Efficacy and safety of antidepressants for the treatment of back pain and osteoarthritis: Systematic review and meta-analysis

Contents

Supplemental file 1. Search strategies

MEDLINE

1	antidepressants.mp. or exp Antidepressive Agents/
2	exp Antidepressive Agents, Second-Generation/
3	exp Antidepressive Agents, Tricyclic/
4	exp Amitriptyline/
5	exp Nortriptyline/
6	exp Desipramine/
7	exp Imipramine/
8	exp Doxepin/
9	exp Trimipramine/
10	exp Clomipramine/
11	exp Protriptyline/
12	Tetracyclic.mp.
13	exp Amoxapine/
14	exp Maprotiline/
15	exp Serotonin Uptake Inhibitors/
16	exp Citalopram/
17	Escitalopram.mp.Fluoxetine
18	exp Fluvoxamine/
19	exp Paroxetine/
20	exp Sertraline/
21	Duloxetine.mp. or exp Duloxetine Hydrochloride/
22	Venlafaxine.mp. or exp Venlafaxine Hydrochloride/
23	Desvenlafaxine.mp. or exp Desvenlafaxine Succinate/
24	exp Milnacipran/
25	exp Monoamine Oxidase Inhibitors/
26	exp Harmaline/
27	exp Iproniazid/
28	exp Isocarboxazid/
29	exp Moclobemide/
30	exp Tranylcypromine/
31	exp Bupropion/
32	exp Trazodone/
33	exp Mirtazapine/
34	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33
35	osteoarthritis.mp. OR exp osteoarthritis/
36	exp low back pain/
37	exp back pain/
38	exp neck pain/
39	("low back pain" OR "back pain" OR "neck pain" OR backache OR lumbago OR "neck ache" OR "spin* pain" OR "knee pain" OR "hip pain").mp.
40	exp Sciatica/
41	exp Radiculopathy/
42	35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41
43	34 AND 42
44	randomized controlled trial.pt. OR exp randomized controlled trial/
45	"randomized controlled trial".mp.
46	exp random allocation/
47	placebo.mp. OR exp placebos/ OR exp placebo effect/
48	(random* adj3 trial).ab,ti.
49	"controlled clinical trial".mp. OR exp controlled clinical trial/
50	Random*.ab,ti.
51	44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50

52	43 AND 51

Pubmed

(((((((Low Back Pain OR back pain OR neck pain OR Sciatica OR Radiculopathy[MeSH Terms])) OR (radiculopathies[Title/Abstract] OR radiculopathy, cervical[Title/Abstract] OR Cervical Radiculopathies[Title/Abstract] OR Cervical Radiculopathy[Title/Abstract] OR Radiculopathies, Cervical[Title/Abstract] OR Nerve Root Disorder[Title/Abstract] OR Radiculitis[Title/Abstract] OR Nerve Root Inflammation[Title/Abstract] OR Compression, Nerve Root[Title/Abstract] OR lumbago[Title/Abstract] OR lower back pain[Title/Abstract] OR low back ache[Title/Abstract] OR low backaches[Title/Abstract] OR postural low back pain[Title/Abstract] OR mechanical low back pain[Title/Abstract] OR recurrent low back pain[Title/Abstract] OR vertebrogenic pain syndrome[Title/Abstract] OR back aches[Title/Abstract] OR back pain with radiation[Title/Abstract] OR neckache[Title/Abstract] OR cervicalgia[Title/Abstract] OR cervicodynias[Title/Abstract] OR cervical pain[Title/Abstract] OR posterior cervical pain[Title/Abstract] OR anterior neck pain[Title/Abstract])) OR (Osteoarthritis OR Osteoarthritis, Spine OR Osteoarthritis, Knee OR Osteoarthritis OR Osteoarthritis, Spine OR Osteoarthritis, Knee[MeSH Terms])) OR (Osteoarthrosis[Title/Abstract] OR Osteoarthroses[Title/Abstract] OR Osteoarthritides[Title/Abstract] OR Arthritis, Degenerative[Title/Abstract] OR Arthritides, Degenerative[Title/Abstract] OR Degenerative Arthritides[Title/Abstract] OR Degenerative Arthritis[Title/Abstract] OR Osteoarthrosis Deformans[Title/Abstract] OR Coxarthrosis[Title/Abstract] OR Coxarthroses[Title/Abstract] OR Osteoarthritis Of Hip[Title/Abstract] OR Osteoarthritis Of Hips[Title/Abstract] OR Knee Osteoarthritides[Title/Abstract] OR Osteoarthritides, Knee[Title/Abstract] OR Osteoarthritis Of Knees[Title/Abstract])))
AND
(((Randomized Controlled Trial [Publication Type] OR Randomized Controlled Trials as Topic OR Controlled Clinical Trial [Publication Type] OR quivalence Trial [Publication Type] OR Random Allocation OR Cross-Over Studies OR Double-Blind Method OR Placebos)) OR (randomization[Title/Abstract] OR Cross-Over Study[Title/Abstract] OR Crossover Studies[Title/Abstract] OR Cross-Over Studies[Title/Abstract] OR Crossover Study[Title/Abstract] OR Crossover Trials[Title/Abstract] OR Crossover design[Title/Abstract] OR Double-Blind Study[Title/Abstract] OR Double-Blind Studies[Title/Abstract] OR allocation[Title/Abstract] OR random[Title/Abstract] OR follow-up[Title/Abstract] OR active placebo[Title/Abstract] OR placebo[Title/Abstract] OR non-inferiority[Title/Abstract] OR superiority[Title/Abstract])))

AND
((((Antidepressive Agents OR Antidepressive Agents, Tricyclic OR Antidepressive Agents, Second-Generation OR Antidepressive Agents, Second-Generation [Pharmacological Action] OR Antidepressive Agents, Tricyclic [Pharmacological Action] OR Adrenergic Uptake Inhibitors OR Antidepressive Agents OR Antidepressive Agents, Tricyclic OR Antidepressive Agents, Second-Generation OR Antidepressive Agents, Second-Generation [Pharmacological Action] OR Antidepressive Agents, Tricyclic [Pharmacological Action] OR Adrenergic Uptake Inhibitors OR))) OR ((Amitriptyline OR Nortriptyline OR Desipramine OR Imipramine OR Doxepin OR Trimipramine OR Clomipramine OR Protriptyline OR Amoxapine OR Maprotiline OR Serotonin Uptake Inhibitors OR Citalopram OR Fluoxetine OR Paroxetine OR Sertraline OR Duloxetine Hydrochloride OR Fluvoxamine OR Venlafaxine Hydrochloride OR Desvenlafaxine Succinate OR Milnacipran OR Monoamine Oxidase Inhibitors OR Harmaline OR Iproniazid OR Isocarboxazid OR Moclobemide OR Tranylcypromine OR Bupropion OR Trazodone OR Mirtazapine[MeSH Terms])))

EMBASE

1	exp knee osteoarthritis/ or exp hip osteoarthritis/ or exp osteoarthritis/
2	exp low back pain/
3	exp neck pain/
4	exp backache/ or exp intervertebral disk hernia/ or exp sciatica/
5	exp radiculopathy/
6	exp cervicobrachial neuralgia/
7	random:.tw.
8	placebo:.mp.
9	double-blind:.tw.
10	antidepressants.mp. or exp antidepressant agent/
11	exp amitriptyline/

12	exp nortriptyline/
13	exp desipramine/
14	Exp imipramine/
15	exp doxepin/
16	exp trimipramine/
17	exp clomipramine/
18	exp protriptyline/
19	exp tetracyclic antidepressant agent/
20	exp amoxapine/
21	exp maprotiline/
22	exp serotonin uptake inhibitor/
23	exp citalopram/
24	exp fluoxetine/
25	exp fluvoxamine/
26	exp paroxetine/
27	exp sertraline/
28	exp duloxetine/
29	exp venlafaxine/
30	exp desvenlafaxine/
31	exp milnacipran/
32	exp monoamine oxidase inhibitor/
33	exp harmaline/
34	exp iproniazid/
35	exp isocarboxazid/
36	exp moclobemide/
37	exp tranylcypromine/
38	Bupropion.mp. or exp amfebutamone/
39	exp trazodone/
40	exp mirtazapine/
41	1 or 2 or 3 or 4 or 5 or 6
42	7 or 8 or 9
43	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
44	41 and 42 and 43

Cochrane Central

Low Back Pain OR back pain OR neck pain OR sciatica OR Radiculopathy OR Osteoarthritis OR Osteoarthritis, Spine OR Osteoarthritis, Knee OR Osteoarthritis, Hip
AND
Antidepressive drugs OR antidepressive agents OR Antidepressive Agents, Tricyclic OR Amitriptyline OR Nortriptyline OR Desipramine OR Imipramine OR Doxepin OR Trimipramine OR Clomipramine OR Protriptyline OR Amoxapine OR Maprotiline OR Serotonin Uptake Inhibitors OR Citalopram OR Fluoxetine OR Paroxetine OR Sertraline OR Duloxetine Hydrochloride OR Fluvoxamine OR Venlafaxine Hydrochloride OR Desvenlafaxine Succinate OR Milnacipran OR Monoamine Oxidase Inhibitors OR Harmaline OR Iproniazid OR Isocarboxazid OR Moclobemide OR Tranylcypromine OR Bupropion OR Trazodone OR Mirtazapine
AND
Randomized Controlled Trial OR Double-Blind Method OR Placebos OR Random Allocation

International Pharmaceutical Abstracts

1	osteoarthritis.mp.
2	knee osteoarthritis.mp.
3	hip osteoarthritis.mp.
4	neck pain.mp.
5	low back pain.mp.
6	back pain.mp.
7	backache.mp.
8	sciatica.mp.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	random.mp.
11	placebo.mp.
12	double-blind.mp.
13	10 or 11 or 12
14	antidepressants.mp
15	amitriptyline.mp.
16	nortriptyline.mp
17	desipramine.mp.
18	imipramine.mp.
19	doxepin.mp.
20	trimipramine.mp.
21	clomipramine.mp.
22	protriptyline.mp.
23	tetracyclic antidepressant agent.mp.
24	amoxapine.mp.
25	maprotiline.mp.
26	serotonin uptake inhibitor.mp.
27	citalopram.mp.
28	fluoxetine.mp.
29	fluvoxamine.mp.
30	paroxetine.mp.
31	sertraline.mp.
32	duloxetine.mp.
33	venlafaxine.mp.
34	desvenlafaxine.mp.
35	milnacipran.mp
36	monoamine oxidase inhibitor.mp.
37	harmaline.mp.
38	iproniazid.mp.
39	isocarboxazid.mp.
40	moclobemide.mp.
41	tranylcypromine.mp.

42	Bupropion.mp.
43	trazodone.mp.
44	mirtazapine.mp.
45	14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44
46	9 AND 13 AND 45

CINAHL

1	(MH "Osteoarthritis+") OR (MH "Osteoarthritis, Spine+") OR (MH "Osteoarthritis, Knee") OR (MH "Osteoarthritis, Hip") OR (MH "Osteoarthritis, Cervical")
2	(MH "Low Back Pain") OR (MH "Back Pain+") OR (MH "Neck Pain")
3	(MH "Sciatica")
4	(MH "Radiculopathy")
5	S1 OR S2 OR S3 OR S4
6	(MH "Randomized Controlled Trials+") OR (MH "Clinical Trials+")
7	(MH "Placebos")
8	(MH "Double-Blind Studies")
9	(MH "Random Sample+") OR (MH "Random Assignment")
10	S6 OR S7 OR S8 OR S9
11	(MH "Antidepressive Agents+")
12	(MH "Amitriptyline")
13	(MH "Nortriptyline")
14	(MH "Desipramine")
15	(MH "Imipramine")
16	(MH "Doxepin")
17	"trimipramine"
18	(MH "Clomipramine")
19	"protriptyline"
20	(MH "Amoxapine")
21	(MH "Maprotiline")
22	(MH "Citalopram")
23	(MH "Fluoxetine+")
24	(MH "Fluvoxamine Maleate")
25	(MH "Paroxetine")
26	(MH "Sertraline Hydrochloride")
27	(MH "Duloxetine Hydrochloride")
28	(MH "Venlafaxine+")
29	(MH "Desvenlafaxine Succinate")
30	(MH "Milnacipran Hydrochloride")
31	"harmaline"
32	"iproniazid"
33	"isocarboxazid"
34	"moclobemide"
35	"tranylcypromine"
36	(MH "Bupropion")
37	(MH "Trazodone")
38	(MH "Mirtazapine")
39	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38
40	S5 AND S10 AND S39

ClinicalTrials.gov and International Clinical Trials Registry Platform*

*Each antidepressant was searched individually

1. Low back pain AND (Amitriptyline OR Nortriptyline OR Desipramine OR Imipramine OR Doxepin OR Trimipramine OR Clomipramine OR protriptyline OR Amoxapine OR Maprotiline OR serotonin uptake inhibitor OR Citalopram OR fluoxetine OR Fluvoxamine OR Paroxetine Sertraline OR Duloxetine OR Venlafaxine OR Desvenlafaxine OR Milnacipran OR Harmaline OR Iproniazid OR Isocarboxazid OR Moclobemide OR Tranylcypromine OR Bupropion OR Trazodone OR mirtazapine)
2. Neck pain AND (Amitriptyline OR Nortriptyline OR Desipramine OR Imipramine OR Doxepin OR Trimipramine OR Clomipramine OR protriptyline OR Amoxapine OR Maprotiline OR serotonin uptake inhibitor OR Citalopram OR fluoxetine OR Fluvoxamine OR Paroxetine Sertraline OR Duloxetine OR Venlafaxine OR Desvenlafaxine OR Milnacipran OR Harmaline OR Iproniazid OR Isocarboxazid OR Moclobemide OR Tranylcypromine OR Bupropion OR Trazodone OR mirtazapine)
3. Sciatica AND (Amitriptyline OR Nortriptyline OR Desipramine OR Imipramine OR Doxepin OR Trimipramine OR Clomipramine OR protriptyline OR Amoxapine OR Maprotiline OR serotonin uptake inhibitor OR Citalopram OR fluoxetine OR Fluvoxamine OR Paroxetine Sertraline OR Duloxetine OR Venlafaxine OR Desvenlafaxine OR Milnacipran OR Harmaline OR Iproniazid OR Isocarboxazid OR Moclobemide OR Tranylcypromine OR Bupropion OR Trazodone OR mirtazapine)
4. Osteoarthritis AND (Amitriptyline OR Nortriptyline OR Desipramine OR Imipramine OR Doxepin OR Trimipramine OR Clomipramine OR protriptyline OR Amoxapine OR Maprotiline OR serotonin uptake inhibitor OR Citalopram OR fluoxetine OR Fluvoxamine OR Paroxetine Sertraline OR Duloxetine OR Venlafaxine OR Desvenlafaxine OR Milnacipran OR Harmaline OR Iproniazid OR Isocarboxazid OR Moclobemide OR Tranylcypromine OR Bupropion OR Trazodone OR mirtazapine)

Supplemental file 2. List of excluded studies after full-text reading

ID	Author/registry identification	Year	Title	Reason for exclusion
1	Konno	2019	An Open-Label, 52-Week, Phase III Trial of Duloxetine in Japanese Patients with Chronic Low Back Pain	Wrong study design
2	Yue	2019	Clinical meaningfulness of duloxetine's effect in Chinese patients with chronic pain due to osteoarthritis: post hoc analyses of a phase 3 randomized trial	Wrong study design
3	Enteshari-Moghaddam	2019	Efficacy of duloxetine and gabapentin in pain reduction in patients with knee osteoarthritis	Wrong comparator
4	Itoh	2019	Efficacy of duloxetine for multi-site pain in patients with knee pain due to osteoarthritis: an exploratory post hoc analysis of a Japanese phase 3 randomized study	Conference abstract
5	Wang	2019	Maintenance of effect of duloxetine in Chinese patients with pain due to osteoarthritis: 13-week open-label extension data	Wrong study design
6	Stahl	2019	Opioid Exposure Negatively Affects Antidepressant Response to Venlafaxine in Older Adults with Chronic Low Back Pain and Depression	Wrong study design
7	Enomoto	2018	Efficacy of duloxetine by prior NSAID use in the treatment of chronic osteoarthritis knee pain: A post hoc subgroup analysis of a randomized, placebo-controlled, phase 3 study in Japan	Wrong study design
8	Itoh	2018	Response to duloxetine in patients with knee pain due to osteoarthritis: an exploratory post hoc analysis of a Japanese Phase III randomized study	Wrong study design
9	Uchio	2018	Safety and efficacy of duloxetine in Japanese patients with chronic knee pain due to osteoarthritis: an open-label, long-term, Phase III extension study	Wrong study design
10	Alev	2017	Duloxetine 60 mg for chronic low back pain: post hoc responder analysis of double-blind, placebo-controlled trials	Combined data from other RCTs
11	Tsuji	2017	Response to duloxetine in chronic low back pain: exploratory post hoc analysis of a Japanese Phase III randomized study	Wrong study design
12	Wang	2016	Maintenance of effect and long-term safety of duloxetine in Chinese patients with pain due to osteoarthritis	Conference abstract
13	Kalita	2014	A randomized controlled trial of pregabalin versus amitriptyline in chronic low backache	Wrong comparator
14	Schukro	2014	Efficacy of duloxetine versus placebo in patients with chronic low back pain and a neuropathic component	Conference abstract
15	Gelijkens	2014	The effectiveness of amitriptyline in the treatment of subacute lumbar radicular pain	Conference abstract
16	Cawston	2013	Efficacy of duloxetine versus alternative oral therapies: an indirect comparison of randomised clinical trials in chronic low back pain	Wrong study design
17	Mathur	2013	Functional testing and pre-to post pain measure outcomes in chronic knee osteoarthritis pain with milnacipran: Interim analysis of a randomized, double-blind, placebo-controlled trial	Conference abstract
18	Risser	2013	Responsiveness of the Intermittent and Constant Osteoarthritis Pain (ICOAP) scale in a trial of duloxetine for treatment of osteoarthritis knee pain	Wrong study design

19	Micca	2013	Safety and efficacy of duloxetine treatment in older and younger patients with osteoarthritis knee pain: a post hoc, subgroup analysis of two randomized, placebo-controlled trials	Combined data from other RCTs
20	Alaka	2013	Safety of duloxetine for the treatment of older patients with osteoarthritis knee pain or chronic low back pain	Conference abstract
21	Weiss-Citrome	2012	Antidepressant Therapy for Pain Associated With Osteoarthritis	Wrong study design
22	Hochberg	2012	Clinically relevant outcomes based on analysis of pooled data from 2 trials of duloxetine in patients with knee osteoarthritis	Combined data from other RCTs
23	Ivanova	2012	Duloxetine use in chronic low back pain: treatment patterns and costs	Wrong study design
24	Hochberg	2011	Duloxetine as treatment for knee pain in patients with osteoarthritis who regularly use nonsteroidal anti-inflammatory drugs (NSAIDS): A post hoc analysis of two randomized, placebo-controlled trials	Conference abstract
25	Johnson	2011	Effects of duloxetine and placebo in patients with chronic low back pain	Conference abstract
26	Micca	2011	The efficacy and safety of duloxetine treatment in older patients with osteoarthritis knee pain: A post hoc, subgroup analysis of data from 2 placebo-controlled trials	Conference abstract
27	Karp	2010	Duloxetine and care management treatment of older adults with comorbid major depressive disorder and chronic low back pain: results of an open-label pilot study	Wrong study design
28	Skljarevski	2010	Efficacy and safety of duloxetine 60 mg once-daily in patients with chronic low back pain	Conference abstract
29	Mazza	2010	Escitalopram 20 mg versus duloxetine 60 mg for the treatment of chronic low back pain	Wrong comparator
30	Skljarevski	2010	Maintenance of effect of duloxetine in patients with chronic low back pain: a 41-week uncontrolled, dose-blinded study	Wrong study design
31	Sullivan	2009	A single-blind, placebo run-in study of duloxetine for activity-limiting osteoarthritis pain	Wrong study design
32	Skljarevski	2009	Efficacy and safety of duloxetine in the treatment of pain associated with knee osteoarthritis	Conference abstract
33	Skljarevski	2009	Maintenance of effect of duloxetine in patients with chronic low back pain	Conference abstract
34	Kwasucki	2002	[Evaluation of analgesic action of fluvoxamine compared with efficacy of imipramine and tramadol for treatment of sciatica--open trial]	Wrong comparator
35	Stein	1996	The efficacy of amitriptyline and acetaminophen in the management of acute low back pain	Wrong comparator
36	Trèves	1991	Prospective study of the analgesic action of clomipramine versus placebo in refractory lumbosciatica (68 cases)	Wrong outcomes
37	Thorpe	1974	The role of an antidepressant, dibenzepin (Noveril), in the relief of pain in chronic arthritic states	Wrong population

38	NCT00945945	2009	A Study of Duloxetine in Patients With Osteoarthritis Knee Pain	Invalid results due to technical problems
39	NCT00386243	2006	Evaluation of Stepped Care for Chronic Pain in Iraq/Afghanistan Veterans (ESCAPE) (ESCAPE)	Wrong intervention
40	NCT00227292	2005	Cipralex in Treatment of Depressive Symptoms and Chronic Back Pain	Withdrawn
41	NCT01221740	2010	Pain Assessment and Quality of Life in Back Pain Patients: Role of Milnacipran	Withdrawn
42	NCT01329406	2011	Study to Evaluate the Efficacy of Milnacipran in the Treatment of Pain Due to Osteoarthritis	Unknown
43	NCT01377038	2011	OASIS: Osteoarthritis Sensitivity Integration Study (OASIS)	Withdrawn
44	NCT01716377	2012	Healing With Venlafaxine After Injury (HELP) (HELP)	Pending assessment
45	NCT02208778	2014	Imaging Pain Relief in Osteoarthritis (IPRO)	Wrong outcomes
46	NCT03249558	2017	Effect of Combined Morphine and Duloxetine on Chronic Pain (Duloxetine)	Recruiting
47	NCT03364075	2017	Genetic Variants Associated With Low Back Pain and Their Response to Treatment With Duloxetine or Propranolol	Terminated
48	ACTRN12614000683639	2014	A randomised placebo controlled trial of nortriptyline for pain in knee osteoarthritis	Pending assessment
49	ACTRN12615000301561	2015	Does low dose amitriptyline reduce pain in knee osteoarthritis? A double blind, randomised, pragmatic, placebo controlled clinical trial of amitriptyline compared to active placebo in addition to usual care	Recruiting
50	ACTRN12619000878178	2019	A randomised controlled trial of venlafaxine to treat patients with knee osteoarthritis pain	Not yet recruiting
51	ACTRN12619001082190	2019	Venlafaxine compared to duloxetine for the treatment of osteoarthritis pain: A double-blind, randomised, non-inferiority trial	Recruiting
52	EUCTR2009-012713-22-AT	2009	Randomized Double-blind Study Comparing the Efficacy of Duloxetine with Placebo in Patients with Chronic Low Back Pain	Pending assessment
53	NCT04224584	2020	A mechanism based proof of concept study of the effects of duloxetine in the treatment of patients with osteoarthritic knee pain	Recruiting
54	NTR4798	2017	Effectiveness and cost-effectiveness of duloxetine added to usual care for patients with chronic pain due to hip or knee osteoarthritis: protocol of a pragmatic open-label cluster randomised trial (the DUO trial).	Wrong comparator
55	NCT00609557	2008	A Single-Blind Placebo Run-in Study of Duloxetine for Activity-Limiting Osteoarthritis Pai	Wrong study design
56	NCT00611676	2008	A Single-Blind Placebo Run-In Study of Venlafaxine for Activity-Limiting Osteoarthritis Pain	Wrong study design

57	NCT00696293	2008	Duloxetine Treatment of Major Depression and Chronic Low Back Pain For Older Adults (ACHIEVE2)	Wrong study design
58	NCT03792828	2019	Pre-emptive Effect of Duloxetine in the Second Knee in Staged Total Knee Arthroplasty	Wrong comparator
59	NCT04111627	2019	Exercise Plus Duloxetine for Knee Osteoarthritis and Depression	Wrong comparator
60	NCT04117893	2019	Duloxetine Combined With Intra-articular Injection of Corticosteroid and Hyaluronic Acid Reduces Pain in the Treatment of Knee Osteoarthritis Patients	Wrong comparator
61	CTRI/2012/07/002833	2012	Efficacy and safety of pregabalin vs amitriptyline in chronic low back pain – A randomized control trial	Wrong comparator
62	NCT01587508	2012	Study Comparing A New Drug Containing The Combination Meloxicam And Cyclobenzaprine In The Treatment Of Acute Lumbago	Wrong comparator
63	NCT02335346	2015	An Extension Study of Duloxetine in Osteoarthritis and Knee Pain (Extension of F1J-JE-HMGX, NCT02248480)	Wrong comparator
64	NCT02600247	2015	Effects of Duloxetine on Pain Relief After Total Knee Arthroplasty in Central Sensitization Patient	Wrong comparator
65	NCT01914666	2013	An Open Label Extension Study of Duloxetine (LY248686) in Participants With Chronic Low Back Pain	Wrong comparator
66	IRCT20170716035126N2	2018	Evaluating the efficacy of duloxetine and gabapentin in pain reduction in patients with knee osteoarthritis	Wrong comparator
67	NCT01124188	2010	ADAPT: Addressing Depression and Pain Together (ADAPT)	Wrong comparator
68	JPRN-JapicCTI-132312	2013	An open label extension study of phase 3 clinical trial of duloxetine in patients with chronic low back pain	Wrong comparator
69	TCTR20190303001	2018	A comparison of analgesic efficacy between Amitriptyline and Mianserin in chronic low back pain patients: A randomized double-blind controlled trial	Wrong comparator
70	NCT01144923	2010	Conservative Therapy Versus Epidural Steroids for Cervical Radiculopathy	Wrong intervention
71	NCT02347579	2015	Neurophysiological Basis of Rehabilitation in Complex Regional Pain Syndrome, Type I and Chronic Low Back Pain (BrainEXPain)	Wrong intervention
72	NCT02453802	2015	Comparison of Topical and Infusion Tranexamic Acid After Total Knee Arthroplasty	Wrong intervention
73	NCT02458729	2015	The Blood Saving Effect of Tranexamic Acid in Total Knee Arthroplasty With Rivaroxaban as Thromboprophylaxis	Wrong intervention
74	NCT02865174	2016	Topical Tranexamic Acid and Floseal® in Total Knee Arthroplasty	Wrong intervention
75	NCT03199417	2017	Trial Evaluating multimOdal toPical Cream In CompArison to pLacebo (TOPICAL) (TOPICAL)	Wrong intervention
76	NCT03328832	2017	Combined Topical Tranexamic Acid With Floseal® in Total Knee Arthroplasty	Wrong intervention

77	ACTRN12617001123336	2017	Safety and Efficacy of Autologous Micro-Fragmented Adipose Tissue Injection for the Treatment of Degenerative Knee Osteoarthritis	Wrong intervention
78	ACTRN12619001299190	2019	Effectiveness of Topical creams in reducing knee pain:	Wrong intervention
79	RBR-662hn2	2019	Effects of treatment by Telecommunication Services on the pain, functionality and amount of fatty tissue between muscles of patients with knee Arthrosis	Wrong intervention
80	NCT02814565	2016	Cyclobenzaprine HCl Extended Release 15 mg Versus Placebo in Treatment of Cervical and/or Lower Back Pain Due to Muscle Spasms of Local Origin	Wrong intervention
81	NCT03090152	2017	Minimal Opioid Use After Total Hip Replacement (THR)	Wrong intervention
82	NCT02903238	2016	Brain Morphometry in OA Patients Treated With Duloxetine	Wrong outcomes
83	NCT03844412	2019	Vestibulodynia: Understanding Pathophysiology and Determining Appropriate Treatments	Wrong population
84	NCT00619983	2008	Three Way Interaction Between Gabapentin, Duloxetine, and Donepezil in Patients With Diabetic Neuropathy	Wrong population
85	NCT02612233	2015	Pain Management in Osteoarthritis Using the Centrally Acting Analgesics Duloxetine and Pregabalin (DUPRO)	Wrong population
86	EUCTR2019-003437-42-DK	2014	A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of MIN-101 in Patients With Negative Symptoms of Schizophrenia, Followed by a 24-Week, Open-Label Extension.	Wrong population
87	NCT01156142	2010	Doxepin Hydrochloride in Treating Oral Mucositis Pain in Patients With Head and Neck Cancer Undergoing Radiation Therapy With or Without Chemotherapy	Wrong population
88	IRCT201406151617N9	2015	Effect of of single dose amitriptiline versus pregabalin on postoperative pain reduction in patients after spinal surgery	Wrong population
89	JPRN-UMIN000031428	2018	Effect of preemptive duloxetine for postoperative pain	Wrong population
90	NCT03047044	2017	The Comparison of Postoperative Pain After Lumbar Fusion Surgery in Intravenous Patient-controlled Analgesia Between Conventional Mode and Optimizing B.I Mode With 'PAINSTOP' Equipment	Wrong population
91	NCT01780389	2013	Open-label Milnacipran for Persistent Knee Pain One Year After Total Knee Arthroplasty (TKA)	Wrong population
92	NCT03110172	2017	Short-term Efficacy of Antidepressant in Patients Underwent TKA	Wrong population
93	NCT03880916	2019	Effects of Duloxetine on Postoperative Wound Complication of Total Knee Arthroplasty (TKA) in Central Sensitization Patients	Wrong population
94	NTR4744	2014	Effect of pre-operative pain treatment by means of duloxetine on postoperative outcome after total hip or knee arthroplasty- The DOA study	Wrong population
95	EUCTR2013-004564-55-HU	2015	A randomized, multicenter, double-blind, placebo controlled, parallel study to examine the efficacy and safety of a combination treatment in subjects with chronic low back pain	Wrong intervention

96	NCT00246389	2005	An Effectiveness and Safety Study of Cyclobenzaprine HCl Alone or in Combination With Ibuprofen for Acute Back or Neck Muscle Pain With Muscle Spasm	Wrong intervention
97	NCT01421433	2011	A Comparative Study Between Lysine Clonixinate+Cyclobenzaprine and Caffeine+Carisoprodol+Sodium Diclofenac+Paracetamol	Wrong intervention
98	NCT03574792	2018	Gabapentin, Methadone, and Oxycodone With or Without Venlafaxine Hydrochloride in Managing Pain in Participants With Stage II-IV Squamous Cell Head and Neck Cancer Undergoing Chemoradiation Therapy	Wrong intervention

Supplemental file 3. GRADE Framework

- Risk of bias: downgrade by one level if more than 25% of participants are from studies at high risk of bias[1] (i.e. one or more bias domains were judged high-risk)
- Inconsistency: downgrade by one level if heterogeneity was large (I^2 statistic value >50%, representing potentially substantial heterogeneity)[2]
- Indirectness: We will not assess indirectness as patients, interventions and comparators will be similar across studies.
- Imprecision:
    - Continuous outcomes: downgrade by one level if the limits of the 95% confidence interval are 20 points different to the point estimate; i.e. twice the minimal clinically important difference of 10 points on a 100-point scale.
    - Dichotomous outcomes: downgrade by one level if the lower or upper limits of the 95% confidence interval include appreciable benefit or harm (i.e 95% CI under 0.75 or over 1.25).[4]
- Small study effects: downgrade by one level if a funnel plot suggests the presence of publication bias,[5] or if more than 25% of participants were from small studies (< 100 participants per arm).

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Supplemental file 4. Calculation of effect sizes for pain outcomes in trials of antidepressants for back pain, sciatica, and osteoarthritis.

Author, year (class)	Outcome scale (range)	Type of data extracted	Type of measure	Point estimate (variability), extracted		Mean (SD), converted		No of participants	
				Antidepressants	Placebo	Antidepressants	Placebo	Antidepressants	Placebo
Back pain									
SNRI (≤ 2 weeks)									
Konno 2016	BPI-average (0-10)	Mean (SE)[2]	CS	-1.13 (0.11)	-0.8 (0.11)	-11.3 (16.6)	-8 (16.5)	230	226
Skljarevski 2009									
20mg	BPI-average (0-10)	Mean (SE)[2]	CS	-0.84 (0.30)	-0.75 (0.22)	-8.4 (22.4)	-7.5 (13.5)	56	38[4]
60mg	BPI-average (0-10)	Mean (SE)[2]	CS	-0.91 (0.22)	-0.75 (0.22)	-9.1 (22.8)	-7.5 (13.5)	108	38[4]
120mg	BPI-average (0-10)	Mean (SE)[2]	CS	-1.22 (0.22)	-0.75 (0.22)	-12.2 (22.8)	-7.5 (13.5)	108	37[4]
Skljarevski 2010b	NPRS (0-10)	Mean (SE)	CS	1.0 (0.19)	0.34 (0.20)	-10.1 (20.4)	-3.4 (21.1)	111	116
SNRI (3-13 weeks)									
Konno 2016	BPI-average (0-10)	Mean (SE)	CS	-2.4 (0.11)	-1.9 (0.11)	-24.3 (15.9)[3]	-19.6 (15.5)[3]	209	200
Skljarevski 2009									
20 mg	BPI-average (0-10)	Mean (SE)	CS	-1.79 (0.30)	-1.87 (0.22)	-17.9 (22.4)[3]	-18.7 (13.5)[3]	56	38[4]
60 mg	BPI-average (0-10)	Mean (SE)	CS	-2.5 (0.22)	-1.87 (0.22)	-25.0 (22.8)[3]	-18.7 (13.5)[3]	108	38[4]
120 mg	BPI-average (0-10)	Mean (SE)	CS	-2.45 (0.22)	-1.87 (0.22)	-24.5 (22.8)[3]	-18.7 (13.5)[3]	108	37[4]
Skljarevski 2010a	BPI-average (0-10)	Mean (SE)	CS	-2.25 (0.15)	-1.65 (0.15)	-22.5 (20.9)[3]	-16.5 (21.1)[3]	195	199
Skljarevski 2010b	BPI-average (0-10)	Mean (SE)	CS	-2.32 (0.28)[7]	-1.50 (0.28)[7]	-23.2 (21.1)[3]	-15 (21.1)[3]	111	116
SSRI (≤ 2 weeks)									
Dickens 2000	VAS (0-100)	Mean (SD)	FV	52.1 (25.5)	56.4 (22.3)	52.1 (25.5)	56.4 (22.3)	44	48
SSRI (3-13 weeks)									
Atkinson 1999	DDS (0-20)	Mean (SD)	FV	8.2 (4.0)	7.7 (4.6)	41.0 (20.0)	38.5 (23.1)	22	14[4]
Atkinson 2007	DDS (0-20)	Mean (SD)	FV	7.5 (3.9)	6.8 (3.8)	37.5 (19.5)	34.0 (19.0)	31	11[4]
Dickens 2000	VAS (0-100)	Mean (SD)	FV	57.0 (23.8)	57.0 (24.3)	57.0 (23.8)	57.0 (24.3)	44	48

TCA (≤ 2 weeks)											
Hameroff 1985	VAS (0-100)	Mean (SE)	FV	65.2 (3.97)[5]	69.8 (3.73)[5]		65.2 (20.6)[3]	69.8 (18.3)[3]		27	24
Jenkins 1976	VAS (0-10)	Mean (SE)	FV	4.2 (0.65)[5]	4.5 (0.64)[5]		42.0 (31.7)[3]	45 (29.3)[3]		23	21
Schliessbach 2018	NPRS (0-10)	MD (95% CI)[1]	FV	0.02 (-0.51 to 0.56)			0.2 (-5.1 to 5.6)			25	25
TCA (3-13 weeks)											
Atkinson 1998	DDS (0-21)	Mean (SD)	CS	-2.6 (4.0)	-0.9 (3.4)		-12.3 (19.0)	-4.33 (16.3)		28	29
Atkinson 2007	DDS (0-20)	Mean (SD)	FV	6.0 (4.1)	6.8 (3.8)		30.0 (20.5)	34.0 (19.0)		30	11[4]
Gould 2020	DDS (0-20)	Mean (SD)	FV	7.5 (5.6)	8.7 (5.5)		37.5 (28)	43.5 (27.5)		37	33
Hameroff 1985	VAS (0-100)	Mean (SE)	FV	61.5 (5.8)[5]	79.6 (3.4)[5]		61.48 (30.2)[3]	79.6 (16.6)[3]		27	24
Jenkins 1976	VAS (0-10)	Mean (SE)	FV	3.6 (0.6)	3.8 (0.6)		36 (28.7)	38 (27.5)		23	21
Maarawi 2018	VAS (0-10)	Mean (SD)	FV	3.3 (1.45)	6.1 (0.92)		33.4 (14.5)	61.2 (9.2)		104	108
Urquhart 2018	VAS (0-100)	MD (95% CI)	FV	-1.1 (-7.9 to 5.8)			-1.1 (-7.9 to 5.8)			58	58
TCA (3-12 months)											
Urquhart 2018	VAS (0-100)	MD (95% CI)	FV	-7.8 (-15.8 to 0.1)			-7.8 (-15.8 to 0.1)			61	57
NDRI (3-13 weeks)											
Katz 2005	VAS (0-10)	Mean (SD)	FV	3.3 (1.9)	3.4 (1.9)		33.0 (19)	34.0 (19.0)		21	23
SARI (3-13 weeks)											
Goodkin 1990	VAS (0-10)	Mean (SD)	FV	5.3 (3.0)	5.9 (2.6)		53.4 (30.0)	58.8 (26.2)		21	19
Tetracyclic (3-13 weeks)											
Atkinson 1999	DDS (0-20)	Mean (SD)	FV	6.8 (4.7)	7.7 (4.6)		34.0 (23.5)	38.5 (23.1)		20	14[4]
Sciatica											
SNRI (≤ 2 weeks)											
Schukro 2016	VAS (0-10)	Mean (SE)[3]	FV	4.35 (0.48)	6.2 (0.50)		43.5 (24)	62.1 (23.9)		25	25
SNRI (3-13 weeks)											
Schukro, 2016	VAS (0-10)	Mean (SD)	FV	3.7 (2.90)	5.7 (2.50)		37 (29)	57 (25)		25	25
NCT01225068 2014	VAS (0-100)	Mean (SD)	FV	31.3 (26.4)	24.8 (32.5)		31.3 (26.4)	24.8 (32.5)		16	19
Marks 2014	VAS-Rad (0-100)	Mean (SD)	FV	13.6 (8.5)	59.7 (43.6)		13.6 (8.5)	59.7 (43.6)		7	4
TCA (≤ 2 weeks)											
Pirbudak 2003	VAS (0-10)	Mean (SD)	FV	2.8 (1.4)	3.1 (2.2)		28 (14)	31 (22)		30	30
Vanelderen, 2015 (TCA)	NPRS (0-10)	MD (95% CI)[1]	FV	-1.41 (-0.05 to 2.8)			-14.1 (-0.5 to -28)			17	17

TCA (3-13 weeks)											
Khoromi 2007	VAS (0-10)	Mean (SD)	FV	3.0 (2.7)	3.7 (2.7)		30.0 (27.0)	37.0 (27.0)		28	28
Pirbudak 2003	VAS (0-10)	Mean (SD)	FV	1 (0.5)	3.3 (2.5)		10.0 (5.0)	33.0 (25.0)		30	30
TCA (3-12 months)											
Pirbudak, 2003 (TCA)	VAS (0-10)	Mean (SD)	FV	0.8 (0.5)	3.5 (2.5)		8.0 (5.0)	35.0 (25.0)		30	30
Osteoarthritis											
SNRI (≤ 2 weeks)											
Chappell 2009	BPI-average (0-10)	Mean (SE)	CS	-1.5 (0.16)[8]	0.95 (0.15)[8]		-15.0 (16.1)[3]	-10 (15.9)[1]		101[8]	112[8]
Chappell 2011	NPRS (0-10)	Mean (SE)	CS	-1.23 (0.20)[2]	-0.81 (0.18)[2]		-12.3 (22.6)[3]	-8.1 (20.3)[3]		121[8]	127[8]
Frakes 2011	BPI-average (0-10)	Mean (SE)	CS	-0.6 (0.1)[2]	-0.3 (0.1)[2]		-6.0 (16.0)[3]	-3.0 (16.0)[3]		259	255
Uchio 2018	BPI-average (0-10)	Mean (SE)	CS	-1.28 (0.09)	-0.68 (0.09)		-12.8 (11.9)[3]	-6.8 (11.9)[3]		177	176
SNRI (3-13 weeks)											
Abou-Raya 2012	WOMAC pain (0-20)	Mean (SD)	FV	6 (4.1)	8.4 (5.4)		30.0 (20.5)	42.0 (27.0)		123	131
Chappell 2009	BPI-average (0-10)	Mean (SE)	CS	-2.93 (0.17)[8]	-1.98 (0.16)[8]		-29.3 (15.2)[3]	-19.8 (15.8)[3]		80	98
Chappell 2011	NPRS (0-10)	Mean (SE)	CS	-2.72 (0.20)[8]	-1.88 (0.18)[8]		-27.2 (20.0)[3]	-18.8 (19.3)[3]		100	116
Frakes 2011	BPI-average (0-10)	Mean (SE)	CS	-2.46 (0.11)	-1.55 (0.11)		-24.6 (17.7)[3]	-15.5 (17.5)[3]		259	255
NCT01510457 2012	VAS (0-100)	Mean (SD)	FV	20 (22)	51 (24)		20 (22)	51 (24)		26	12
Tetreault 2016	VAS (0-10)	Mean (SD)	FV	5.3 (1.6)	5.6 (2.0)		53.0 (16.0)	56.0 (20.0)		19	20
Uchio 2018	BPI-average (0-10)	Mean (SE)	CS	-2.57 (0.12)	-1.28 (0.12)		-25.7 (15.9)	-12.8 (15.9)		177	176
Wang 2017	BPI-average (0-10)	MD (95% CI)	CS	-0.50 (-0.80 to -0.20)			-5.0 (-8.0 to -2.0)			172	177

SD, standard deviation; MD, mean difference; 95% CI, 95% confidence interval; FV, Final Value; CS, Change Score; NPRS, Numerical Pain Rating Scale; BPI, Brief Pain Inventory; VAS, Visual Analogue Scale; VAS-Rad, Visual Analogue Scale for radicular symptoms; DDS, Descriptor Differential Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; TCA, Tricyclic antidepressants, SNRI, Serotonin-Norepinephrine Reuptake inhibitors; SSRI, Selective serotonin reuptake inhibitors; NDRI, Norepinephrine–dopamine reuptake inhibitor; SARI, Serotonin antagonist and reuptake inhibitors

[1]MD (95% CI) were extracted directly when point estimate and variability measures were not available;

[2]Means extracted from figure; standard error adopted from another time point within the same study;

[3]Standard deviation estimated from standard error;

[4]Sample size in the placebo group was divided by the number of groups to avoid double-counting;

[5]Point estimate and variability measures extracted from figure;

[6]MD (95% CI) were extracted because effect estimates reported in the paper were adjusted by baseline scores;

[7]Standard error estimated from p-value, t-value and number of participants.

[8]Data extracted from the trial registration

Supplemental file 5. Calculation of effect sizes for disability outcomes in trials of antidepressants for back pain, sciatica, and osteoarthritis.

Study (year)	Outcome scale (range)	Type of data extracted	Type of measure	Point estimate (variability), extracted		Mean (SD), converted		No of participants	
				Antidepressants	Placebo	Antidepressants	Placebo	Antidepressants	Placebo
Back pain									
SNRI (3-13 weeks)									
Konno 2016	RMDQ (0-24)	Mean (SE)	CS	-3.9 (0.22)	-3.2 (0.22)	-16.1 (13.2)[2]	-13.5 (13.0)[2]	230	226
Skljarevski 2009									
20mg	RMDQ (0-24)	Mean (SD)	CS	-2.3 (4.3)[4]	-1.3 (4.3)[4]	-9.4 (17.8)	-5.4 (17.8)	56	38
60mg	RMDQ (0-24)	Mean (SD)	CS	-2.7 (4.3)[4]	-1.3 (4.3)[4]	-11.2 (17.8)	-5.4 (17.8)	108	38
120mg	RMDQ (0-24)	Mean (SD)	CS	-2.8 (4.3)	-1.3 (4.3)[4]	-11.7 (17.8)	-5.4 (17.8)	108	37
Skljarevski 2010a	RMDQ (0-24)	Mean (SE)	CS	-2.7 (0.31)	-2.2 (0.32)	-11.2 (17.2)[2]	-9.2 (17.8)[2]	178	179
Skljarevski 2010b	RMDQ (0-24)	Mean (SE)	CS	-3.6 (4.3)[3]	-1.9 (4.3)[3]	-15.0 (17.8)[2]	-8.0 (17.8)[2]	109	116
SSRI (3-13 weeks)									
Dickens 2000	ODI (0-100)	Mean (SD)	FV	50.2 (15.2)	52.4 (13.6)	50.2 (15.2)	52.4 (13.6)	44	48
TCA (3-13 weeks)									
Atkinson 2007	RMDQ (0-24)	Mean (SD)	FV	2.3 (2.5)[5]	4.1 (2.5)[5]	9.6 (10.4)	17.1 (10.4)	30	11
Gould 2020	RMDQ (0-24)	Mean (SD)	FV	7.7 (6.0)	9.5 (5.2)	32 (25.0)	39.6 (21.5)	37	33
Maarrawi 2018	NDI (0-100)	Mean (SD)	CS	-42.2 (15.5)	-13.7 (9.6)	-42.2 (15.5)	-13.7 (9.6)	104	108
Urquhart 2018	RMDQ (0-23)	MD (95% CI)	FV	-1.6 (-2.9 to -0.4)[1]		-7.0 (-12.5 to -1.5)		58	58
TCA (3-12 months)									
Urquhart 2018	RMDQ (0-23)	MD (95% CI)	FV	-0.98 (-2.4 to 0.5)[1]		-4.3 (-10.5 to 2.0)		61	57
SARI (3-13 weeks)									
Goodkin 1990	SIP (0-100)	Mean (SD)	FV	25.4 (17.0)	22.8 (12.7)	25.4 (17.0)	22.8 (12.7)	21	19
Sciatica									
SNRI (3-13 weeks)									
Marks 2014	ODI (0-100)	Mean (SD)	FV	18.1 (8..0)	22.5 (15.0)	18.1 (8..0)	22.5 (15.0)	5	3
TCA (≤ 2 weeks)									
Pirbudak 2003	ODI (0-100)	Mean (SD)	FV	36.0 (13.2)	41.0 (15.3)	36.0 (13.2)	41.0 (15.3)	30	30
TCA (3-13 weeks)									
Khoromi 2007	ODI (0-100)	Mean (SD)	FV	27.5 (16.7)	30.5 (15.9)	27.5 (16.7)	30.5 (15.9)	28	28
Pirbudak 2003	ODI (0-100)	Mean (SD)	FV	22.0 (11.2)	35.0 (14.0)	22.0 (11.2)	35.0 (14.0)	30	30
TCA (3-12 months)									

Pirbudak 2003	ODI (0-100)	MD (95% CI)	FV	18.0 (12.0)	38.0 (18.0)		18.0 (12.0)	38.0 (18.0)		30	30
Osteoarthritis											
SNRI (≤ 2 weeks)											
Uchio 2018	WOMAC-Total (0-96)	Mean (SE)	CS	-10.1 (0.75)	-5.08 (0.74)		-10.4 (10.6)[1]	-5.3 (10.6)[1]		177	176
SNRI (3-13 weeks)											
Abou-Raya 2012	WOMAC-Physical function (0-68)	Mean (SD)	FV	24.6 (8.4)	30.3 (9.8)		36.2 (12.3)	44.5 (14.4)		123	131
Chappell 2011	WOMAC-Total (0-96)	Mean (SE)	CS	-17.5 (1.5)	-13.7 (1.5)		-18.2 (18.1)[1]	-14.3 (17.3) [1]		128	128
Frakes (2011)	WOMAC-Physical function (0-100)	Mean (SE)	CS	-21.3 (1.1)	-14.4 (1.1)		-21.3 (17.3) [1]	-14.4 (17.7)[1]		251	253
NCT01510457 (2012)	PDI (0-70)	Mean (SD)	FV	15.0 (10.0)	26.0 (18.0)		21.4 (14.3)	37.1 (25.7)		26	12
Tetreault (2016)	WOMAC-Total (0-96)	Mean (SD)	FV	39.9 (17.4)	39.1 (18.9)		41.5 (18.1)	40.7 (19.7)		19	20
Uchio (2018)	WOMAC-Total (0-96)	Mean (SE)	CS	-17.41 (0.91)	-10.45 (0.91)		-18.1 (12.0)[1]	-10.9 (12.0)[1]		177	176
Wang (2017)	WOMAC-Total (0-96)	MD (95% CI)	CS	-3.5 (-5.6 to -1.4)[5]			-3.6 (-5.8 to -1.5)			184	182

SD, standard deviation; 95% CI, 95% confidence interval; FV, Final Value; CS, Change Score; ODI, Oswestry Disability Index; RMDQ, Roland-Morris Disability Questionnaire; SIP, Sickness Impact Profile; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PDI, Pain Disability Index; TCA, Tricyclic antidepressant; SNRI, Serotonin-norepinephrine receptor inhibitor; SSRI, Selective serotonin reuptake inhibitors; SARI, Serotonin receptor antagonists and reuptake inhibitors.

[1]MD (95% CI) were extracted because effect estimates reported in the paper were adjusted by baseline scores);

[2]Standard deviation estimated from standard error;

[3]Standard error estimated from p-value, t-value and number of participants;

[4]Standard deviation from Skljarevski (2010)b

[5]MD (95% CI) were extracted directly when point estimate and variability measures were not readily available

Supplemental file 6. Characteristics of the included studies (n = 33)

Author year	Study design	Characteristics of participants	Interventions and dose regimens	Industry sponsorship (sponsor)	Source of data
Back pain (19 trials, 23 comparisons)					
Gould 2020[1]	Parallel group	**Condition**: Chronic low back pain (≥ 6 months) **Mean age (SD):** intervention 55.6 (11.7), control 57.9 (10.9) **Neuropathic pain:** not mentioned **Depression**: No	**Drug (class):** Desipramine (TCA) **Dose:** dose targeted to achieve a serum concentration of 5-60 ng/ml (20-60 mg/day) **Duration:** 12 weeks **Control:** Active placebo (Benztropine) 0.125 mg/day, single dose, for 12 weeks **Participants enrolled**: 142	No	Published
Schliessbach 2018[2]	Crossover	**Condition**: Chronic low back pain (≥ 3 months) **Mean age (SD)**: 54.4 (17.3) **Neuropathic pain**: Not mentioned **Depression**: No	**Drug (class)**: Imipramine (TCA) **Dose**: 75 mg/day **Duration**: single treatment **Participants enrolled**: 90 **Control**: Active placebo (Tolterodine) 1mg/day, single dose; single treatment **Rescue medication**: allowed **Washout period**: 1 week;	No	Published
Urquhart 2018[3]	Parallel group	**Condition**: Chronic low back pain (≥ 3 months) **Mean age (SD)**: Intervention 53.5 (14.2), control 56.0 (13.2) **Neuropathic pain**: Not mentioned **Depression**: No	**Drug (class):** Low-dose Amitriptyline (TCA) **Dose:** 25 mg/day **Duration:** 26 weeks **Participants enrolled:** 146 **Control:** Active placebo (Benztropine) 1 mg/day, single dose, for 26 weeks **Rescue medication:** Not mentioned	No	Published
Maarrawi 2018[4]	Parallel group	**Condition**: Chronic neck pain (≥ 3 months) **Mean age (SD)**: intervention 43.5 (11.1), control 45.1 (11.5) **Neuropathic pain**: Not mentioned **Depression**: No	**Drug (class):** Low-dose Amitriptyline (TCA) **Dose:** 5 mg/day **Duration:** 8 weeks **Participants enrolled:** 332 **Control:** Inert placebo **Rescue medication:** Not mentioned	No	Published
Konno 2016[5]	Parallel group	**Condition**: Chronic low back pain (≥ 6 months) **Mean age (SD)**: Intervention 57.8 (13.7), control 60.0 (13.2) **Neuropathic pain**: Not mentioned **Depression**: No	**Drug (class):** Duloxetine (SNRI) **Dose:** 60 mg/day **Duration:** 14 weeks **Participants enrolled:** 458	Yes (Eli Lilly Company)	Published

			Control: Inert placebo **Rescue medication:** Not mentioned		
Skljarevski 2010[6]	Parallel group	**Condition**: Chronic low back pain (≥ 6 months) **Mean age (SD)**: Intervention 54.9 (13.7), control 53.4 (14.2) **Neuropathic pain**: No **Depression**: No	**Drug (class):** Duloxetine (SNRI) **Dose:** 60 mg/day **Duration:** 12 weeks **Participants enrolled:** 401 **Control:** Inert placebo **Rescue medication:** Allowed	Yes (Eli Lilly Company)	Published
Skljarevski 2010[7]	Parallel group	**Condition**: Chronic low back pain (≥ 6 months) **Mean age (SD)**: Mean age (SD): intervention 51.8 (14.9), control 51.2 (13.5) **Neuropathic pain**: No **Depression**: No	**Drug (class):** Duloxetine (SNRI) **Dose:** 60-120 mg/day **Duration:** 13 weeks **Participants enrolled:** 236 **Control:** Inert placebo **Rescue medication:** Allowed	Yes (Eli Lilly Company)	Published
Skljarevski 2009[8]	Parallel group	**Condition**: Chronic low back pain (≥ 6 months) **Mean age (SD)**: Intervention (20 mg/day) 52.9 (12.8), intervention (60 mg/day) 53.3 (14.7), intervention (60 mg/day) 54.9 (14.8), control 54.0 (13.5) **Neuropathic pain**: No **Depression**: No	**Drug (class):** Duloxetine (SNRI) **Dose:** 20, 60 and 120 mg/day **Duration:** 13 weeks **Participants enrolled:** 404 **Control:** Inert placebo **Rescue medication**: Allowed;	Yes (Eli Lilly Company)	Published
Atkinson 2007[9]	Parallel group	**Condition**: Chronic low back pain (≥ 6 months) **Mean age (SD)**: 46.4 (10.2) **Neuropathic pain**: Not mentioned **Depression**: No	**Drug (class):** Desipramine (TCA) **Dose:** Target dose between 50 and 150 ng/ml **Duration:** 12 weeks **Drug (class):** Fluoxetine (SSRI) **Dose:** Target dose between 100 to 400 ng/ml **Duration:** 12 weeks **Participants enrolled:** 121 **Control:** Active placebo (Benztropine 0.5 mg/day) **Rescue medication**: Not mentioned	No	Published
Katz 2005[10]	Crossover	**Condition**: Chronic low back pain (≥ 3 months) **Mean age (SD)**: Intervention 49.8 (10.0), control 51.4 (11.4) **Neuropathic pain**: No **Depression**: Not mentioned	**Drug (class):** Bupropion (NDRI) **Dose:** 300 mg/day **Duration:** 7 weeks **Participants enrolled**: 54 **Control:** Inert placebo **Washout period**: 1 week	Yes (GlaxoSmithKline)	Published
Dickens 2000[11]	Parallel group	**Condition**: Chronic low back pain (≥ 6 months) **Mean age (SD)**: Intervention 44 (9.7), control 46.0 (10.6) **Neuropathic pain**: No	**Drug (class):** Paroxetine (SSRI) **Dose:** 20 mg/day **Duration:** 8 weeks	Yes (SmithKline Beecham)	Published

		Depression: Yes (MADRS ≥ 16)	**Participants enrolled**: 98 **Control:** Inert placebo **Rescue medication:** Allowed		
Atkinson 1999[12]	Parallel group	**Condition**: Chronic low back pain (≥ 6 months) **Mean age (SD)**: 49.2 (9.4) **Neuropathic pain**: No **Depression**: No	**Drug (class):** Maprotiline (Tetracyclic) **Dose:** 150 mg/day **Duration:** 8 weeks **Drug (class):** Paroxetine (SSRI) **Dose:** 30 mg/day **Duration:** 8 weeks **Participants enrolled:** 103 **Control:** Active placebo (Diphenhydramine 37.5 mg/day) **Rescue medication:** Not mentioned	No	Published
Atkinson 1998[13]	Parallel group	**Condition:** Chronic low back pain (≥ 6 months) **Mean age (SD):** Intervention 45.7 (10.6), control 47.1 (10.6) **Neuropathic pain:** Not mentioned **Depression**: No	**Drug (class):** Nortriptyline (TCA) **Dose:** 100 mg/day **Duration:** 8 weeks **Participants enrolled:** 78 **Control:** Inert placebo **Rescue medication:** Not mentioned	No	Published
Goodkin 1990[14]	Parallel group	**Condition**: Chronic low back pain (≥ 12 months or acute low back pain ≥ 2 weeks duration) **Mean age (SD)**: Intervention 51.4 (13.1), control 56.1 (12.6) **Neuropathic pain**: Not mentioned **Depression**: 40% had clinical depression comorbid to pain	**Drug (class):** Trazodone (SARI) **Dose:** 600 mg/day **Duration:** 6 weeks **Participants enrolled**: 42 **Control:** Inert placebo	Yes (Procter & Gamble)	Published
Hameroff 1985[15]	Parallel group	**Condition**: Chronic low back and/or neck pain (duration not reported) **Mean age (SD)**: Intervention 48.9 (2.4), control 48.4 (2.0) **Neuropathic pain**: Not mentioned **Depression**: Yes (HDS ≥ 18)	**Drug (class):** Doxepin (TCA) **Dose:** 300 mg/day **Duration:** 6 weeks **Participants enrolled:** 60 **Control:** Inert placebo **Rescue medication**: Not mentioned	Unclear	Published
Pheasant 1983[16]	Crossover	**Condition**: Chronic low back pain (≥ 12 months) **Mean age (SD)**: 47.2 (22-68) **Neuropathic pain**: Not mentioned **Depression**: Not mentioned	**Drug (class):** Amitriptyline (TCA) **Dose:** 150 mg/day **Duration:** 6 weeks **Participants enrolled**: 16 **Control:** Active placebo (Atropine 0.2 mg/day) **Washout period**: 2 weeks	Unclear	Published
Alcoff 1982[17]	Parallel group	**Condition**: Chronic low back pain (duration not reported) **Mean age (SD)**: Intervention 29.2, control 33.8 **Neuropathic pain**: Not mentioned	**Drug (class):** Imipramine (TCA) **Dose:** 150 mg/day **Duration:** 8 weeks	Unclear	Published

		Depression: Yes (clinical diagnosis) in 6 (21.4) and 4 (18.2) participants in group intervention and control, respectively.	**Participants enrolled**: 50 **Control:** Inert placebo **Rescue medication:** Not mentioned		
Hameroff 1982[18]	Parallel group	**Condition**: Chronic neck and/or low back pain (≥ 2 months) **Mean age (SD)**: 46.6 (2.3) **Neuropathic pain**: Not mentioned **Depression**: Yes (clinical depression)	**Drug (class):** Doxepin (TCA) **Dose:** 50-300 mg/day **Duration:** 6 weeks **Participants enrolled:** 30 **Control:** Inert placebo **Rescue medication:** Not mentioned	Unclear	Published
Jenkins 1976[19]	Parallel group	**Condition**: Chronic low back pain (duration not reported) **Mean age (SD)**: Intervention 26.0 (18-45), control 26.7 (18-49) **Neuropathic pain**: Not mentioned **Depression**: Half of participants in each group had a clinical diagnosis of depression.	**Drug (class):** Imipramine (TCA) **Dose:** 75 mg/day **Duration:** 4 weeks **Participants enrolled**: 44 **Control:** Inert placebo **Rescue medication:** Not mentioned	Yes (Geigy Pharmaceuticals)	Published
Sciatica (Six trial, 6 comparisons)					
Schukro 2016[20]	Crossover	**Condition**: Chronic sciatica (> 6 months) **Mean age (SD)**: 57.9 (13.4) **Neuropathic pain**: Neuropathic pain: Yes (clinical features + painDETECT ≥ 12) **Depression**: No	**Drug (class):** Duloxetine (SNRI) **Dose:** 120 mg/day **Duration:** 4 weeks **Participants enrolled**: 41 **Control:** Inert placebo **Rescue medication:** Allowed **Washout period:** 2 weeks	No	Published
Vanelderen 2015[21]	Parallel group	**Condition**: Sciatica (duration not reported) **Mean age (SD)**: Intervention 50.0 (3.0), control 51.0 (3.0) **Neuropathic pain**: Yes (clinical features + DN4 ≥ 4) **Depression**: No	**Drug (class):** Amitriptyline (TCA) **Dose:** 25 mg/day **Duration:** 2 weeks **Participants enrolled**: 60 **Control:** Inert placebo **Rescue medication**: Allowed	No	Published
NCT01225068 2014[22]	Parallel group	**Condition**: Chronic sciatica (≥ 6 months) **Mean age (SD)**: intervention 47.1 (11.6), control 48.3 (9.1) **Neuropathic pain**: Yes (clinical features) **Depression**: No	**Drug (class):** Milnacipran (SNRI) **Dose:** 100 mg/day **Duration:** 6 weeks **Participants enrolled**: 40 **Control:** Inert placebo **Rescue medication**: Not mentioned	No	Clinical trial registry
Marks 2014[23]	Parallel group	**Condition**: Chronic sciatica (≥ 6 months) **Mean age (SD)**: Not reported **Neuropathic pain**: Yes (clinical features)	**Drug (class):** Milnacipran (SNRI) **Dose:** 100 mg/day **Duration:** 10 weeks	Yes (Forest Laboratories)	Published

		Depression: No	**Participants enrolled:** 11 **Control:** Inert placebo **Rescue medication:** Not allowed		
Khoromi 2007[24]	Crossover	**Condition**: Chronic sciatica (≥ 3 months) **Median age (range)**: 53 (19-65) **Neuropathic pain**: Yes (clinical features) **Depression**: No	**Drug (class):** Nortriptyline (TCA) **Dose:** 100 mg/day **Duration:** 4 weeks **Participants enrolled**: 55 **Control:** Inert placebo **Rescue medication**: Not mentioned **Washout period**: 2 weeks	No	Published
Pirbudak 2003[25]	Parallel group	**Condition**: Acute sciatica (≤ months) **Mean age (SD)**: Intervention 35.1 (4.4), control 35.7 (7.5) **Neuropathic pain**: Yes (clinical features) **Depression**: Not mentioned	**Drug (class):** Amitriptyline (TCA) (in addition to epidural corticosteroid injection) **Dose:** 50 mg/day **Duration:** 26 weeks **Participants enrolled**: 60 **Control:** Inert placebo (in addition to epidural corticosteroid injection **Rescue medication:** Not mentioned	No	Published
Osteoarthritis (8 trials, 8 comparisons)					
Uchio 2018[26]	Parallel group	**Condition**: Knee osteoarthritis (ACR criteria ≥ 3 months) **Mean age (SD)**: Intervention 65.5 (8.0), control 66.4 (8.4) **Neuropathic pain**: Not mentioned **Depression**: Not mentioned	**Drug (class):** Duloxetine (SNRI) **Dose:** 60 mg/day **Duration:** 14 weeks **Participants enrolled**: 354 **Control:** Inert placebo **Rescue medication:** Allowed	Yes (Eli Lilly Company)	Published
Wang 2017[27]	Parallel group	**Condition**: Knee osteoarthritis (ACR criteria ≥ 3 months) **Mean age (SD)**: Intervention 61.2 (8.2), control 59.8 (8.4) **Neuropathic pain**: Not mentioned **Depression**: No	**Drug (class):** Duloxetine (SNRI) **Dose:** 60 mg/day **Duration:** 13 weeks **Participants enrolled**: 407 **Control:** Inert placebo **Rescue medication:** Allowed	Yes (Eli Lilly Company)	Published
Tetreault 2016[28]	Parallel group	**Condition**: Knee osteoarthritis (ACR criteria ≥ 12 months) **Mean age (SD)**: Intervention 57.6 (0.8) to 60.3 (1.7), control 54.7 (3.0) to 62.0 (2.6) **Neuropathic pain**: Not mentioned **Depression**: No	**Drug (class):** Duloxetine (SNRI) **Dose:** 60 mg/day **Duration:** 12 weeks **Participants enrolled**: 40 **Control:** Inert placebo **Rescue medication**: Allowed;	No	Published

Abou-Raya 2012[29]	Parallel group	**Condition**: Knee osteoarthritis (ACR criteria ≥ 3 months) **Mean age (SD)**: Intervention 68.9 (6.2), control 68.5 (5.8) **Neuropathic pain**: Not mentioned **Depression**: Yes (GDS ≥ 5)	**Drug (class):** Duloxetine (SNRI) **Dose:** 60 mg/day **Duration:** 14 weeks **Participants enrolled**: 288 **Control:** Inert placebo **Rescue medication**: Allowed	No	Published
Chappell 2011[30]	Parallel group	**Condition**: Knee osteoarthritis (ACR criteria ≥ 3 months) **Mean age (SD)**: Intervention 63.2 (8.8), control 61.9 (9.2) **Neuropathic pain**: Not mentioned **Depression**: Not mentioned	**Drug (class):** Duloxetine (SNRI) **Dose:** 60 mg/day **Duration:** 13 weeks **Participants enrolled:** 256 **Control:** Inert placebo **Rescue medication:** Allowed	Yes (Eli Lilly Company)	Published
Frakes 2011[31]	Parallel group	**Condition**: Knee osteoarthritis (ACR criteria ≥ 3 months) **Mean age (SD)**: Intervention 61.6 (9.2), control 60.3 (9.2) **Neuropathic pain**: Not mentioned **Depression**: Not mentioned	**Drug (class):** Duloxetine (SNRI) **Dose:** 120 mg/day **Duration:** 10 weeks **Participants enrolled**: 524 **Control:** Inert placebo **Rescue medication**: Allowed	Yes (Eli Lilly Company)	Published
NCT01510457 2012[32]	Parallel group	**Condition**: Knee osteoarthritis (ACR criteria ≥ 6 months) **Mean age (SD)**: Intervention 57.0 (9.0), control 53.0 (7.0) **Neuropathic pain**: Not mentioned **Depression**: Not mentioned	**Drug (class):** Milnacipran (SNRI) **Dose:** 200 mg/day **Duration:** Approximately 8 weeks **Participants enrolled:** 46 **Control:** Inert placebo **Rescue medication**: Not mentioned	Unclear	Clinical trial registry
Chappell 2009[33]	Parallel group	**Condition**: Knee osteoarthritis (ACR criteria ≥ 3 months) **Mean age (SD)**: Intervention 62.1 (9.6), control 62.5 (9.3) **Neuropathic pain**: Not mentioned **Depression**: No	**Drug (class):** Duloxetine (SNRI) **Dose:** 120 mg/day **Duration:** 13 weeks **Participants enrolled:** 231 **Control:** Inert placebo **Rescue medication:** Allowed	Yes (Eli Lilly Company)	Published

Legend: IG, intervention group; CG, control group; NPRS, Numerical Pain Rating Scale; VAS, Visual Analogue Scale; RMDQ, Roland-Morris Disability Questionnaire; NDI, Neck Disability Index; BPI, Brief Pain Inventory; ODI, Oswestry Disability Index; DDS, Descriptor Differential Scale; SIP, Sickness Impact Profile; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; MPQ-SF, McGill Pain Questionnaire Short-Form; PDI, Pain Disability Index; DN4, Douleur Neuropathique 4; MADRS, Montgomery–Åsberg Depression Rating Scale; GDS, Geriatric Depression Scale; HDS, Hospital Depression Scale; SNRI, Serotonin–norepinephrine reuptake inhibitors; SSRI, Selective serotonin reuptake inhibitors

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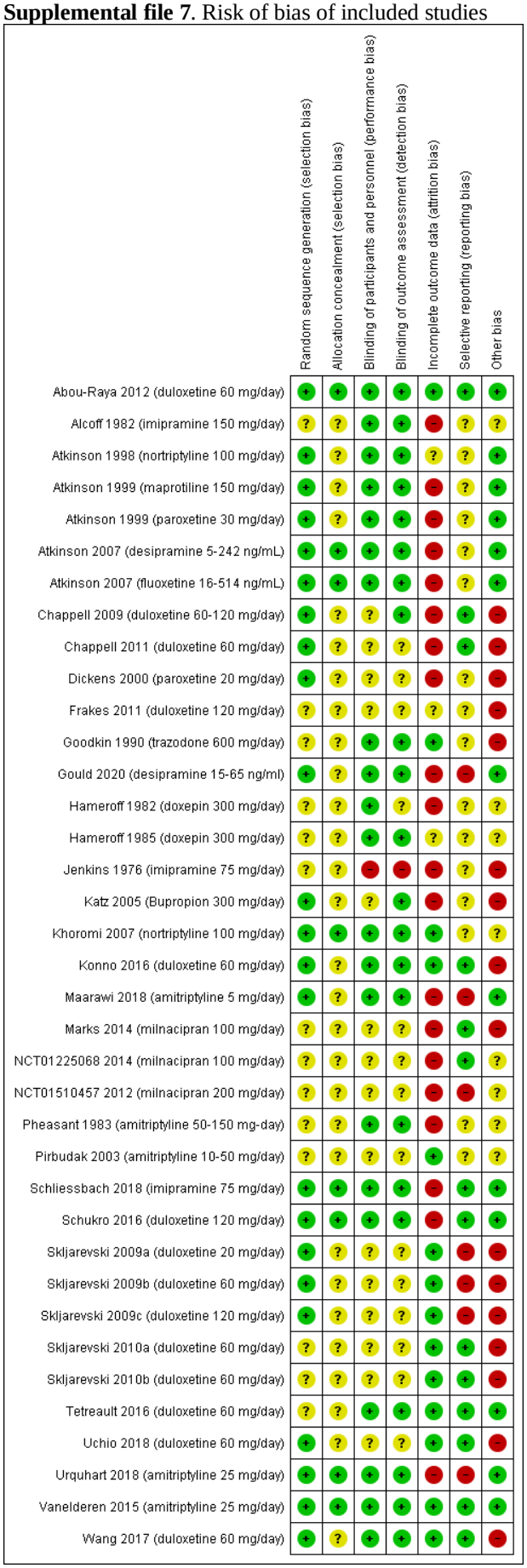
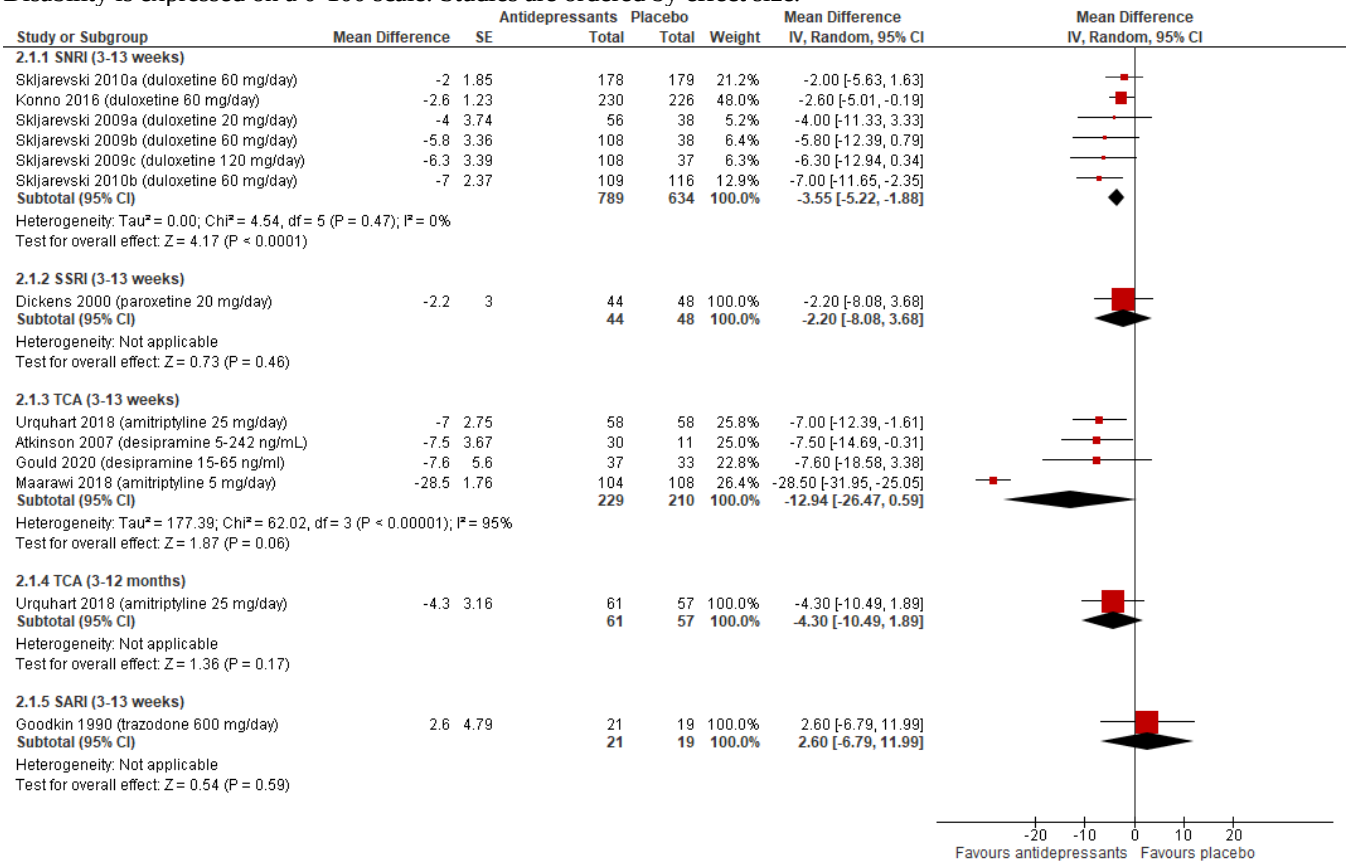
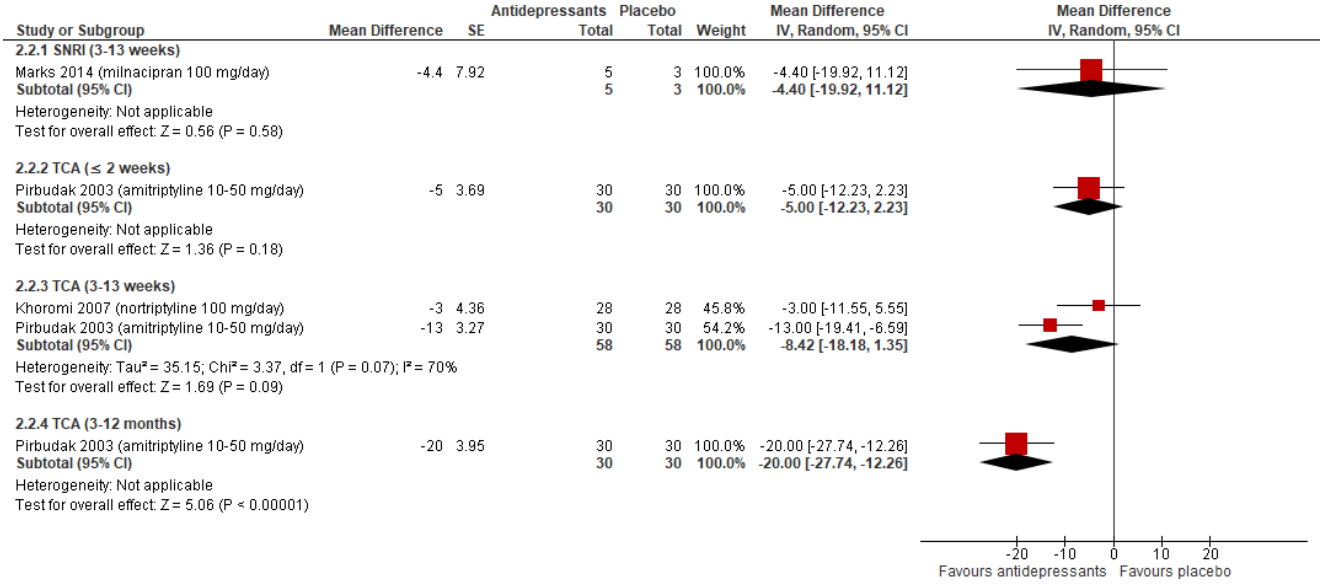
Supplemental file 7. Risk of bias of included studies



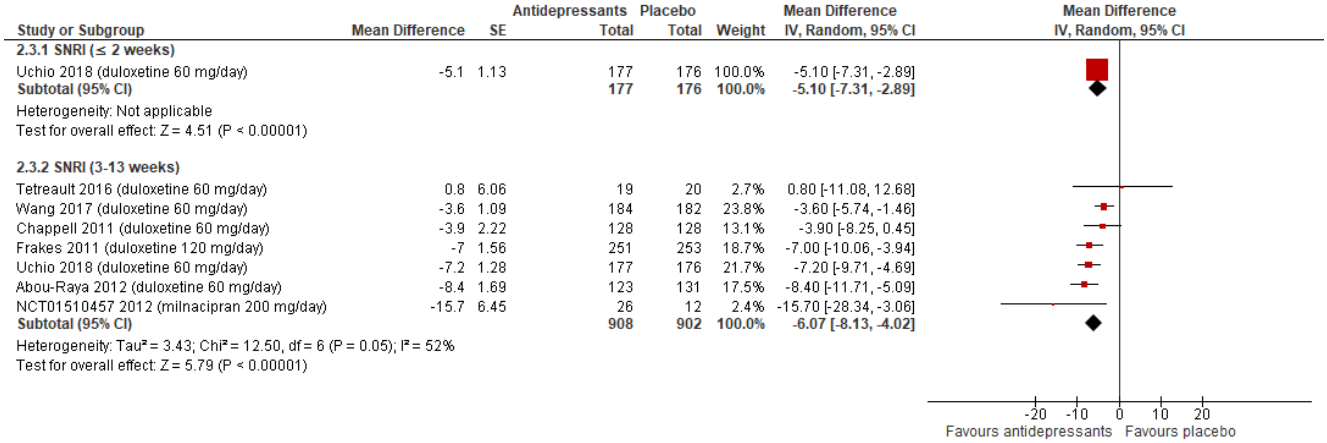
Supplemental file 8. Mean differences (95% CI) for disability in trials assessing the efficacy of antidepressants for back pain. Disability is expressed on a 0-100 scale. Studies are ordered by effect size.



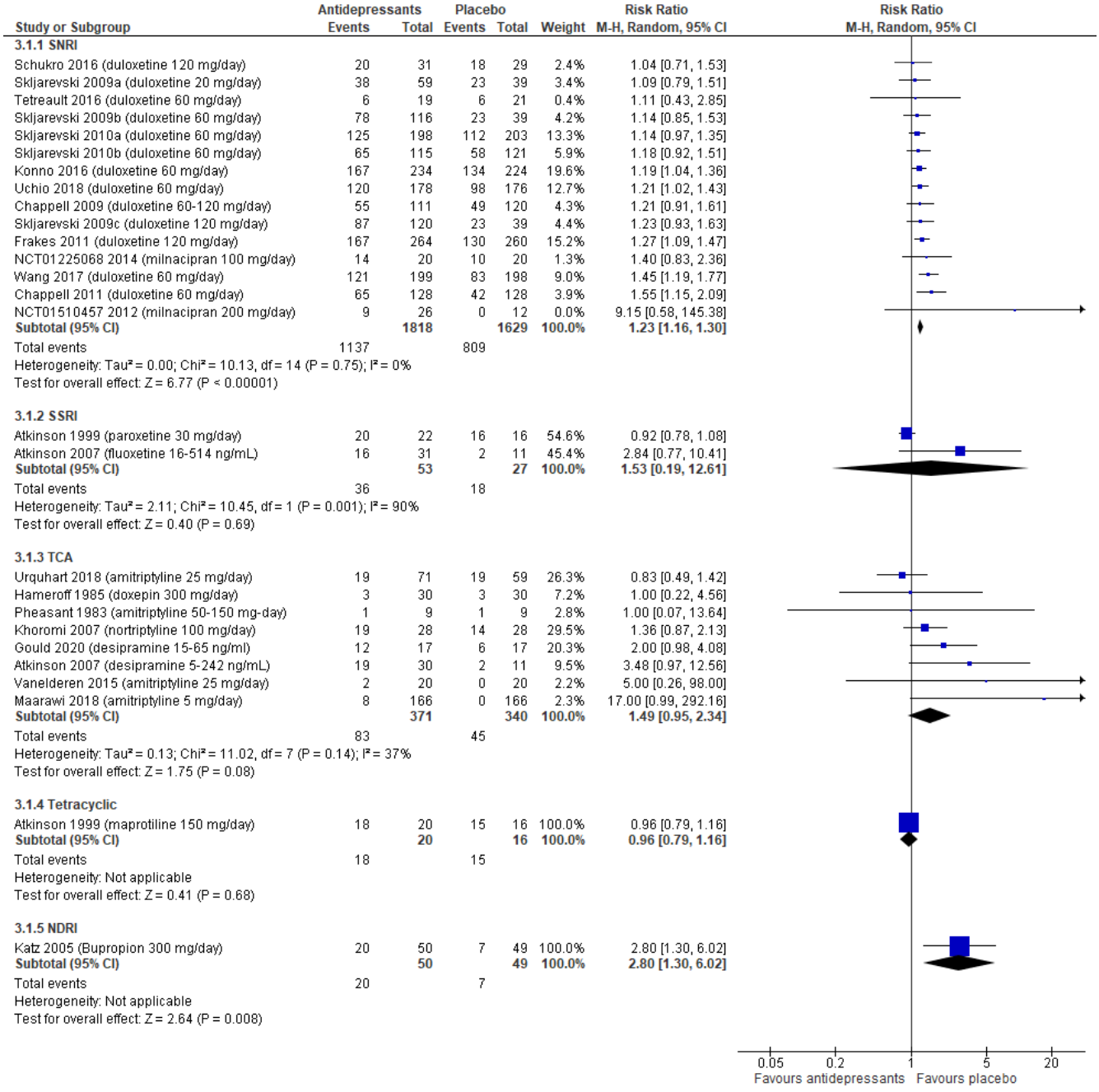
Supplemental file 9. Mean differences (95% CI) for disability in trials assessing the efficacy of antidepressants for sciatica. Disability is expressed on a 0-100 scale. Studies are ordered by effect size.



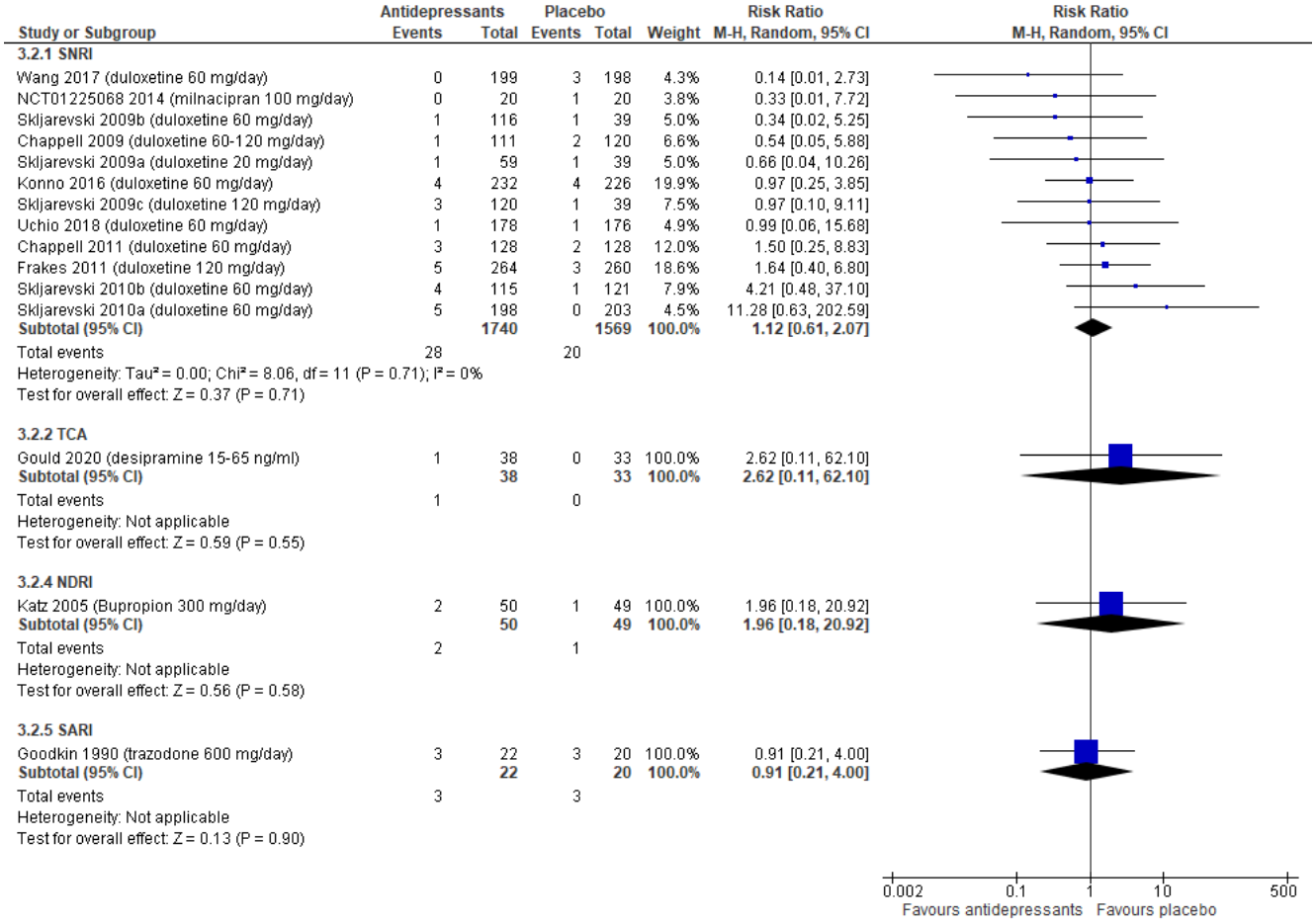
Supplemental file 10. Mean differences (95% CI) for disability in trials assessing the efficacy of antidepressants for osteoarthritis. Disability is expressed on a 0-100 scale. Studies are ordered by effect size.



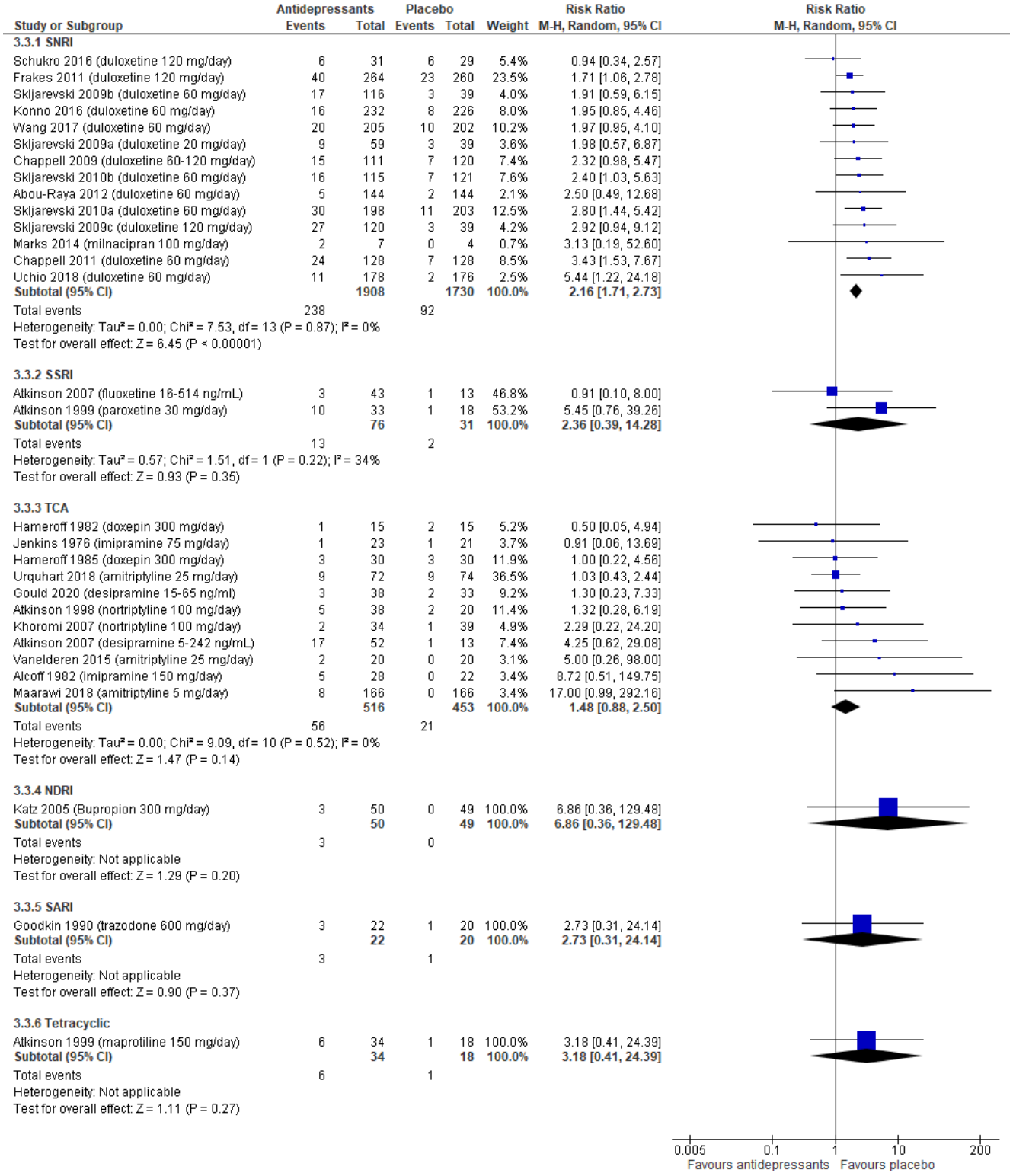
Supplemental file 11. Risk ratio (95% CI) for any adverse events in trials assessing the efficacy of antidepressants for back pain, sciatica, and osteoarthritis. Studies are ordered by effect size.



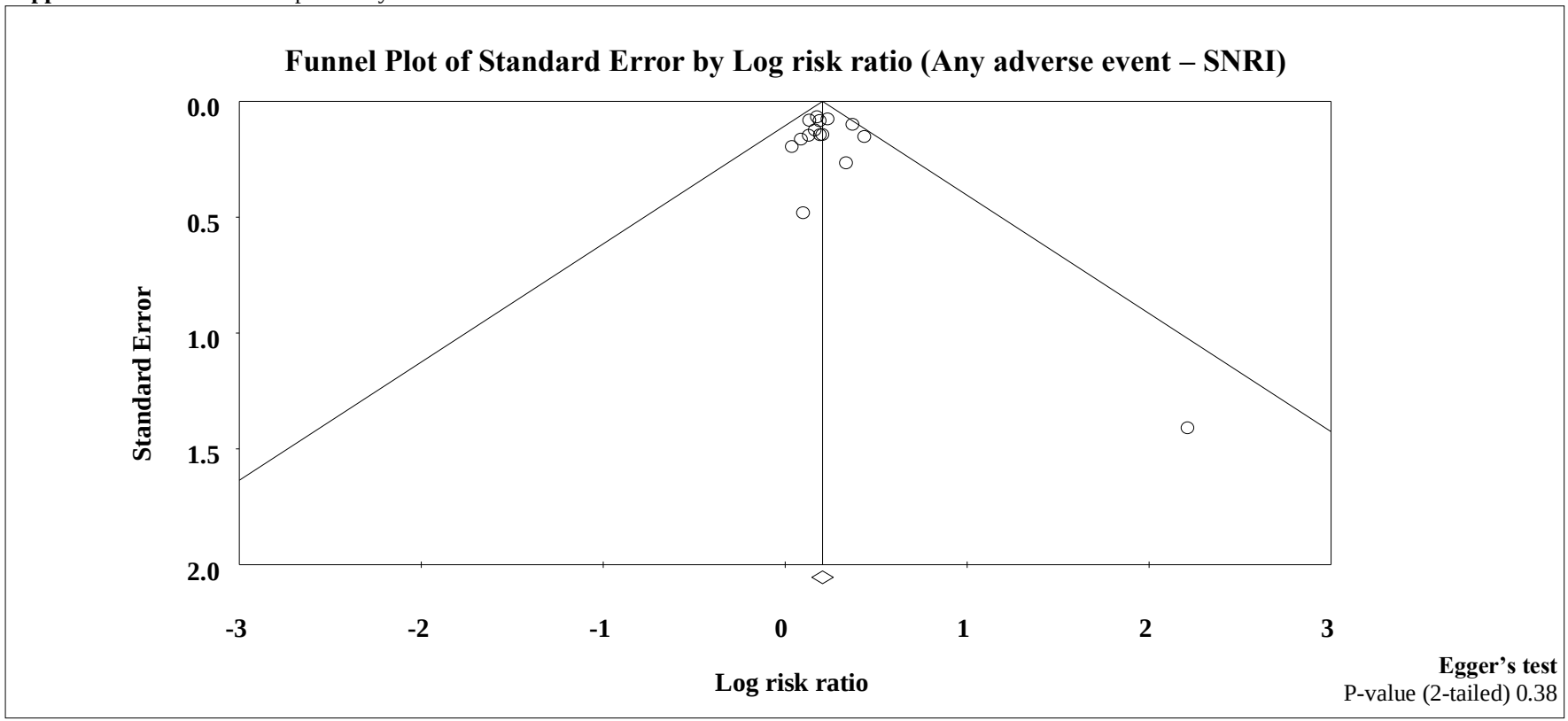
Supplemental file 12. Risk ratio (95% CI) for serious adverse events in trials assessing the efficacy of antidepressants for back pain, sciatica, and osteoarthritis. Studies are ordered by effect size.



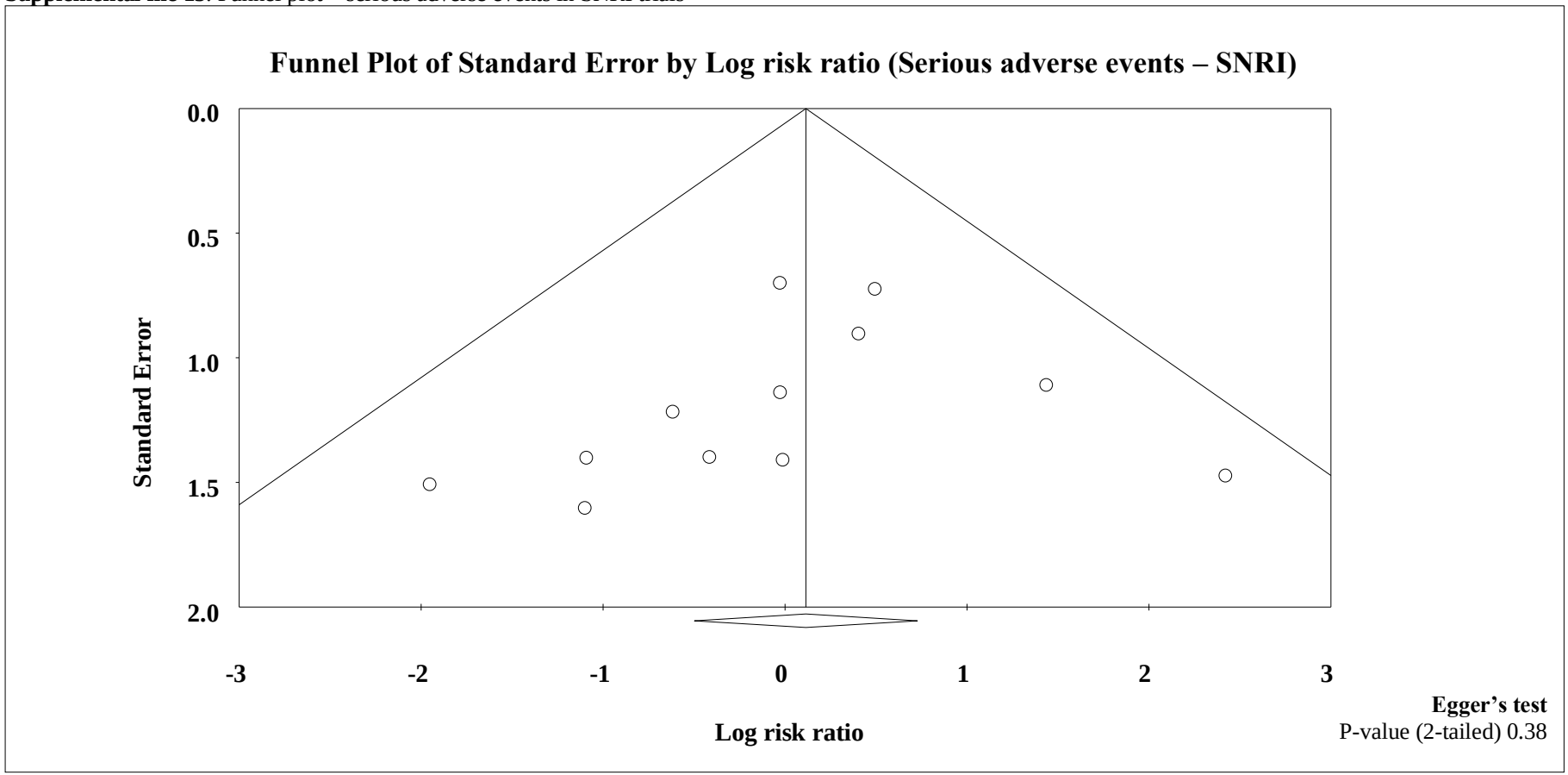
Supplemental file 13. Risk ratio (95% CI) for participants withdrawing from trials due to adverse events in trials assessing the efficacy of antidepressants for back pain, sciatica, and osteoarthritis. Studies are ordered by effect size.



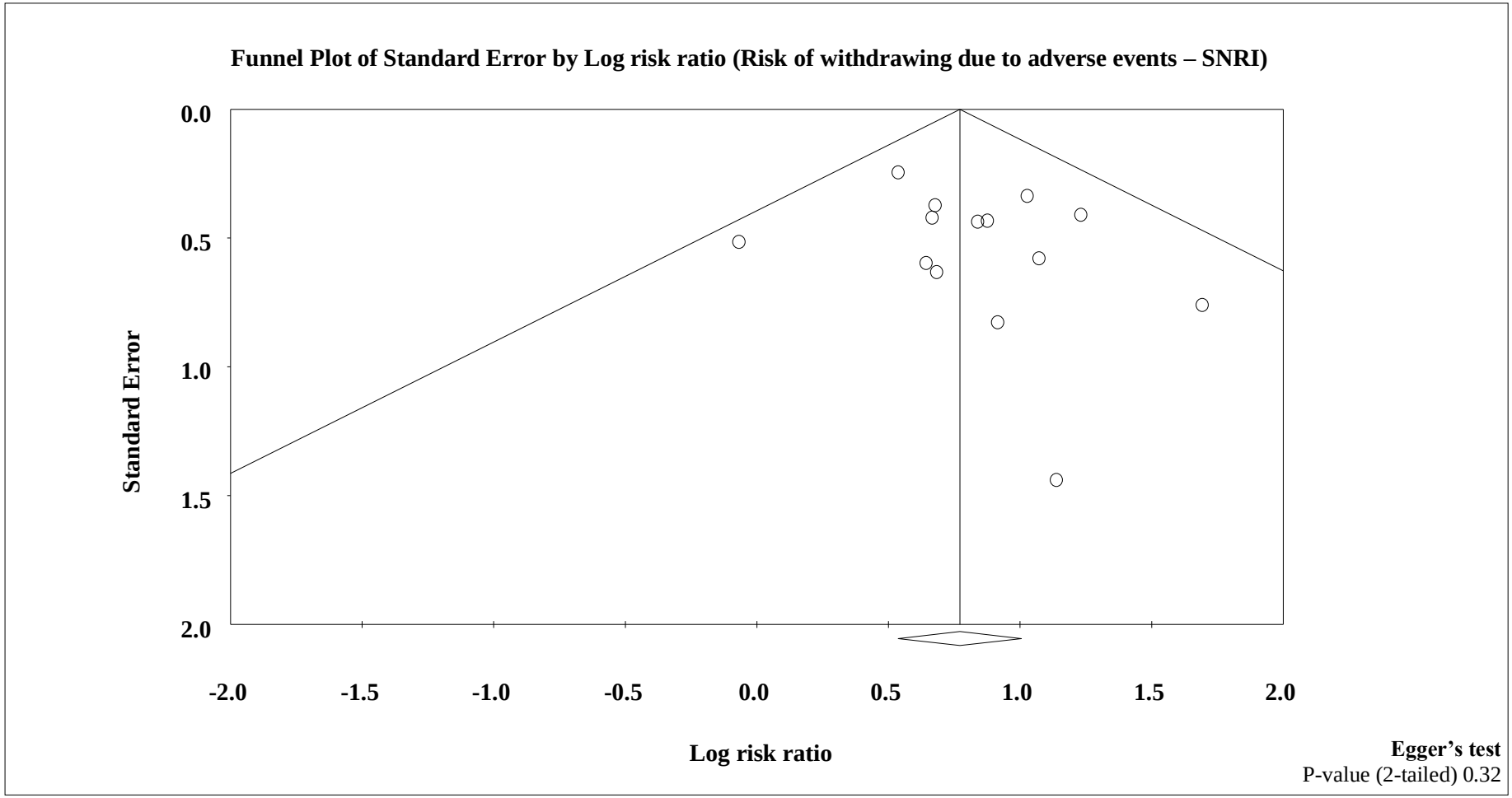
Supplemental file 14. Funnel plot – any adverse events in SNRI trials



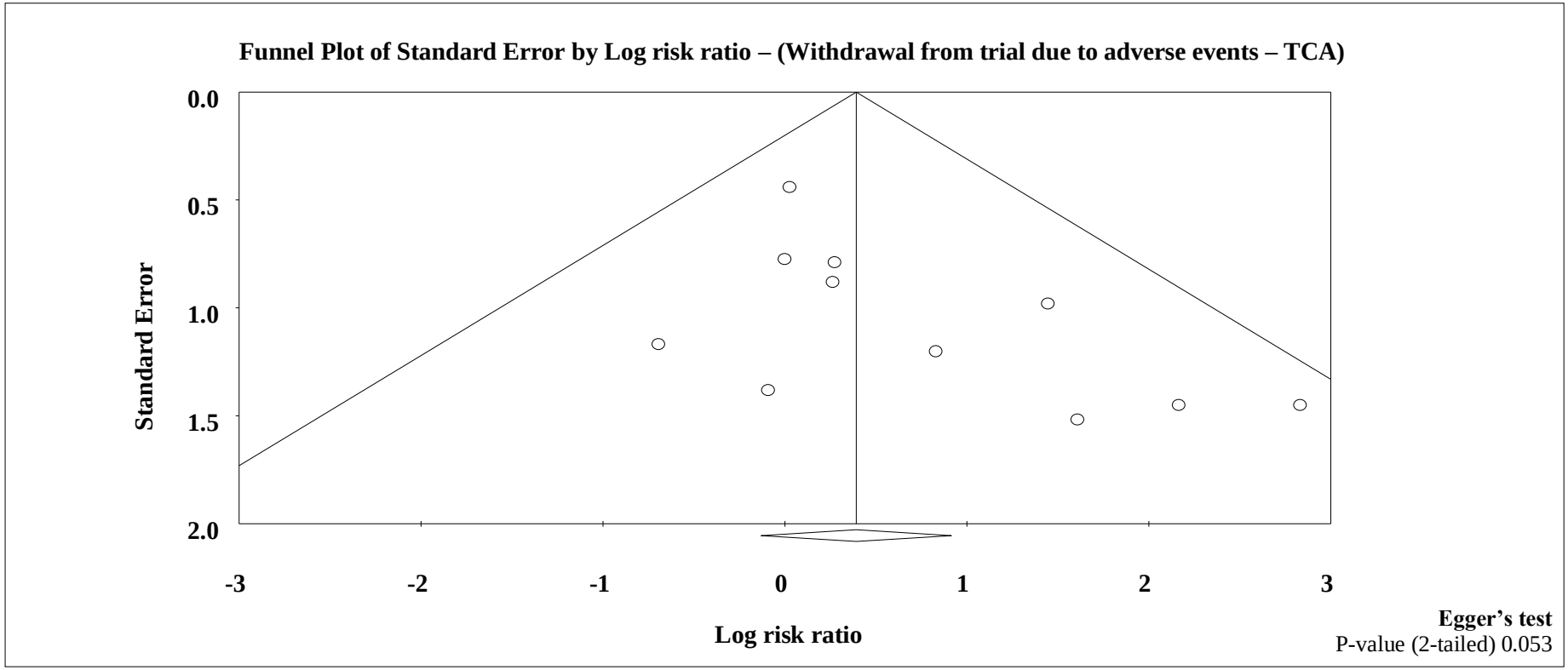
Supplemental file 15. Funnel plot – serious adverse events in SNRI trials



Supplemental file 16. Funnel plot – risk of withdrawing due to adverse events in SNRI trials



Supplemental file 17. Funnel plot – risk of withdrawing due to adverse events in TCA trials



Supplemental file 18. Exploratory meta-regression analyses of risk of bias, small study effects, industry sponsorship, depression diagnosis and daily dosage antidepressants on pain.

Moderator	Mean difference (95% CI)	I^2	P-value for interaction
Risk of bias			
High (25 trials)	-7.6 (-11.0. to – 4.3)	86.5%	0.56
Low (5 trials)	-9.8 (-13.9 to -5.7)	0%	
Small study			
Yes (20 trials)	-6.7 (-10.3 to -3.2)	55.1%	0.49
No (10 trials)	-9.0 (-13.6 to -4.4)	92.9%	
Industry sponsorship			
Yes (14 trials)	-6.9 (-9.0 to -4.8)	53.8%	0.24
No (11 trials)	-7.5 (-15.2 to 0.3)	91.1%	
Unclear (5 trials)	-13.3 (-21.9 to -4.7)	55.1%	
Depression diagnosis			
Yes (4 trials)	-8.4 (-16.3 to -0.5)	54.4%	0.25
No (26 trials)	-7.8 (-11.0 to -4.6)	85.8%	
Daily dosage			
duloxetine 20 mg/day (1 trial)	0.8 (-7.2 to 8.8)	0%	0.13
duloxetine 60 mg/day (9 trials)	-7.6 (-10.1 to -5.2)	59.4%	
duloxetine 120 mg/day (4 trials)	-9.2 (-11.6 to -6.8)	0%	