Tapentadol ER 100-250mg BID • Tapentadol PR 200mg BID • Cebranopadol 200-600mg QD • Tramadol/Acetaminopen ER 37.5/325mg 1-2tabs BID • Tramadol ER 200mg QD • Tramadol/Acetaminopen ER 37.5/325mg 3-8 tabs per day • Tramadol/Acetaminopen ER 37.5/325mg 1-8 tabs per day • Placebo	6	2737	24% (409/1722)	8% (80/1007)	RR 2.77 (95% CI 2.21, 3.47)	**7**
Opioids	Fatigue	Buynak 2010, Cristoph 2017, Ruoff 2003, Uberall 2012	• Oxycodone CR 20-50mg BID • Tapentadol ER 100-250mg BID • Tapentadol PR 200mg BID • Cebranopadol 200-600mg QD • Tramadol ER 200mg QD • Tramadol/Acetaminopen ER 37.5/325mg 1-8 tabs per day • Placebo	4	2156	9% (136/1434)	3% (23/722)	RR 2.30 (95% CI 1.46, 3.62)	**16**
Opioids	Headache	Buynak 2010, Cristoph 2017, Lee 2013, Peloso 2004, Ruoff 2003, Uberall 2012	• Oxycodone CR 20-50mg BID • Tapentadol ER 100-250mg BID • Tapentadol PR 200mg BID • Cebranopadol 200-600mg QD • Tramadol/Acetaminopen ER 37.5/325mg 1-2tabs BID • Tramadol ER 200mg QD	6	2737	14% (244/1726)	10% (106/1011)	RR 1.35 (95% CI 1.09, 1.67)	**28**

			• Tramadol/Acetaminopen ER 37.5/325mg 3-8 tabs per day • Tramadol/Acetaminopen ER 37.5/325mg 1-8 tabs per day • Placebo						
Opioids	Abdominal Discomfort	Uberall 2012	• Tramadol ER 200mg QD • Placebo	1	236	4.3% (5/116)	5.0% (6/120)	RR 0.86 (95% CI 0.27, 2.75)	NSS
Opioids	Diarrhea	Buynak 2010	• Oxycodone CR 20-50mg BID • Tapentadol ER 100-250mg BID • Placebo	1	965	4% (27/646)	7% (23/319)	RR 0.56 (95% CI 0.25, 1.23)	NSS
Opioids	Dyspepsia	Buynak 2010, Lee 2013, Uberall 2012	• Oxycodone CR 20-50mg BID • Tapentadol ER 100-250mg BID • Tramadol/Acetaminopen ER 37.5/325mg 1-2tabs BID • Tramadol ER 200mg QD • Placebo	3	1146	4% (38/887)	4% (21/559)	RR 1.22 (95% CI 0.71, 2.08)	NSS
Opioids	Hepatic Enzyme Increased	Uberall 2012	• Tramadol ER 200mg QD • Placebo	1	236	0% (0/115)	4.2% (5/120)	RR 0.09 (95% CI 0.01, 1.68)	NSS
Opioids	Insomnia	Buynak 2010	• Oxycodone CR 20-50mg BID • Tapentadol ER 100-250mg BID • Placebo	1	965	5.9% (38/646)	2.8% (9/319)	RR 1.98 (95% CI 0.86, 4.53)	NSS
Opioids	Serious Adverse Event	Buynak 2010, Cristoph 2017, Uberall 2012	• Oxycodone CR 20-50mg BID • Tapentadol ER 100-250mg BID • Tapentadol PR 200mg BID • Cebranopadol 200-600mg QD • Tramadol ER 200mg QD • Placebo	3	2166	2.4% (30/1273)	0.88% (5/565)	RR 2.10 (95% CI 0.81, 5.48)	NSS

Opioids	Sinusitis	Ruoff 2003	• Tramadol/Acetaminopen ER 37.5/325mg 1-8 tabs per day • Placebo	1	318	5.0% (8/161)	3.2% (5/157)	RR 1.56 (95% CI 0.52, 4.67)	NSS
Opioids	Upper Respiratory Tract Infection	Ruoff 2003	• Tramadol/Acetaminopen ER 37.5/325mg 1-8 tabs per day • Placebo	1	318	5.6% (9/161)	7.6% (12/157)	RR 0.73 (95% CI 0.32, 1.69)	NSS
Oral NSAIDs	≥1 Adverse Event	Coats 2004	Valdecoxib 40 mg daily Placebo	1	293	35% (52/148)	24% (35/145)	RR 1.46 (95% CI 1.01, 2.09)*	**10**
Oral NSAIDs	Any adverse event	Katz 2003	Rofecoxib 25 mg Placebo	1	461	48.1% (112/233)	40.8% (93/228)	RR 1.78 (95% CI 0.96, 1.45)*	NSS
Oral NSAIDs	Any adverse event	Katz 2003	Rofecoxib 50 mg Placebo	1	457	46.3% (106/229)	40.8% (93/228)	RR 1.13 (95% CI 0.92, 1.40)*	NSS
Oral NSAIDs	Any adverse event	Katz 2011	Naproxen 1000 mg daily Placebo	1	129	61.4% (54/88)	65.9% (27/41)	RR 0.93 (95% CI 0.71, 1.23)*	NSS
Oral NSAIDs	Arthralgia	Kivitz 2013	Naproxen 1000 mg daily Placebo	1	525	1.4% (4/295)	1.7% (4/230)	RR 0.78 (95% CI 0.20, 3.08)	NSS
Oral NSAIDs	Congestive Heart Failure	Katz 2003	Rofecoxib 25 mg Placebo	1	461	0.4% (1/233)	0% (0/228)	RR 2.94 (95% CI 0.12, 71.70)	NSS
Oral NSAIDs	Diarrhea	Katz 2003	Rofecoxib 25 mg Placebo	1	461	7.3% (17/233)	3.5% (8/228)	RR 2.08 (95% CI 0.92, 4.72)*	NSS
Oral NSAIDs	Diarrhea	Katz 2003	Rofecoxib 50 mg Placebo	1	457	4.8% (11/229)	3.5% (8/228)	RR 1.37 (95% CI 0.56, 3.34)	NSS

Oral NSAIDs	Dizziness	Kivitz 2013	Naproxen 1000 mg daily Placebo	1	525	1.4% (4/295)	3.0% (7/230)	RR 0.45 (95% CI 0.13, 1.50)	NSS
Oral NSAIDs	Edema	Katz 2003a Katz 2003b Kivitz 2013	Oral NSAIDs Placebo	2	1215	2.2% (17/757)	0.87% (4/458)	RR 2.12 (95% CI 0.68, 6.65)	NSS
Oral NSAIDs	Headache	Katz 2003a Katz 2003b Kivitz 2013	Oral NSAIDs Placebo	2	1215	5.9% (45/757)	7.0% (32/458)	RR 0.78 (95% CI 0.50, 1.21)	NSS
Oral NSAIDs	Hyperesthesia	Kivitz 2013	Naproxen 1000 mg daily Placebo	1	525	0% (0/295)	0.87% (2/230)	RR 0.16 (95% CI 0.01, 3.24)	NSS
Oral NSAIDs	Hypertension	Katz 2003	Rofecoxib 25 mg Placebo	1	461	0.86% (2/233)	0.88% (2/228)	RR 0.98 (95% CI 0.14, 6.89)	NSS
Oral NSAIDs	Hypertension	Katz 2003	Rofecoxib 50 mg Placebo	1	457	2.2% (5/229)	0.88% (2/228)	RR 2.49 (95% CI 0.49, 12.70)	NSS
Oral NSAIDs	Hypoesthesia	Kivitz 2013	Naproxen 1000 mg daily Placebo	1	525	2.7% (8/295)	2.6% (6/230)	RR 1.04 (95% CI 0.37, 2.95)	NSS
Oral NSAIDs	MSK Pain	Kivitz 2013	Naproxen 1000 mg daily Placebo	1	525	1.0% (3/295)	3.0% (7/230)	RR 0.33 (95% CI 0.09, 1.28)	NSS
Oral NSAIDs	Muscle Spasms	Kivitz 2013	Naproxen 1000 mg daily Placebo	1	525	0.68% (2/295)	0.87% (2/230)	RR 0.78 (95% CI 0.11, 5.49)	NSS
Oral NSAIDs	Myocardial Infarction	Katz 2003	Rofecoxib 50 mg Placebo	1	457	0.4% (1/229)	0% (0/228)	RR 2.99 (95% CI 0.12, 72.94)	NSS
Oral NSAIDs	Nasopharyngitis	Kivitz 2013	Naproxen 1000 mg daily Placebo	1	525	3.1% (9/295)	0.87% (2/230)	RR 3.51 (95% CI 0.77, 16.08)	NSS

Oral NSAIDs	Nausea	Kivitz 2013	Naproxen 1000 mg daily Placebo	1	525	3.1% (9/295)	0.87% (2/230)	RR 3.51 (95% CI 0.77, 16.08)	NSS
Oral NSAIDs	Pain in extremity	Kivitz 2013	Naproxen 1000 mg daily Placebo	1	525	0.68% (2/295)	1.7% (4/230)	RR 0.39 (95% CI 0.07, 2.11)	NSS
Oral NSAIDs	Paresthesia	Kivitz 2013	Naproxen 1000 mg daily Placebo	1	525	1.7% (5/295)	2.2% (5/230)	RR 0.78 (95% CI 0.23, 2.66)	NSS
Oral NSAIDs	Serious Adverse Events	Coats 2004 Katz 2011	Oral NSAIDs Placebo	2	422	3.0% (7/236)	2.7% (5/186)	RR 1.11 (95% CI 0.36, 3.43)	NSS
Oral NSAIDs	Treatment-related adverse events	Katz 2011	Naproxen 1000 mg daily Placebo	1	129	18.2% (16/88)	22.0% (9/41)	RR 0.83 (95% CI 0.40, 1.71)*	NSS
Oral NSAIDs	Upper Respiratory Infection	Katz 2003a Katz 2003b Kivitz 2013	Oral NSAIDs Placebo	2	1215	4.5% (34/757)	4.4% (20/458)	RR 1.01 (95% CI 0.59, 1.75)	NSS
Oral NSAIDs	Urinary Tract Infection	Kivitz 2013	Naproxen 1000 mg daily Placebo	1	525	2.0% (6/295)	3.5% (8/230)	RR 0.58 (95% CI 0.21, 1.66)	NSS
Oral NSAIDs	Withdrawal due to Adverse Events	Coats 2004 Katz 2003a Katz 2003b Katz 2011 Kivitz 2013	Oral NSAIDs Placebo	4	1637	3.7% (37/993)	3.1% (20/644)	RR 1.36 (95% CI 0.53, 3.51)	NSS
Oral NSAIDs	≥1 adverse event	Kivitz 2013	Naproxen 1000 mg daily Placebo	1	525	48.1% (142/295)	52.2% (120/230)	RR 0.92 (95% CI 0.78, 1.10)	NSS
Rubefacients	Heat Sensation	Chrubasik 2010, Keitel 2001	Capsaicin 0.05% Cream applied 3x/day Placebo Cream	2	292	78.9% (127/145)	32.4% (60/147)	RR 2.10 (95% CI 1.73, 2.56)	3

			Capsaicin Plaster Placebo Plaster						
Rubefacients	Mild or Moderate Local Erythema	Frerick 2003	Capsaicin Plaster applied once daily for 4-8 hours Placebo Plaster	1	301	67.6% (100/148)	48.4% (75/153)	RR 1.38 (95% CI 1.13, 1.68)	6
Rubefacients	Local Mild Inflammation	Frerick 2003	Capsaicin Plaster applied once daily for 4-8 hours Placebo Plaster	1	301	18.9% (28/148)	11.8% (18/153)	RR 1.61 (95% CI 0.93, 2.78)	NSS
Rubefacients	Pruritus	Chrubasik 2010, Keitel 2001	Capsaicin 0.05% Cream applied 3x/day Placebo Cream Capsaicin Plaster Placebo Plaster	2	292	29.0% (42/145)	17.7% (26/147)	RR 1.86 (95% CI 0.78, 4.45)	NSS
SNRI (Duloxetine)	Dizziness	Konno 2016, Skljarevski 2010	Duloxetine 60mg/day Placebo	2	859	5.3% (23/430)	0.93% (4/429)	RR 5.55 (95% CI 1.92, 16.02)	23
SNRI (Duloxetine)	Nausea	Konno 2016, Skljarevski 2010	Duloxetine 60mg/day Placebo	2	859	13.3% (57/430)	2.8% (12/429)	RR 4.65 (95% CI 2.53, 8.57)	10
SNRI (Duloxetine)	Somnolence	Konno 2016	Duloxetine 60mg/day Placebo	1	458	19.4% (45/232)	7.1% (16/226)	RR 2.74 (95% CI 1.60, 4.70)	9
SNRI (Duloxetine)	Withdrawal due to AE	Sklijarevski 2010	Duloxetine 60mg/day Placebo	1	458	18.5% (53/287)	8.5% (10/117)	RR 2.16 (95% CI 1.14, 4.10)	11
SNRI (Duloxetine)	At Least one Treatment Emergent Adverse Event	Sklijarevski 2010a	Duloxetine 60-120mg/day Placebo	1	236	56.5% (65/115)	47.9% (58/121)	RR 1.41 (95% CI 0.85, 2.36)	NSS

SNRI (Duloxetine)	At Least one Serious Adverse Event	Sklijarevski 2009, Sklijarevski 2010a	Duloxetine 60-120mg/day Placebo	2	640	2.2% (9/402)	1.7% (4/238)	RR 1.18 (95% CI 0.35, 3.98)	NSS
SNRI (Duloxetine)	Constipation	Konno 2016, Skljarevski 2010	Duloxetine 60mg/day Placebo	2	859	8.1% (35/430)	3.0% (13/429)	RR 2.48 (95% CI 0.66, 9.31)	NSS
SNRI (Duloxetine)	Contusion	Konno 2016	Duloxetine 60mg/day Placebo	1	458	6.9% (16/232)	3.1% (7/226)	RR 2.23 (95% CI 0.93, 5.31)	NSS
SNRI (Duloxetine)	Dry Mouth	Konno 2016, Skljarevski 2010	Duloxetine 60mg/day Placebo	2	859	6.0% (26/430)	1.0% (4/429)	RR 6.76 (95% CI 0.68, 67.37)	NSS
SNRI (Duloxetine)	Nasopharyngitis	Konno 2016	Duloxetine 60mg/day Placebo	1	458	11.2% (26/232)	17.3% (39/226)	RR 0.65 (95% CI 0.41, 1.03)	NSS
SNRI (Duloxetine)	Serious Adverse Events	Sklijarevski 2010	Duloxetine 60mg/day Placebo	1	458	1.7% (5/287)	2.6% (3/117)	RR 0.68 (95% CI 0.17, 2.80)	NSS
Spinal Manipulation	Adverse Events	Goertz 2017	Spinal Manipulation + Medical Care Medical Care	1	83	50.0% (22/44)	5.1% (2/39)	RR 9.75 (95% CI 2.45, 38.83)	3
Spinal Manipulation	Adverse Events	Bond 2020	Spinal Manipulation Sham Manipulation	1	29	7.1% (1/14)	0% (0/15)	RR 3.2 (95% CI 0.14, 72.63)	NSS
Spinal Manipulation	Adverse Events	Licciardone 2013	Spinal Manipulation Sham Manipulation	1	455	7.0% (16/230)	4.9% (11/225)	RR 1.42 (95% CI 0.68, 3.00)	NSS
Spinal Manipulation	Local, mild joint pain	Bond 2020	Spinal Manipulation Sham Manipulation	1	29	7.1% (1/14)	0% (0/15)	RR 3.2 (95% CI 0.14, 72.63)	NSS

Spinal Manipulation	Serious Adverse Events	Licciardone 2013	Spinal Manipulation Sham Manipulation	1	455	2.6% (6/230)	1.3% (3/225)	RR 1.96 (95% CI 0.50, 7.73)	NSS
Topical NSAIDs	Adverse Events	Song 2008	Flubiprofen Tape (63 mg/day); Worn 12-24 hours/day Placebo	1	127	25.9% (22/85)	50% (21/42)	RR 0.52 (95% CI 0.32, 0.83)*	5
Topical NSAIDs	Application Site Rash	Song 2008	Flubiprofen Tape (63 mg/day); Worn 12-24 hours/day Placebo	1	127	3.5% (3/85)	9.5% (4/42)	RR 0.37 (95% CI 0.09, 1.58)*	NSS
Topical NSAIDs	Arthalgia	Song 2008	Flubiprofen Tape (63 mg/day); Worn 12-24 hours/day Placebo	1	127	0% (0/85)	4.8% (2/42)	RR 0.10 (95 % CI 0.00, 2.04)*	NSS
Topical NSAIDs	Dizziness	Song 2008	Flubiprofen Tape (63 mg/day); Worn 12-24 hours/day Placebo	1	127	2.4% (2/85)	4.8% (2/42)	RR 0.49 (95% CI 0.07, 3.39)*	NSS
Topical NSAIDs	Erythema at Application Site	Song 2008	Flubiprofen Tape (63 mg/day); Worn 12-24 hours/day Placebo	1	127	7.1% (6/85)	9.5% (4/42)	RR 0.74 (95% CI 0.22, 2.49)*	NSS
Topical NSAIDs	Headache	Song 2008	Flubiprofen Tape (63 mg/day); Worn 12-24 hours/day Placebo	1	127	3.5% (3/85)	9.5% (4/42)	RR 0.37 (95% CI 0.09, 1.58)*	NSS
Topical NSAIDs	Insomnia	Song 2008	Flubiprofen Tape (63 mg/day); Worn 12-24 hours/day Placebo	1	127	0% (0/85)	4.8% (2/42)	RR 0.10 (95% CI 0.00, 2.04)*	NSS
Topical NSAIDs	Irritation at Application Site	Song 2008	Flubiprofen Tape (63 mg/day); Worn 12-24 hours/day Placebo	1	127	7.1% (6/85)	7.1% (3/42)	RR 0.99 (95% CI 0.26, 3.76)*	NSS

Topical NSAIDs	Joint Stiffness	Song 2008	Flubiprofen Tape (63 mg/day); Worn 12-24 hours/day Placebo	1	127	0% (0/85)	2.4% (1/42)	RR 0.17 (95% CI 0.01, 4.01)*	NSS
Topical NSAIDs	Neck Pain	Song 2008	Flubiprofen Tape (63 mg/day); Worn 12-24 hours/day Placebo	1	127	0% (0/85)	2.4% (1/42)	RR 0.17 (95% CI 0.01, 4.01)*	NSS
Topical NSAIDs	Pain in Extremities	Song 2008	Flubiprofen Tape (63 mg/day); Worn 12 hours/day Placebo	1	127	0% (0/85)	2.4% (1/42)	RR 0.17 (95% CI 0.01, 4.01)*	NSS
Topical NSAIDs	Papular Rash	Song 2008	Flubiprofen Tape (63 mg/day); Worn 12 hours/day Placebo	1	127	0% (0/85)	2.4% (1/42)	RR 0.17 (95% CI 0.01, 4.01)*	NSS
Topical NSAIDs	Paraesthesia at Application Site	Song 2008	Flubiprofen Tape (63 mg/day); Worn 12-24 hours/day Placebo	1	127	0% (0/85)	2.4% (1/42)	RR 0.17 (95% CI 0.01, 4.01)*	NSS
Topical NSAIDs	Pruritus at Application Site	Song 2008	Flubiprofen Tape (63 mg/day); Worn 12-24 hours/day Placebo	1	127	7.1% (6/85)	14.3% (6/42)	RR 0.49 (95% CI 0.17, 1.44)*	NSS
Topical NSAIDs	Stomach Discomfort	Song 2008	Flubiprofen Tape (63 mg/day); Worn 12-24 hours/day Placebo	1	127	1.2% (1/85)	4.8% (2/42)	RR 0.25 (95% CI 0.02, 2.65)*	NSS

RR: Risk Ratio; Cl: Confidence Interval; RR: Risk Ratio; NNH: Number Needed to Harm; NSS: Not statistically significant; ER: Extended Release; CR: Controlled Release; QD: Once Daily; BID: Twice daily; mg: Milligrams

Data Analysis of Adverse Events

Oral NSAIDs

Figure 12.1 Oral NSAIDs versus placebo; Withdrawals due to Adverse Events

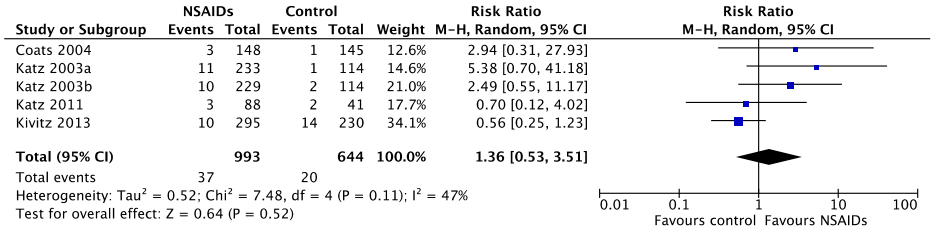


Figure 12.2 Oral NSAIDs versus placebo; Serious Adverse Events

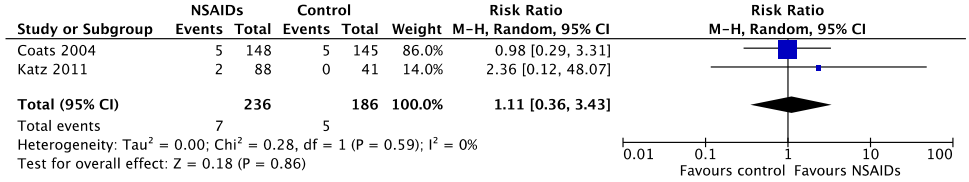


Figure 12.3 Oral NSAIDs versus placebo; Adverse Event: Edema

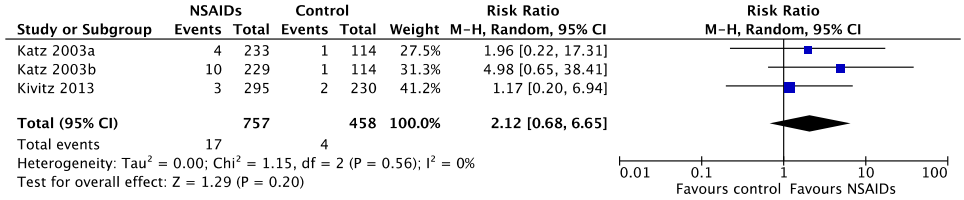


Figure 12.4 Oral NSAIDs versus placebo; Adverse Event: Headache

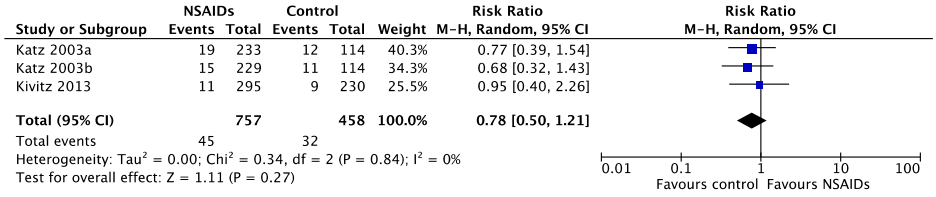
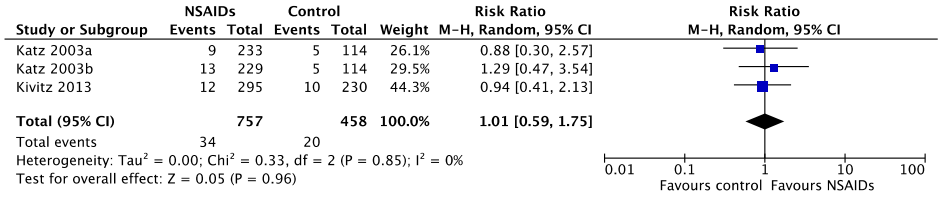


Figure 12.5 Oral NSAIDs versus placebo; Adverse Event: Upper Respiratory Infection



Rubefacients

Figure 13.1 Rubefacients versus placebo; Adverse Event: Heat Sensation

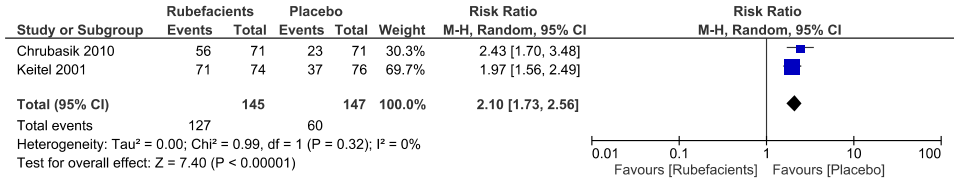
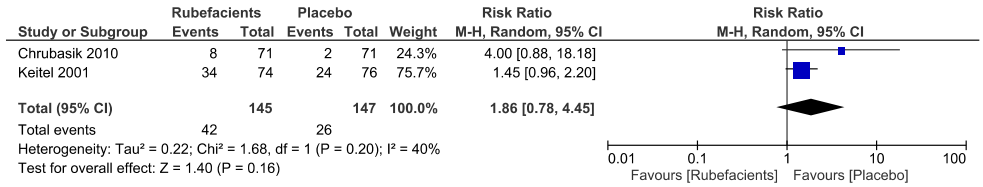


Figure 13.2 Rubefacients versus placebo; Adverse Event: Pruritus



Opioids

Figure 14.1 Opioids versus placebo; Withdrawals due to Adverse Events

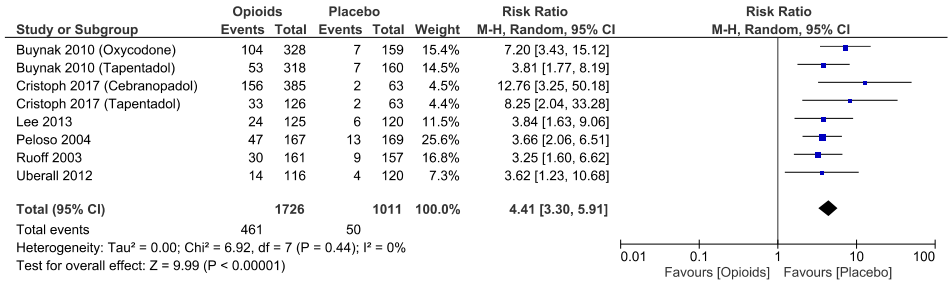


Figure 14.2 Opioids versus placebo; Serious Adverse Events

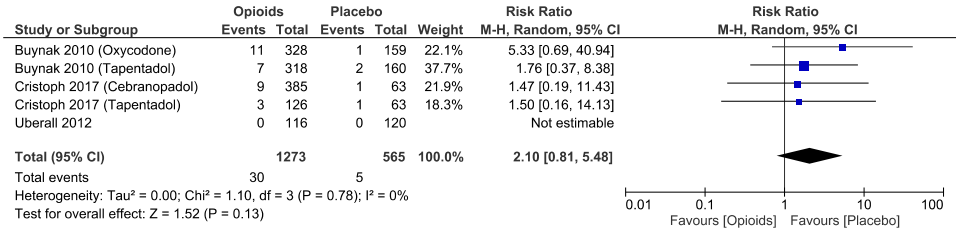


Figure 14.3 Opioids versus placebo; Adverse Event: Constipation

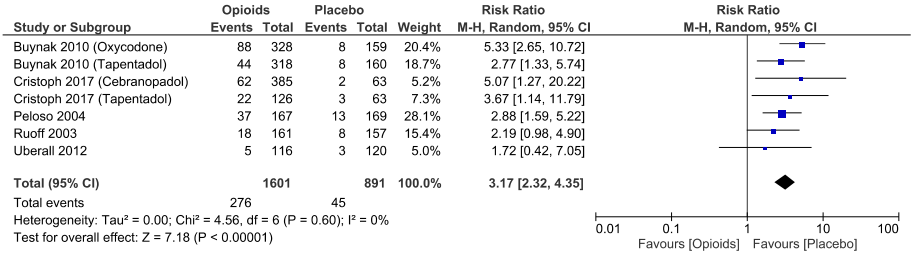


Figure 14.4 Opioids versus placebo; Adverse Event: Diarrhea

Figure 14.5 Opioids versus placebo; Adverse Event: Dizziness

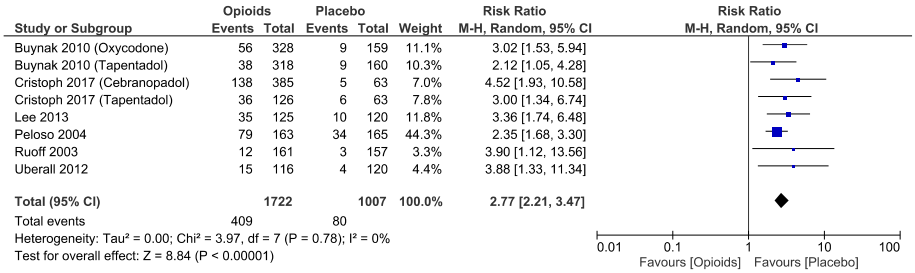


Figure 14.6 Opioids versus placebo; Adverse Event: Dry Mouth

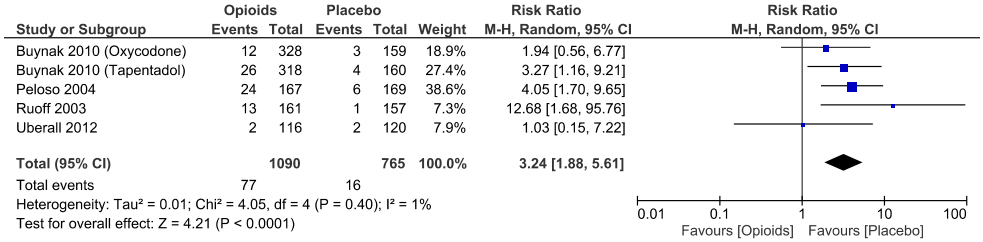


Figure 14.7 Opioids versus placebo; Adverse Event: Dyspepsia

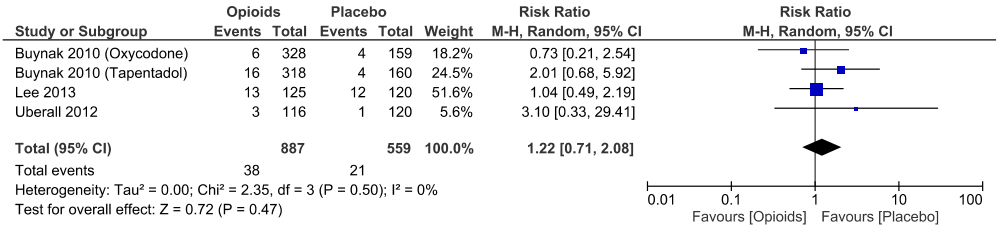


Figure 14.8 Opioids versus placebo; Adverse Event: Fatigue

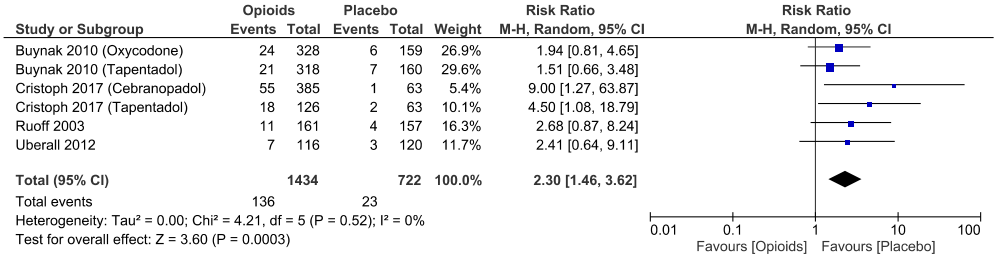


Figure 14.9 Opioids versus placebo; Adverse Event: Headache

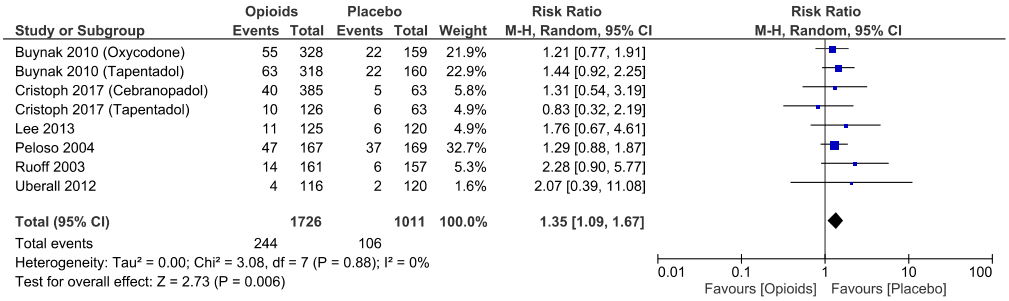


Figure 14.10 Opioids versus placebo; Adverse Event: Hyperhydrosis

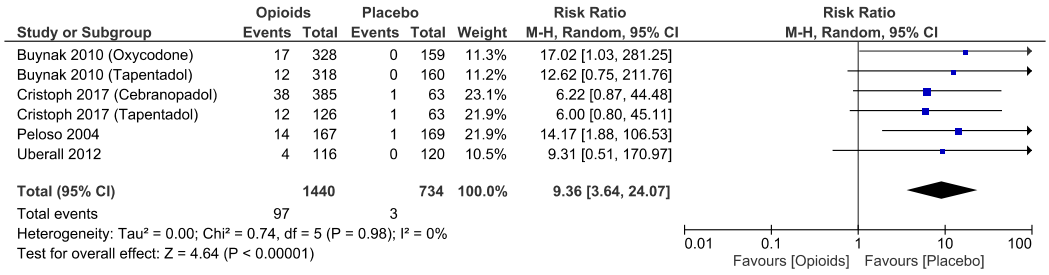


Figure 14.11 Opioids versus placebo; Adverse Event: Insomnia

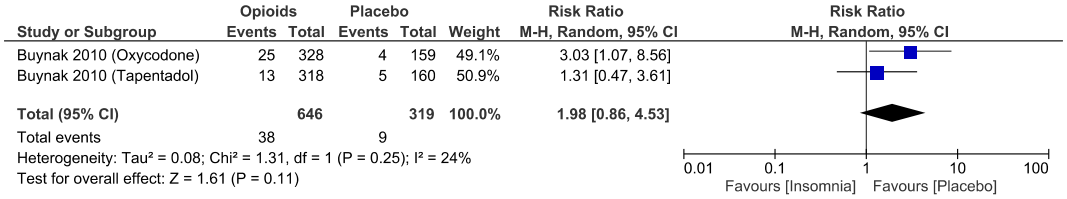


Figure 14.12 Opioids versus placebo; Adverse Event: Nausea

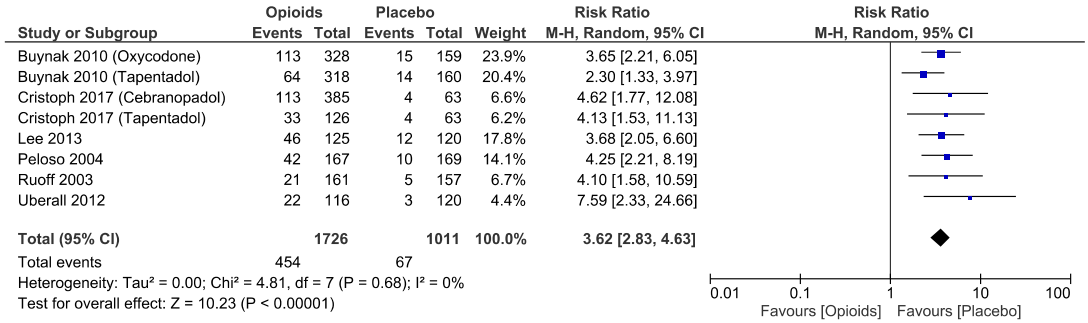


Figure 14.13 Opioids versus placebo; Adverse Event: Pruritis

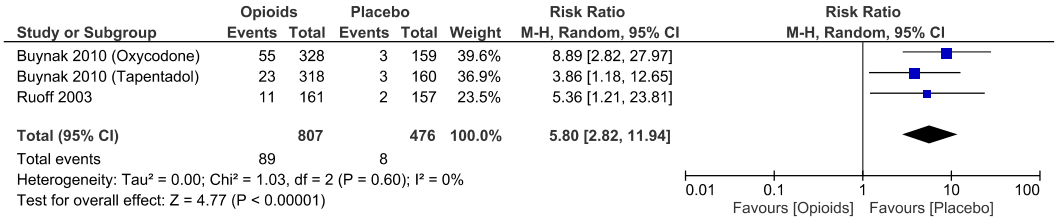


Figure 14.14 Opioids versus placebo; Adverse Event: Somnolence

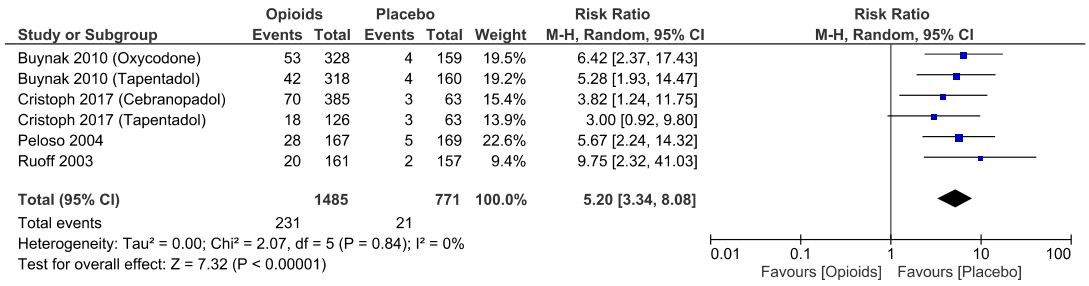
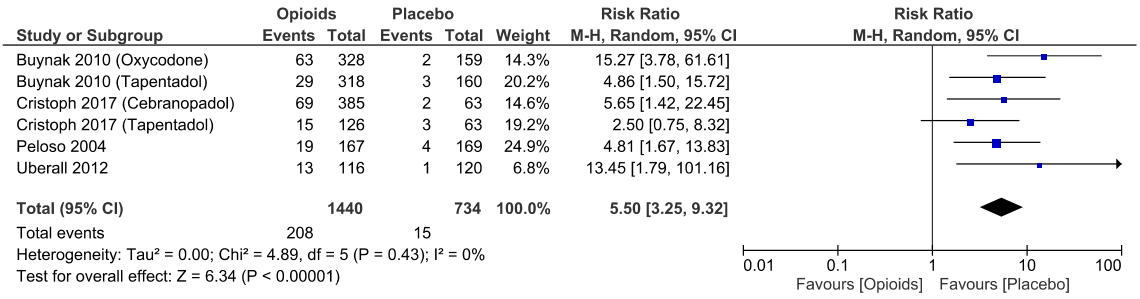


Figure 14.15 Opioids versus placebo; Adverse Event: Vomiting



SNRI (Duloxetine)

Figure 15.1 SNRI (Duloxetine) versus placebo; Withdrawals due to Adverse Events

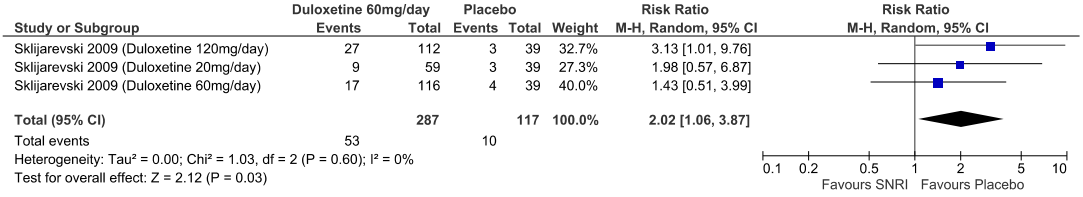


Figure 15.2 SNRI (Duloxetine) versus placebo; Serious Adverse Events

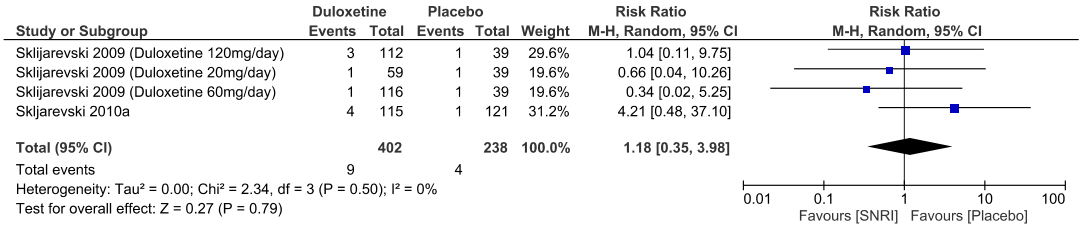


Figure 15.3 SNRI (Duloxetine) versus placebo; Adverse Event: Constipation

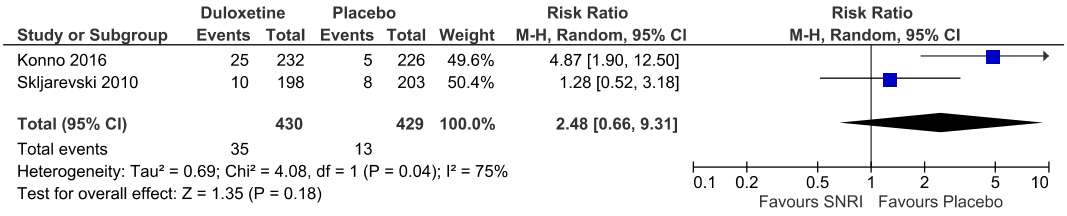


Figure 15.4 SNRI (Duloxetine) versus placebo; Adverse Event: Dizziness

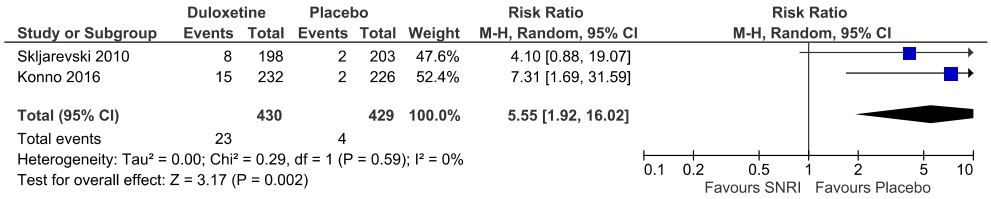


Figure 15.5 SNRI (Duloxetine) versus placebo; Adverse Event: Dry Mouth

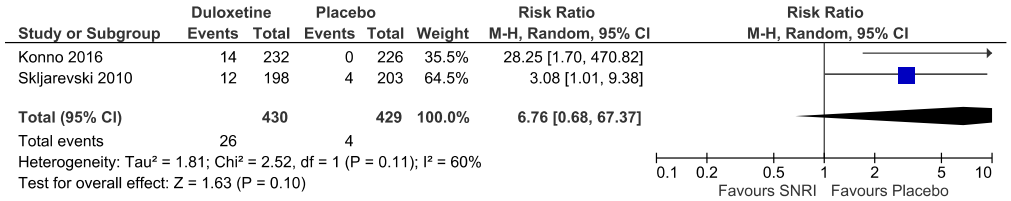
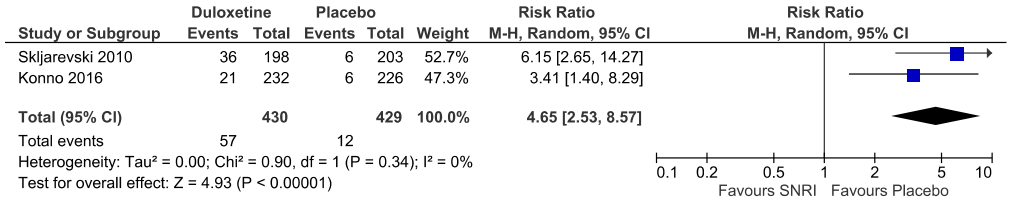


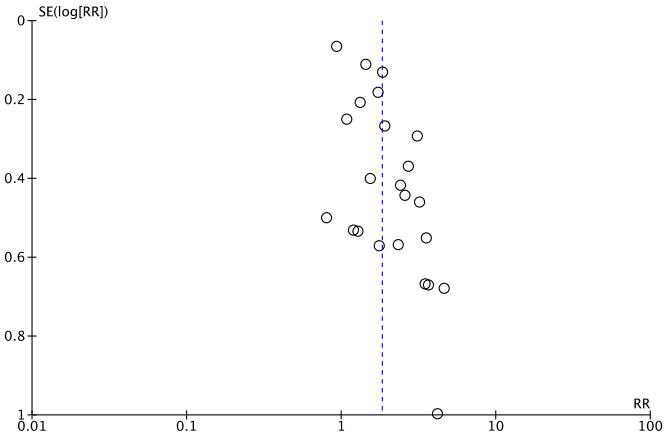
Figure 15.6 SNRI (Duloxetine) versus placebo; Adverse Event: Nausea



Funnel Plots

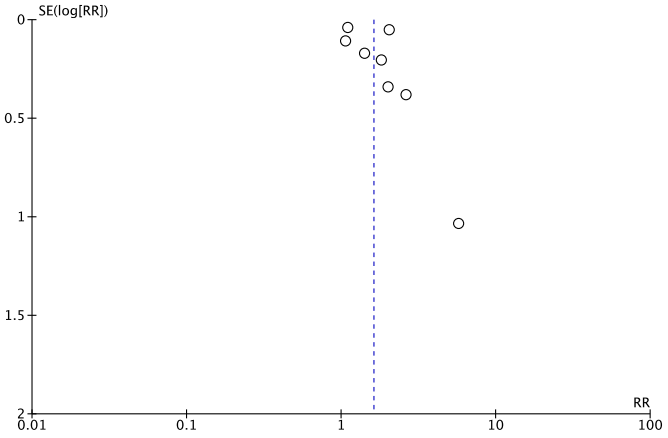
Funnel plots were generated via RevMan for interventions with ≥8 studies. This information was used in the GRADE process to assess potential publication bias.

Figure 17.1 Exercise studies



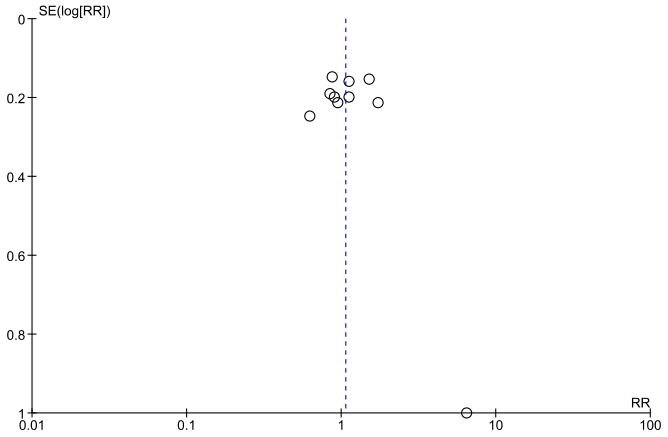
Smaller studies appear to be missing to the left of the effect line which may suggest some publication bias, but otherwise well balanced.

Figure 17.2 Acupuncture studies



Smaller and larger studies appear to be missing to the left of the effect line which suggests publication bias.

Figure 17.3 Corticosteroid Injection studies



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). Each study had their domain assigned a number and the sum was found for each study. We determined the median and divided studies into two subgroups: Less than the median and Equal to or greater than the median.

Table 8.1 Exercise

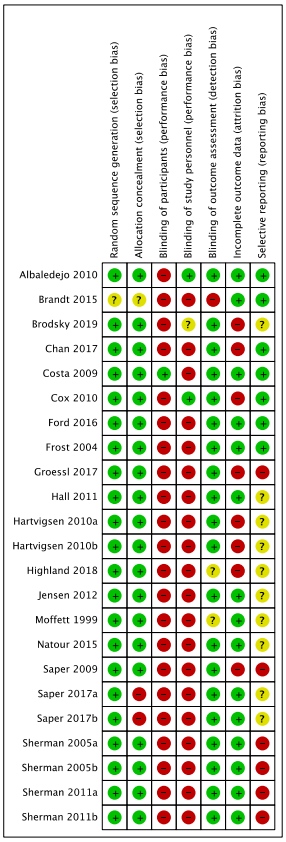


Table 8.2 Acupuncture

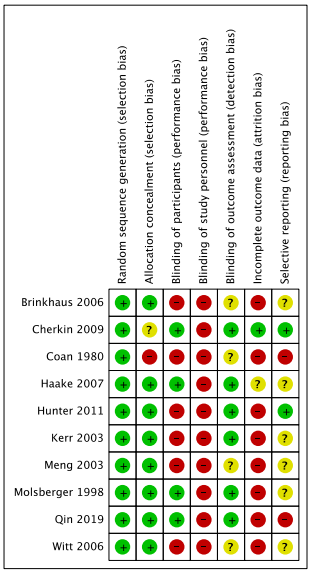


Table 8.3 Spinal manipulation

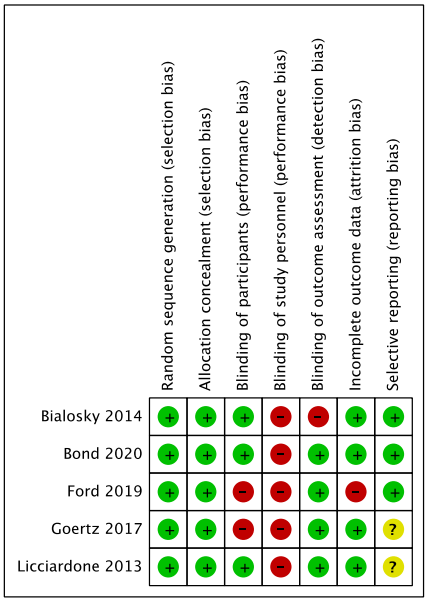


Table 8.4 Oral NSAIDs

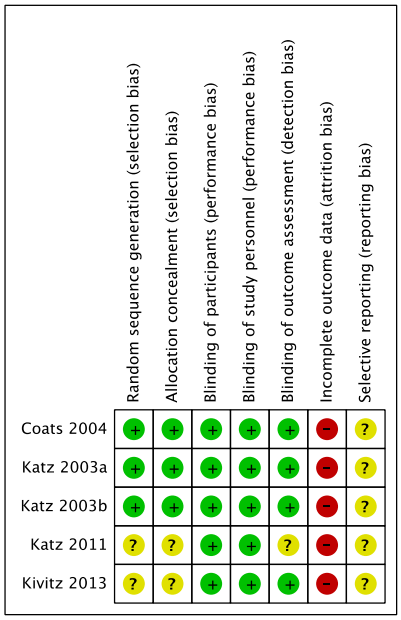


Table 8.5 Rubefacients

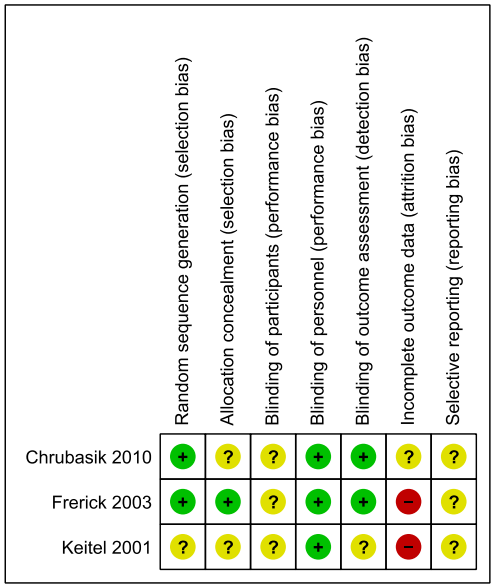


Table 8.6 Opioids

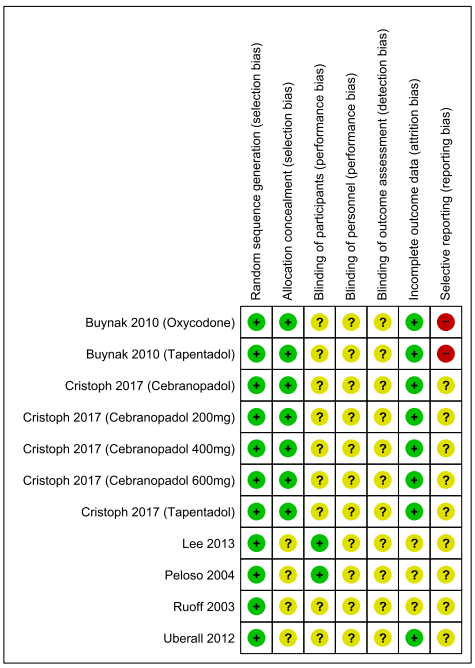


Table 8.7 SNRI (Duloxetine)

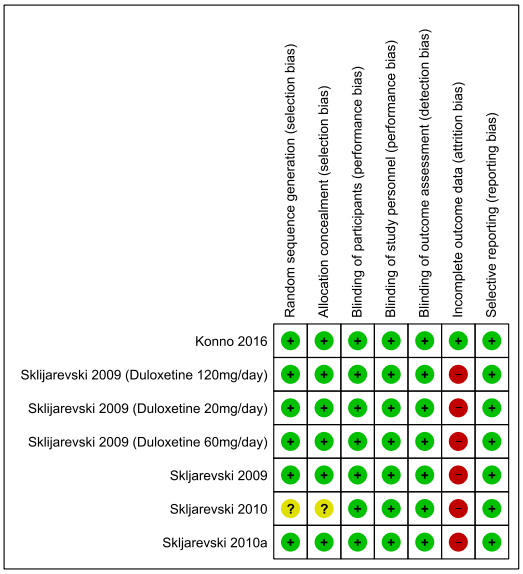


Table 8.8 Corticosteroid injections

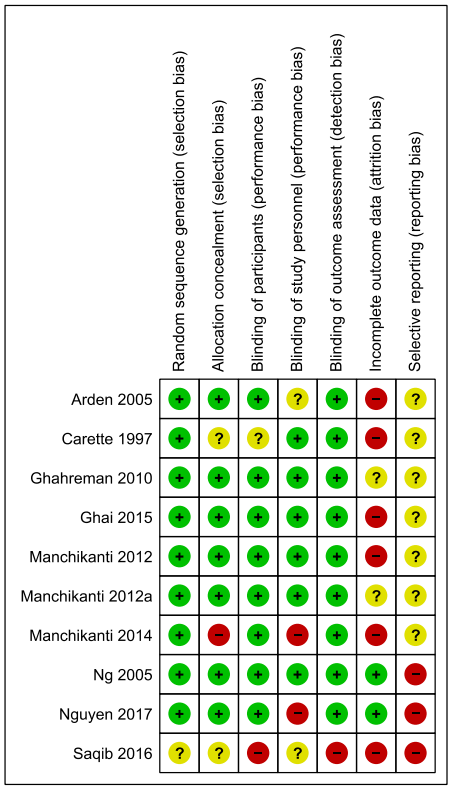


Table 9: GRADE Evaluation of Evidence Quality

Ordered Interventions by Certainty in Evidence Followed by Highest Risk Ratio to Lowest Risk Ratio.

Intervention	Number of RCTs	Risk Ratio	Reasons for Downgrading	Certainty in Evidence
Exercise	19	RR 1.71 (95% CI 1.37, 2.15)	Risk of Bias (-1)	Moderate
Oral NSAIDs	4	RR 1.44 (95% CI 1.17, 1.78)	Risk of Bias (-1)	Moderate
SNRI (duloxetine)	4	RR 1.25 (95% CI 1.13, 1.38)	Risk of Bias (-1)	Moderate
Spinal Manipulation	5	RR 1.54 (95% CI 1.11, 2.12)	Risk of Bias (-1) Inconsistency (-1)	Low
Rubefacients	3	RR 1.39 (95% CI 1.20, 1.61)	Risk of Bias (-1) Indirectness (-1)	Low
Acupuncture	10	RR 1.58 (95% CI 1.13, 2.21)	Risk of Bias (-1) Inconsistency (-1) Publication Bias (-1)	Very low
Opioids	6	RR 1.26 (95% CI 1.02, 1.55)	Risk of Bias (-1) Indirectness (-1) Imprecision (-1)	Very low
Corticosteroid Injections	10	RR 1.07 (95% CI 0.87, 1.30)	Risk of Bias (-1) Inconsistency (-1) Imprecision (-1)	Very low

RCTs: Randomized Controlled Trials; RR: Risk Ratio; CI: Confidence Interval; RR: Risk Ratio NSAIDs: Nonsteroidal Anti-Inflammatory drugs SNRIs: Serotonin Norepinephrine Reuptake Inhibitor

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 2013. The GRADE Working Group, 2013. Available from guidelinedevelopment.org/handbook.	

Peer Review Comments/Feedback

Peer Reviewer Information
5 reviewers including family physicians and allied health care professionals
*NO competing conflicts of interest declared

Strengths of the Systematic Review
This is an exceptionally good and helpful review of a common issue in primary care, low back pain. This review focuses on single interventions and included RCTs of adults with chronic (greater than 90 days) radicular or non-radicular low back pain. A list of pharmacological and non-pharmacological interventions are utilized with the primary outcome being a 30% reduction in pain. Multiple databases were used to search a large number of articles with 61 articles in the final review. The a-priori analyses to explore funding sources and duration of outcomes reported was a strength as was the examination of low back pain in a primary care setting. It was interesting to note acetaminophen, cannabinoids, muscle relaxants, SSRIs or TCAs did not meet inclusion criteria with an opportunity for future research.

Broad, looking at more or less every possible intervention out there. Sensitivity analyses were established a priori. Meta-analysis was done on an easily translatable outcome, that being percentage of patients who responded meaningfully, not some esoteric pain or function scale that means nothing to anyone.

Overall, congrats to the team on this excellent work. I appreciate the massive amount of work that goes into a SR/MA on one topic, let alone 15 in a review like this. However, I do have a few comments for the author team to consider… I think a main strength is that the process used in the review appears credible. - Inclusion criteria – RCT, Responder analysis - Primary Studies assessed for risk of bias - Pre-specified analysis to explore heterogeneity - Use of the GRADE approach to determine Confidence in estimates.

Strengths of the systemic review are the breadth of articles reviewed and the choice of commonly used and commonly available treatment modalities. Limitation to responder analysis increases the strength of conclusions for a particular modality. The use of NNT's and NNH's as descriptors is for me , valuable. The use of the tables and forest plots is visually helpful.

Sufficient number of studies reviewed reasonable conclusions based on evidence reviewed.

Weaknesses of the Systematic Review

As noted in the limitations section of the manuscript, the decision to combine heterogeneous interventions into one intervention category and the relatively few RCT's utilizing responder analysis are the weakness of this review. The diverse factors, subjective nature and varying responses to low back pain could be considered a challenge and weakness.

I was somewhat concerned that some of the questions addressed in the SR/MA may be a bit broad and because different interventions were combined the analyses display high heterogeneity (e.g., combining all exercise interventions: I2 = 75%;)

Authors' response: Manuscript revised. We felt that in an effort to limit additional sub-group analysis (and the risk of chance findings), that grouping potentially heterogenous non-pharmacological and pharmacological interventions was appropriate for this review. Whether groups that choose to sub-

group interventions (e.g. different types of exercise or different classes of NSAIDs) find consistent and reliable, or inconsistent and confusing results remains to be seen.

Potentially the broad scope of the SR is a weakness, as stated in the discussion. Given the screening process and inclusion criteria of trials, it's likely any weakness that might have come from that was effectively mitigated.

Search: Search appears quite comprehensive (but others (Ioannidis see below) have included other databases (Central, Cinhal, Psychinfo, Lilacs)
Authors' response: Manuscript modified. Cochrane database was formally named "Central" and was included in search. Cinhal, Psychinfo and Lilacs databases were not applicable for this review.

Context: The paper lacks context about other existing reviews and guideline recommendations for the interventions reviewed. (Introduction and discussion section). A cursory search shows that several individual SR/MA have been done on the interventions included in this review.

- https://pubmed.ncbi.nlm.nih.gov/25681408/
- https://pubmed.ncbi.nlm.nih.gov/26863524/
- https://pubmed.ncbi.nlm.nih.gov/18253994/

o Also, it seems other papers have combined several SR/MA like done in this paper
https://pubmed.ncbi.nlm.nih.gov/30563712/
o How do the findings compare to previous reviews (particularly those that focused on SMD?)
Authors' response: Manuscript modified

o What specifically does this paper add to the large body of existing reviews?
Authors' response: Manuscript modified. Our systematic review was the first synthesis of multiple (15) different interventions for chronic low back pain that was led by primary care, reported outcomes through responder analysis, and included robust reporting of adverse events.

In the discussion section the short-term benefits of a modality eg. acupuncture <4 weeks may be helpful to point out to a greater extend as clinicians often separate short term and long-term management modalities in assessing their armamentarium for a condition. (listed line 234 , 235)
Authors' response: This review focused on chronic (≥3 months) low back pain. Whether findings should be re-analyzed into interventions that may be most effective for 'early' chronic low back pain (e.g. 3-6 months) or 'late' chronic low back pain (e.g. >6 months) will be forwarded to our chronic pain guideline committee.

Not sure if possible to separate out back pain studies done in chronic back pain aimed at return to work only -done by employers (probably future work/ review). Wondering if in return to work there is a greater problem than return to function in non-work groups?
Authors' response: Beyond the scope of this systematic review.

Comments, considerations or changes

1. Publication Bias: 3 Funnel plots are presented in figures 17.1-17.3. but the manuscript is missing a description of how publication bias was assessed, the results of these assessments, and a conclusion regarding how publication bias affects confidence.
Authors' response: Manuscript and Appendix modified

2. Limitations: Given this is a paper that combines 15 different systematic reviews, I was watching to see if the any comments were going to be made about the comparative efficacy of the different interventions. It appears that the authors have avoided this temptation, although it was hard as a reader to not make comparisons between the interventions based on the way the manuscript is presented, which is not really appropriate based on the design (not a network MA). Address problem more head on in the limitations. It appears John Ioannides and his group are doing a SR & network MA of drug and non-drug interventions for chronic low back pain which will address these indirect comparisons.
o https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-020-01398-3

Authors' response: Addressed in knowledge translation tool (which was not available at time of manuscript peer review)

Comments: Overall great article to better alter poor management habits or support good management habits in a problem that is huge in primary care. Thanks for your effort.

Line 29 - you may define in brackets a rubefacient - not a common term used in general practice.
Authors' response: Manuscript modified

Line 123 Would it be helpful as a comparator to have NNH of oral NSAID's, as adverse effects often quoted as reason not to use and this review suggests some benefit?
Authors' response: NNH was not calculated due to no statistical difference between NSAIDs and placebo in withdrawals due to adverse events.

No specific comments, helpful review for family physicians, confirms my clinical experience, though the use of SNRI's is interesting and not common practice in my experience

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Exercise

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