The efficacy and safety of antidepressants for pain: an overview of systematic reviews

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Supplementary file 1. Search strategy

Databases
Pubmed
#1 "antidepressive agents"[MeSH Terms] OR "antidepressive agents"[MeSH Terms] OR "antidepressive agents, second generation"[MeSH Terms] OR "antidepressive agents, tricyclic"[MeSH Terms] OR "antidepressive agents second generation"[Pharmacological Action] OR "adrenergic uptake inhibitors"[MeSH Terms] OR "serotonin and noradrenaline reuptake inhibitors"[MeSH Terms] OR "amitriptyline"[MeSH Terms] OR "nortriptyline"[MeSH Terms] OR "desipramine"[MeSH Terms] OR "doxepin"[MeSH Terms] OR "trimipramine"[MeSH Terms] OR "clomipramine"[MeSH Terms] OR "protriptyline"[MeSH Terms] OR "amoxapine"[MeSH Terms] OR "maprotiline"[MeSH Terms] OR "serotonin uptake inhibitors"[MeSH Terms] OR "escitalopram"[MeSH Terms] OR "citalopram"[MeSH Terms] OR "fluoxetine"[MeSH Terms] OR "paroxetine"[MeSH Terms] OR "sertraline"[MeSH Terms] OR "duloxetine hydrochloride"[MeSH Terms] OR "duloxetine"[Title/Abstract] OR "fluvoxamine"[MeSH Terms] OR "venlafaxine hydrochloride"[MeSH Terms] OR "Venlafaxine"[Title/Abstract] OR "desvenlafaxine succinate"[MeSH Terms] OR "milnacipran"[MeSH Terms] OR "monoamine oxidase inhibitors"[MeSH Terms] OR "harmaline"[MeSH Terms] OR "iproniazid"[MeSH Terms] OR "isocarboxazid"[MeSH Terms] OR "moclobemide"[MeSH Terms] OR "tranylcypromine"[MeSH Terms] OR "bupropion"[MeSH Terms] OR "trazodone"[MeSH Terms] OR "mirtazapine"[MeSH Terms] OR "Antidepressant"[Title/Abstract] OR "Antidepressants"[Title/Abstract] #2 "pain"[MeSH Terms] OR "acute pain"[MeSH Terms] OR "pain management"[MeSH Terms] OR "pelvic girdle pain"[MeSH Terms] OR "musculoskeletal pain"[MeSH Terms] OR "chronic pain"[MeSH Terms] OR "visceral pain"[MeSH Terms] OR "nociceptive pain"[MeSH Terms] OR "eye pain"[MeSH Terms] OR "pain, referred"[MeSH Terms] OR "complex regional pain syndromes"[MeSH Terms] OR "shoulder pain"[MeSH Terms] OR "neck pain"[MeSH Terms] OR "low back pain"[MeSH Terms] OR "abdominal pain"[MeSH Terms] OR "pain, postoperative"[MeSH Terms] OR "pain, intractable"[MeSH Terms] OR "myofascial pain syndromes"[MeSH Terms] OR "facial pain"[MeSH Terms] OR "chest pain"[MeSH Terms] OR "back pain"[MeSH Terms] OR "pain, procedural"[MeSH Terms] OR "facial neuralgia"[MeSH Terms] OR "neuralgia"[MeSH Terms] OR "somatosensory disorders"[MeSH Terms] OR "phantom limb"[MeSH Terms] OR "headache"[MeSH Terms] OR "cystitis, interstitial"[MeSH Terms] OR "myalgia"[MeSH Terms] OR "fibromyalgia"[MeSH Terms] OR "temporomandibular joint dysfunction syndrome"[MeSH Terms] OR "somatoform disorders"[MeSH Terms] OR "prostatitis"[MeSH Terms] #3 ((((Systematic Review [Publication Type]) OR (Systematic Reviews as Topic[MeSH Terms])) OR (Meta-Analysis [Publication Type])) OR (Meta-Analysis as Topic[MeSH Terms])) OR (Network Meta-Analysis[MeSH Terms]) #1 AND #2 AND #3
EMBASE
#1 exp "antidepressive agents"/ or exp "antidepressive agents"/ or exp "antidepressive agents, second generation"/ or exp "antidepressive agents, tricyclic"/ or "antidepressive agents second generation".mp. or exp "adrenergic uptake inhibitors"/ or exp "serotonin and noradrenaline reuptake inhibitors"/ or exp amitriptyline/ or exp nortriptyline/ or exp desipramine/ or exp doxepin/ or exp trimipramine/ or exp clomipramine/ or exp protriptyline/ or exp amoxapine/ or exp maprotiline/ or exp "serotonin uptake inhibitors"/ or exp escitalopram/ or exp citalopram/ or exp fluoxetine/ or exp paroxetine/ or exp sertraline/ or exp "duloxetine hydrochloride"/ or duloxetine.tw. or exp fluvoxamine/ or exp "venlafaxine hydrochloride"/ or Venlafaxine.tw. or exp "desvenlafaxine succinate"/ or exp milnacipran/ or exp "monoamine oxidase inhibitors"/ or exp harmaline/ or exp iproniazid/ or exp isocarboxazid/ or exp moclobemide/ or exp tranylcypromine/ or exp bupropion/ or exp trazodone/ or exp mirtazapine/ or Antidepressant.tw. or Antidepressants.tw.

#2 exp pain/ or exp "acute pain"/ or exp "pain management"/ or exp "pelvic girdle pain"/ or exp "musculoskeletal pain"/ or exp "chronic pain"/ or exp "visceral pain"/ or exp "nociceptive pain"/ or exp "eye pain"/ or exp "pain, referred"/ or exp "complex regional pain syndromes"/ or exp "shoulder pain"/ or exp "neck pain"/ or exp "low back pain"/ or exp "abdominal pain"/ or exp "pain, postoperative"/ or exp "pain, intractable"/ or exp "myofascial pain syndromes"/ or exp "facial pain"/ or exp "chest pain"/ or exp "back pain"/ or exp "pain, procedural"/ or exp "facial neuralgia"/ or exp neuralgia/ or exp "somatosensory disorders"/ or exp "phantom limb"/ or exp headache/ or exp "cystitis, interstitial"/ or exp myalgia/ or exp fibromyalgia/ or exp "temporomandibular joint dysfunction syndrome"/ or exp "somatoform disorders"/ or exp prostatitis/

#3 exp "systematic review"/ or exp meta analysis/

#4 1 and 2 and 3

Cochrane Database of Systematic Reviews

#1 [mh "antidepressive agents"] OR [mh "antidepressive agents"] OR [mh "antidepressive agents, second generation"] OR [mh "antidepressive agents, tricyclic"] OR "antidepressive agents second generation" OR [mh "adrenergic uptake inhibitors"] OR [mh "serotonin and noradrenaline reuptake inhibitors"] OR [mh amitriptyline] OR [mh nortriptyline] OR [mh desipramine] OR [mh doxepin] OR [mh trimipramine] OR [mh clomipramine] OR [mh protriptyline] OR [mh amoxapine] OR [mh maprotiline] OR [mh "serotonin uptake inhibitors"] OR [mh escitalopram] OR [mh citalopram] OR [mh fluoxetine] OR [mh paroxetine] OR [mh sertraline] OR [mh "duloxetine hydrochloride"] OR duloxetine:ti,ab OR [mh fluvoxamine] OR [mh "venlafaxine hydrochloride"] OR Venlafaxine:ti,ab OR [mh "desvenlafaxine succinate"] OR [mh milnacipran] OR [mh "monoamine oxidase inhibitors"] OR [mh harmaline] OR [mh iproniazid] OR [mh isocarboxazid] OR [mh moclobemide] OR [mh tranylcypromine] OR [mh bupropion] OR [mh trazodone] OR [mh mirtazapine] OR Antidepressant:ti,ab OR Antidepressants:ti,ab

#2 [mh pain] OR [mh "acute pain"] OR [mh "pain management"] OR [mh "pelvic girdle pain"] OR [mh "musculoskeletal pain"] OR [mh "chronic pain"] OR [mh "visceral pain"] OR [mh "nociceptive pain"] OR [mh "eye pain"] OR [mh "pain, referred"] OR [mh "complex regional pain syndromes"] OR [mh "shoulder pain"] OR [mh "neck pain"] OR [mh "low back pain"] OR [mh "abdominal pain"] OR [mh "pain, postoperative"] OR [mh "pain, intractable"] OR [mh "myofascial pain syndromes"] OR [mh "facial pain"] OR [mh "chest pain"] OR [mh "back pain"] OR [mh "pain, procedural"] OR [mh "facial neuralgia"] OR [mh neuralgia] OR [mh "somatosensory disorders"] OR [mh "phantom limb"] OR [mh headache] OR [mh "cystitis, interstitial"] OR [mh myalgia] OR [mh fibromyalgia] OR [mh "temporomandibular joint dysfunction syndrome"] OR [mh "somatoform disorders"] OR [mh prostatitis]

#1 AND #2
Limit to Cochrane Reviews

Psychinfo

#1 exp "antidepressive agents"/ or exp "antidepressive agents"/ or exp "antidepressive agents, second generation"/ or exp "antidepressive agents, tricyclic"/ or "antidepressive agents second generation".mp. or exp "adrenergic uptake inhibitors"/ or exp "serotonin and noradrenaline reuptake inhibitors"/ or exp amitriptyline/ or exp nortriptyline/ or exp desipramine/ or exp doxepin/ or exp trimipramine/ or exp clomipramine/ or exp protriptyline/ or exp amoxapine/ or exp maprotiline/ or exp "serotonin uptake inhibitors"/ or exp escitalopram/ or exp citalopram/ or exp fluoxetine/ or exp paroxetine/ or exp sertraline/ or exp "duloxetine hydrochloride"/ or duloxetine.tw. or exp fluvoxamine/ or exp "venlafaxine hydrochloride"/ or Venlafaxine.tw. or exp "desvenlafaxine succinate"/ or exp milnacipran/ or exp "monoamine oxidase inhibitors"/ or exp harmaline/ or exp iproniazid/ or exp isocarboxazid/ or exp moclobemide/ or exp tranylcypromine/ or exp bupropion/ or exp trazodone/ or exp mirtazapine/ or Antidepressant.tw. or Antidepressants.tw.

#2 exp pain/ or exp "acute pain"/ or exp "pain management"/ or exp "pelvic girdle pain"/ or exp "musculoskeletal pain"/ or exp "chronic pain"/ or exp "visceral pain"/ or exp "nociceptive pain"/ or exp "eye pain"/ or exp "pain, referred"/ or exp "complex regional pain syndromes"/ or exp "shoulder pain"/ or exp "neck pain"/ or exp "low back pain"/ or exp "abdominal pain"/ or exp "pain, postoperative"/ or exp "pain, intractable"/ or exp "myofascial pain syndromes"/ or exp "facial pain"/ or exp "chest pain"/ or exp "back pain"/ or exp "pain, procedural"/ or exp "facial neuralgia"/ or exp neuralgia/ or exp "somatosensory disorders"/ or exp "phantom limb"/ or exp headache/ or exp "cystitis, interstitial"/ or exp myalgia/ or exp fibromyalgia/ or exp "temporomandibular joint dysfunction syndrome"/ or exp "somatoform disorders"/ or exp prostatitis/

#3 exp "systematic review"/ or exp meta analysis/

#4 1 and 2 and 3

Supplementary file 2. Excluded reviews after full-text reading, with reasons

	Reference	Reason for exclusion
1	Riediger, C.: Schuster, T.: Barlinn, K.: Maier, S.: Weitz, J.: Siepmann, T. Adverse Effects of Antidepressants for Chronic Pain: A Systematic Review and Meta-analysis. Front Neurol. 2017;8(0)	Exclusion reason: Incomplete selection of trials;
2	Ottman, A. A.: Warner, C. B.: Brown, J. N. The role of mirtazapine in patients with fibromyalgia: a systematic review. Rheumatol Int.2018;38(12)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
3	Cording, M.: Derry, S.: Phillips, T.: Moore, R. A.: Wiffen, P. J. Milnacipran for pain in fibromyalgia in adults. Cochrane Database Syst Rev.2015;2015(10)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
4	Richards, B. L.: Whittle, S. L.: van der Heijde, D. M.: Buchbinder, R. The efficacy and safety of antidepressants in inflammatory arthritis: a Cochrane systematic review. J Rheumatol Suppl.2012;90(0)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
5	McMillan, R.: Forssell, H.: Buchanan, J. A. G.: Glenny, A. M.: Weldon, J. C.: Zakrzewska, J. M. Interventions for treating burning mouth syndrome. Cochrane Database of Systematic Reviews.2016;0(11)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
6	Xie, C.; Tang, Y.; Wang, Y.; Yu, T.; Wang, Y.; Jiang, L.; Lin, L. Efficacy and Safety of Antidepressants for the Treatment of Irritable Bowel Syndrome: A Meta-Analysis. PLoS One.2015;10(8)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
7	Ford, A. C.: Luthra, P.: Tack, J.: Boeckxstaens, G. E.: Moayyedi, P.: Talley, N. J. Efficacy of psychotropic drugs in functional dyspepsia: systematic review and meta-analysis. Gut.2017;66(3)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
8	Waldfogel, J. M.; Nesbit, S. A.; Dy, S. M.; Sharma, R.; Zhang, A.; Wilson, L. M.; Bennett, W. L.; Yeh, H. C.; Chelladurai, Y.; Feldman, D.; Robinson, K. A. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: A systematic review. Neurology.2017;88(20)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
9	Martin, W. J.: Perez, R. S.: Tuinzing, D. B.: Forouzanfar, T. Efficacy of antidepressants on orofacial pain: a systematic review. Int J Oral Maxillofac Surg.2012;41(12)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
10	Mujakperuo, H. R.: Watson, M.: Morrison, R.: Macfarlane, T. V. Pharmacological interventions for pain in patients with temporomandibular disorders. Cochrane Database of Systematic Reviews.2010;0(10)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
11	Hojo, M.: Nagahara, A.: Asaoka, D.: Shimada, Y.: Sasaki, H.: Matsumoto, K.: Takeda, T.: Ueyama, H.: Matsumoto, K.: Watanabe, S. A Systematic Review of the Effectiveness of Antianxiety and Antidepressive Agents for Functional Dyspepsia. Intern Med.2017;56(23)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
12	Ąšlebioda, Z.; Lukaszewska-Kuska, M.; Dorocka-Bobkowska, B. Evaluation of the efficacy of treatment modalities in burning mouth syndrome-A systematic review. J Oral Rehabil.2020;47(11)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
13	Griebeler, M. L.: Morey-Vargas, O. L.: Brito, J. P.: Tsapas, A.: Wang, Z.: Carranza Leon, B. G.: Phung, O. J.: Montori, V. M.: Murad, M. H. Pharmacologic interventions for painful diabetic neuropathy: An umbrella systematic review and comparative	Exclusion reason: Ineligible study design;

	effectiveness network meta-analysis. Ann Intern Med.2014;161(9)	
14	Guan, J.: Tanaka, S.: Kawakami, K. Anticonvulsants or Antidepressants in Combination Pharmacotherapy for Treatment of Neuropathic Pain in Cancer Patients: A Systematic Review and Meta-analysis. Clin J Pain.2016;32(8)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
15	Mascarenhas, R. O.; Souza, M. B.; Oliveira, M. X.; Lacerda, A. C.; MendonÃ§a, V. A.; Henschke, N.; Oliveira, V. C. Association of Therapies With Reduced Pain and Improved Quality of Life in Patients With Fibromyalgia: A Systematic Review and Meta-analysis. JAMA Intern Med.2021;181(1)	Exclusion reason: Pooled data from different classes of antidepressants;
16	Schnabel, A.; Weibel, S.; Reichl, S. U.; MeiÃŸner, M.; Kranke, P.; Zahn, P. K.; Pogatzki-Zahn, E. M.; Meyer-FrieÃŸem, C. H. Efficacy and adverse events of selective serotonin noradrenaline reuptake inhibitors in the management of postoperative pain: A systematic review and meta-analysis. J Clin Anesth.2021;75(0)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
17	Rexwinkel, R.; Zeevenhooven, J.; van Etten-Jamaludin, F. S.; Benninga, M. A.; Tabbers, M. M. Side effects associated with pharmacotherapy for pediatric irritable bowel syndrome and functional abdominal pain - not otherwise specified: a systematic review. Expert Opin Drug Saf.2019;18(2)	Exclusion reason: Children/adolescents;
18	Song, D.; He, A.; Xu, R.; Xiu, X.; Wei, Y. Efficacy of Pain Relief in Different Postherpetic Neuralgia Therapies: A Network Meta-Analysis. Pain Physician.2018;21(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
19	Kolla, B. P.: Mansukhani, M. P.: Bostwick, J. M. The influence of antidepressants on restless legs syndrome and periodic limb movements: A systematic review. Sleep Med Rev.2018;38(0)	Exclusion reason: Ineligible outcomes;
20	Chaparro, L. E.: Wiffen, P. J.: Moore, R. A.: Gilron, I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Database Syst Rev.2012;2012(7)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
21	Zakrzewska, J. M.: Glenny, A. M.: Forssell, H. Interventions for the treatment of burning mouth syndrome. Cochrane Database Syst Rev.2001;0(3)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
22	Lin, C. S.; Lin, Y. C.; Lao, H. C.; Chen, C. C. Interventional Treatments for Postherpetic Neuralgia: A Systematic Review. Pain Physician.2019;22(3)	Exclusion reason: Ineligible intervention;
23	Lian, Y. N.: Wang, Y.: Zhang, Y.: Yang, C. X. Duloxetine for pain in fibromyalgia in adults: a systematic review and a meta-analysis. Int J Neurosci.2020;130(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
24	Moore, R. A.: Derry, S.: Aldington, D.: Cole, P.: Wiffen, P. J. Amitriptyline for neuropathic pain in adults. Cochrane Database of Systematic Reviews.2015;0(7)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
25	GrubiÅ¡iÄ‡, F. Are serotonin and noradrenaline reuptake inhibitors effective, tolerable, and safe for adults with fibromyalgia? A Cochrane Review summary with commentary. J Musculoskelet Neuronal Interact.2018;18(4)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
26	Lee, Y. H.; Song, G. G. Comparative efficacy and tolerability of duloxetine, pregabalin, and milnacipran for the treatment of fibromyalgia: a Bayesian network meta-analysis of randomized controlled trials. Rheumatol Int.2016;36(5)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
27	Quartero, A. O.: Meineche-Schmidt, V.: Muris, J.: Rubin, G.: de Wit, N. Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome. Cochrane Database Syst Rev.2005;0(2)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;

28	Wang, W.; Sun, Y. H.; Wang, Y. Y.; Wang, Y. T.; Wang, W.; Li, Y. Q.; Wu, S. X. Treatment of functional chest pain with antidepressants: a meta-analysis. Pain Physician.2012;15(2)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
29	Carville, S. F.: Arendt-Nielsen, L.: Bliddal, H.: Blotman, F.: Branco, J. C.: Buskila, D.: Da Silva, J. A.: Danneskiold-SamsÃ¸e, B.: Dincer, F.: Henriksson, C.: Henriksson, K. G.: Kosek, E.: Longley, K.: McCarthy, G. M.: Perrot, S.: Puszczewicz, M.: Sarzi-Puttini, P.: Silman, A.: SpÃ¤th, M.: Choy, E. H. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. Ann Rheum Dis.2008;67(4)	Exclusion reason: Ineligible study design;
30	McCormick, Z.: Chang-Chien, G.: Marshall, B.: Huang, M.: Harden, R. N. Phantom limb pain: a systematic neuroanatomical-based review of pharmacologic treatment. Pain Med.2014;15(2)	Exclusion reason: Ineligible study design;
31	DÃaz-Heredia, J.; Loza, E.; Cebreiro, I.; Ruiz Iban, MÃ• Preventive analgesia in hip or knee arthroplasty: a systematic review. Rev Esp Cir Ortop Traumatol.2015;59(2)	Exclusion reason: Ineligible study design;
32	Mehta, S.; Guy, S.; Lam, T.; Teasell, R.; Loh, E. Antidepressants Are Effective in Decreasing Neuropathic Pain After SCI: A Meta-Analysis. Top Spinal Cord Inj Rehabil.2015;21(2)	Exclusion reason: Pooled data from different classes of antidepressants;
33	Welsch, P.; Sommer, C.; Schiltenwolf, M.; HÃ¤user, W. [Opioids in chronic noncancer pain-are opioids superior to nonopioid analgesics? A systematic review and meta-analysis of efficacy, tolerability and safety in randomized head-to-head comparisons of opioids versus nonopioid analgesics of at least four week's duration]. Schmerz.2015;29(1)	Exclusion reason: Ineligible comparator;
34	Radner, H.: Ramiro, S.: Buchbinder, R.: LandewÃ©, R. B. M.: van der Heijde, D.: Aletaha, D. Pain management for inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and other spondyloarthritis) and gastrointestinal or liver comorbidity. Cochrane Database of Systematic Reviews.2012;0(1)	Exclusion reason: Ineligible intervention;
35	Lorenz, K. A.; Lynn, J.; Dy, S. M.; Shugarman, L. R.; Wilkinson, A.; Mularski, R. A.; Morton, S. C.; Hughes, R. G.; Hilton, L. K.; Maglione, M.; Rhodes, S. L.; Rolon, C.; Sun, V. C.; Shekelle, P. G. Evidence for improving palliative care at the end of life: a systematic review. Ann Intern Med.2008;148(2)	Exclusion reason: Ineligible outcomes;
36	Branton, M. W.; Hopkins, T. J.; Nemec, E. C. Duloxetine for the reduction of opioid use in elective orthopedic surgery: a systematic review and meta-analysis. Int J Clin Pharm.2021;43(2)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
37	Richards, B. L.: Whittle, S. L.: Buchbinder, R. Neuromodulators for pain management in rheumatoid arthritis. Cochrane Database of Systematic Reviews.2012;0(1)	Exclusion reason: Ineligible intervention;
38	Russell, J. M.; Weisberg, R.; Fava, M.; Hartford, J. T.; Erickson, J. S.; D'Souza, D. N. Efficacy of duloxetine in the treatment of generalized anxiety disorder in patients with clinically significant pain symptoms. Depress Anxiety.2008;25(7)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
39	Santos, T. G. D.: Miranda, I. A. S.: Nygaard, C. C.: Schreiner, L.: Castro, R. A.: Haddad, J. M. Systematic Review of Oral Therapy for the Treatment of Symptoms of Bladder Pain	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;

	Syndrome: The Brazilian Guidelines. Rev Bras Ginecol Obstet.2018;40(2)	
40	Santos, J.: AlarcÃ£o, J.: Fareleira, F.: Vaz-Carneiro, A.: Costa, J. Tapentadol for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev.2015;2015(5)	Exclusion reason: Ineligible intervention;
41	Wolff, R. F.: Bala, M. M.: Westwood, M.: Kessels, A. G.: Kleijnen, J. 5% lidocaine medicated plaster in painful diabetic peripheral neuropathy (DPN): a systematic review. Swiss Med Wkly.2010;140(21-22)	Exclusion reason: Ineligible intervention;
42	Chen, L.; Gong, M.; Liu, G.; Xing, F.; Liu, J.; Xiang, Z. Efficacy and tolerability of duloxetine in patients with knee osteoarthritis: a meta-analysis of randomised controlled trials. Intern Med J.2019;49(12)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
43	Chen, B.; Duan, J.; Wen, S.; Pang, J.; Zhang, M.; Zhan, H.; Zheng, Y. An Updated Systematic Review and Meta-analysis of Duloxetine for Knee Osteoarthritis Pain. Clin J Pain.2021;37(11)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
44	Chaparro, L. E.; Smith, S. A.; Moore, R. A.; Wiffen, P. J.; Gilron, I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Database Syst Rev.2013;2013(7)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
45	Osani, M. C.: Bannuru, R. R. Efficacy and safety of duloxetine in osteoarthritis: a systematic review and meta-analysis. Korean J Intern Med.2019;34(5)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
46	Weng, C.; Xu, J.; Wang, Q.; Lu, W.; Liu, Z. Efficacy and safety of duloxetine in osteoarthritis or chronic low back pain: a Systematic review and meta-analysis. Osteoarthritis Cartilage.2020;28(6)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
47	Wang, Z. Y.; Shi, S. Y.; Li, S. J.; Chen, F.; Chen, H.; Lin, H. Z.; Lin, J. M. Efficacy and Safety of Duloxetine on Osteoarthritis Knee Pain: A Meta-Analysis of Randomized Controlled Trials. Pain Med.2015;16(7)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
48	Bronfort, G.: Nilsson, N.: Haas, M.: Evans, R.: Goldsmith, C. H.: Assendelft, W. J.: Bouter, L. M. Non-invasive physical treatments for chronic/recurrent headache. Cochrane Database Syst Rev.2004;0(3)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
49	Stones, R. W.: Mountfield, J. Interventions for treating chronic pelvic pain in women. Cochrane Database Syst Rev.2000;0(4)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
50	Plaghki, L.; Adriaensen, H.; Morlion, B.; Lossignol, D.; Devulder, J. Systematic overview of the pharmacological management of postherpetic neuralgia. An evaluation of the clinical value of critically selected drug treatments based on efficacy and safety outcomes from randomized controlled studies. Dermatology.2004;208(3)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
51	Chou, R.: Deyo, R.: Friedly, J.: Skelly, A.: Weimer, M.: Fu, R.: Dana, T.: Kraegel, P.: Griffin, J.: Grusing, S. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. Ann Intern Med.2017;166(7)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
52	Giannantoni, A.: Bini, V.: Dmochowski, R.: Hanno, P.: Nickel, J. C.: Proietti, S.: Wyndaele, J. J. Contemporary management of the painful bladder: a systematic review. Eur Urol.2012;61(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;

53	Asrar, M. M.: Kumari, S.: Sekhar, B. C.: Bhansali, A.: Bansal, D. Relative Efficacy and Safety of Pharmacotherapeutic Interventions for Diabetic Peripheral Neuropathy: A Systematic Review and Bayesian Network Meta-Analysis. Pain Physician.2021;24(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
54	Hossain, S. M.: Hussain, S. M.: Ekram, A. R. Duloxetine in Painful Diabetic Neuropathy: A Systematic Review. Clin J Pain.2016;32(11)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
55	Frese, A.: Husstedt, I. W.: Ringelstein, E. B.: Evers, S. Pharmacologic treatment of central post-stroke pain. Clin J Pain.2006;22(3)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
56	Snedecor, S. J.: Sudharshan, L.: Cappelleri, J. C.: Sadosky, A.: Mehta, S.: Botteman, M. Systematic review and meta-analysis of pharmacological therapies for painful diabetic peripheral neuropathy. Pain Pract.2014;14(2)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
57	Tomkins, G. E.; Jackson, J. L.; O'Malley, P. G.; Balden, E.; Santoro, J. E. Treatment of chronic headache with antidepressants: a meta-analysis. Am J Med.2001;111(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
58	Pearson, R. L. How effective are antidepressant medications in the treatment of irritable bowel syndrome and nonulcer dyspepsia?. J Fam Pract.2000;49(5)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
59	Zakrzewska, J. M.: Forssell, H.: Glenny, A. M. Interventions for the treatment of burning mouth syndrome: a systematic review. J Orofac Pain.2003;17(4)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
60	Phillips, T. J.: Cherry, C. L.: Cox, S.: Marshall, S. J.: Rice, A. S. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. PLoS One.2010;5(12)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
61	Chou, R.; Huffman, L. H. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med.2007;147(7)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
62	Fava, M.; Mallinckrodt, C. H.; Detke, M. J.; Watkin, J. G.; Wohlreich, M. M. The effect of duloxetine on painful physical symptoms in depressed patients: do improvements in these symptoms result in higher remission rates?. J Clin Psychiatry.2004;65(4)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
63	Passos Mdo, C.; Duro, D.; Fregni, F. CNS or classic drugs for the treatment of pain in functional dyspepsia? A systematic review and meta-analysis of the literature. Pain Physician.2008;11(5)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
64	Moja, P. L.: Cusi, C.: Sterzi, R. R.: Canepari, C. Selective serotonin re-uptake inhibitors (SSRIs) for preventing migraine and tension-type headaches. Cochrane Database Syst Rev.2005;0(3)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
65	Tack, J.: Fried, M.: Houghton, L. A.: Spicak, J.: Fisher, G. Systematic review: the efficacy of treatments for irritable bowel syndrome--a European perspective. Aliment Pharmacol Ther.2006;24(2)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
66	Zakrzewska, J. M.: Forssell, H.: Glenny, A. M. Interventions for the treatment of burning mouth syndrome. Cochrane Database Syst Rev.2005;0(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;

67	Ramiro, S.: Radner, H.: van der Heijde, D.: van Tubergen, A.: Buchbinder, R.: Aletaha, D.: LandewÃ©, R. B. M. Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis). Cochrane Database of Systematic Reviews.2011;0(10)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
68	Kolber, M. R.; Ton, J.; Thomas, B.; Kirkwood, J.; Moe, S.; DugrÃ©, N.; Chan, K.; Lindblad, A. J.; McCormack, J.; Garrison, S.; Allan, G. M.; Korownyk, C. S.; Craig, R.; Sept, L.; Rouble, A. N.; Perry, D. PEER systematic review of randomized controlled trials: Management of chronic low back pain in primary care. Can Fam Physician.2021;67(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
69	Ferraro, M. C.; Bagg, M. K.; Wewege, M. A.; Cashin, A. G.; Leake, H. B.; Rizzo, R. R. N.; Jones, M. D.; Gustin, S. M.; Day, R.; Loo, C. K.; McAuley, J. H. Efficacy, acceptability, and safety of antidepressants for low back pain: a systematic review and meta-analysis. Syst Rev.2021;10(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
70	Urquhart, D. M.: Hoving, J. L.: Assendelft, W. J. J.: Roland, M.: van Tulder, M. W. Antidepressants for nonâ€• specific low back pain. Cochrane Database of Systematic Reviews.2008;0(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
71	Volmink, J.: Lancaster, T.: Gray, S.: Silagy, C. Treatments for postherpetic neuralgia--a systematic review of randomized controlled trials. Fam Pract.1996;13(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
72	Wong, M. C.: Chung, J. W.: Wong, T. K. Effects of treatments for symptoms of painful diabetic neuropathy: systematic review. Bmj.2007;335(7610)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
73	Verhagen, A. P.: Damen, L.: Berger, M. Y.: Passchier, J.: Koes, B. W. Lack of benefit for prophylactic drugs of tension-type headache in adults: a systematic review. Fam Pract.2010;27(2)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
74	Alper, B. S.; Lewis, P. R. Treatment of postherpetic neuralgia: a systematic review of the literature. J Fam Pract.2002;51(2)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
75	Hall, H.; McIntosh, G. Low back pain (chronic). BMJ Clin Evid.2008;2008(0)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
76	Binder, A. I. Neck pain. BMJ Clin Evid.2008;2008(0)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
77	Onghena, Patrick; Van Houdenhove, Boudewijn Antidepressant-induced analgesia in chronic non-malignant pain: A meta-analysis of 39 placebo-controlled studies.. Pain.1992;49(2)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
78	Alviar, M. J.: Hale, T.: Dungca, M. Pharmacologic interventions for treating phantom limb pain. Cochrane Database Syst Rev.2011;0(12)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
79	Ramiro, S.: Radner, H.: van der Heijde, D. M.: Buchbinder, R.: Aletaha, D.: LandewÃ©, R. B. Combination therapy for pain management in inflammatory arthritis: a Cochrane systematic review. J Rheumatol Suppl.2012;90(0)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
80	Cascos-Romero, J.: VÃ¡zquez-Delgado, E.: VÃ¡zquez-RodrÃ-guez, E.: Gay-Escoda, C. The use of tricyclic antidepressants in the treatment of temporomandibular joint disorders: systematic review of the literature of the last 20 years. Med Oral Patol Oral Cir Bucal.2009;14(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;

81	Thaler, K. J.: Morgan, L. C.: Van Noord, M.: Gaynes, B. N.: Hansen, R. A.: Lux, L. J.: Krebs, E. E.: Lohr, K. N.: Gartlehner, G. Comparative effectiveness of second-generation antidepressants for accompanying anxiety, insomnia, and pain in depressed patients: a systematic review. Depress Anxiety.2012;29(6)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
82	Collins, S. L.: Moore, R. A.: McQuayHj,: Wiffen, P. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. J Pain Symptom Manage.2000;20(6)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
83	van den Driest, J. J.: Bierma-Zeinstra, S. M. A.: Bindels, P. J. E.: Schiphof, D. Amitriptyline for musculoskeletal complaints: a systematic review. Fam Pract.2017;34(2)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
84	McQuay, H. J.: TramÃ¨r, M.: Nye, B. A.: Carroll, D.: Wiffen, P. J.: Moore, R. A. A systematic review of antidepressants in neuropathic pain. Pain.1996;68(44622)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
85	Saarto, T.: Wiffen, P. J. Antidepressants for neuropathic pain. Cochrane Database Syst Rev.2005;0(3)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
86	Saarto, T.: Wiffen, P. J. Antidepressants for neuropathic pain. Cochrane Database of Systematic Reviews.2007;0(4)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
87	Cornelius, V. R.; Sauzet, O.; Williams, J. E.; Ayis, S.; Farquhar-Smith, P.; Ross, J. R.; Branford, R. A.; Peacock, J. L. Adverse event reporting in randomised controlled trials of neuropathic pain: considerations for future practice. Pain.2013;154(2)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
88	Liu, Y. F.: Kim, Y.: Yoo, T.: Han, P.: Inman, J. C. Burning mouth syndrome: a systematic review of treatments. Oral Dis.2018;24(3)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
89	Hempenstall, K.: Nurmikko, T. J.: Johnson, R. W.: A'Hern, R. P.: Rice, A. S. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. PLoS Med.2005;2(7)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
90	Edelsberg, J. S.: Lord, C.: Oster, G. Systematic review and meta-analysis of efficacy, safety, and tolerability data from randomized controlled trials of drugs used to treat postherpetic neuralgia. Ann Pharmacother.2011;45(12)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
91	Mulla, S. M.: Wang, L.: Khokhar, R.: Izhar, Z.: Agarwal, A.: Couban, R.: Buckley, D. N.: Moulin, D. E.: Panju, A.: Makosso-Kallyth, S.: Turan, A.: Montori, V. M.: Sessler, D. I.: Thabane, L.: Guyatt, G. H.: Busse, J. W. Management of Central Poststroke Pain: Systematic Review of Randomized Controlled Trials. Stroke.2015;46(10)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
92	Thompson, D. F.: Brooks, K. G. Systematic review of topical amitriptyline for the treatment of neuropathic pain. J Clin Pharm Ther.2015;40(5)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
93	Falk, J.; Thomas, B.; Kirkwood, J.; Korownyk, C. S.; Lindblad, A. J.; Ton, J.; Moe, S.; Allan, G. M.; McCormack, J.; Garrison, S.; DugrÃ©, N.; Chan, K.; Kolber, M. R.; Train, A.; Froentjes, L.; Sept, L.; Wollin, M.; Craig, R.; Perry, D. PEER systematic review of randomized controlled trials: Management of chronic neuropathic pain in primary care. Can Fam Physician.2021;67(5)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;

94	Di Stefano, G.; Di Lionardo, A.; Di Pietro, G.; Cruccu, G.; Truini, A. Pharmacotherapeutic Options for Managing Neuropathic Pain: A Systematic Review and Meta-Analysis. Pain Res Manag.2021;2021(0)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
95	Ney, J. P.; Devine, E. B.; Watanabe, J. H.; Sullivan, S. D. Comparative efficacy of oral pharmaceuticals for the treatment of chronic peripheral neuropathic pain: meta-analysis and indirect treatment comparisons. Pain Med.2013;14(5)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
96	Chung, J. W.; Zeng, Y.; Wong, T. K. Drug therapy for the treatment of chronic nonspecific low back pain: systematic review and meta-analysis. Pain Physician.2013;16(6)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
97	Liampas, A.; Rekatsina, M.; Vadalouca, A.; Paladini, A.; Varrassi, G.; Zis, P. Pharmacological Management of Painful Peripheral Neuropathies: A Systematic Review. Pain Ther.2021;10(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
98	Roche Bueno, J. C. Meta-analysis and P-curve analysis of the efficacy of venlafaxine versus placebo in the treatment of neuropathic pain. Neurologia (Engl Ed).2020;35(8)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
99	Liampas, A.: Rekatsina, M.: Vadalouca, A.: Paladini, A.: Varrassi, G.: Zis, P. Pharmacological Management of Painful Peripheral Neuropathies: A Systematic Review. Pain Ther.2020;0(0)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
100	Gallagher, H. C.: Gallagher, R. M.: Butler, M.: Buggy, D. J.: Henman, M. C. Venlafaxine for neuropathic pain in adults. Cochrane Database of Systematic Reviews.2015;0(8)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
101	Snedecor, S. J.: Sudharshan, L.: Cappelleri, J. C.: Sadosky, A.: Desai, P.: Jalundhwala, Y. J.: Botteman, M. Systematic review and comparison of pharmacologic therapies for neuropathic pain associated with spinal cord injury. J Pain Res.2013;6(0)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
102	Hearn, L.: Moore, R. A.: Derry, S.: Wiffen, P. J.: Phillips, T. Desipramine for neuropathic pain in adults. Cochrane Database of Systematic Reviews.2014;0(9)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
103	Hearn, L.: Derry, S.: Phillips, T.: Moore, R. A.: Wiffen, P. J. Imipramine for neuropathic pain in adults. Cochrane Database of Systematic Reviews.2014;0(5)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
104	Aiyer, R.: Barkin, R. L.: Bhatia, A. Treatment of Neuropathic Pain with Venlafaxine: A Systematic Review. Pain Med.2017;18(10)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
105	Teasell, R. W.: Mehta, S.: Aubut, J. A.: Foulon, B.: Wolfe, D. L.: Hsieh, J. T.: Townson, A. F.: Short, C. A systematic review of pharmacologic treatments of pain after spinal cord injury. Arch Phys Med Rehabil.2010;91(5)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
106	Moisset, X.: Bouhassira, D.: Avez Couturier, J.: Alchaar, H.: Conradi, S.: Delmotte, M. H.: Lanteri-Minet, M.: Lefaucheur, J. P.: Mick, G.: Piano, V.: Pickering, G.: Piquet, E.: Regis, C.: Salvat, E.: Attal, N. Pharmacological and non-pharmacological treatments for neuropathic pain: Systematic review and French recommendations. Rev Neurol (Paris).2020;176(5)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
107	Derry, S.: Wiffen, P. J.: Aldington, D.: Moore, R. A. Nortriptyline for neuropathic pain in adults. Cochrane Database of Systematic Reviews.2015;0(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
108	Argoff, C. E. Topical analgesics in the management of acute and chronic pain. Mayo Clin Proc.2013;88(2)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;

109	Plested, M.: Budhia, S.: Gabriel, Z. Pregabalin, the lidocaine plaster and duloxetine in patients with refractory neuropathic pain: a systematic review. BMC Neurol.2010;10(0)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
110	Bayoumi, A. B.: Ikizgul, O.: Karaali, C. N.: Bozkurt, S.: Konya, D.: Toktas, Z. O. Antidepressants in Spine Surgery: A Systematic Review to Determine Benefits and Risks. Asian Spine J.2019;13(6)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
111	Arnold, L. M.; Keck, P. E., Jr.; Welge, J. A. Antidepressant treatment of fibromyalgia. A meta-analysis and review. Psychosomatics.2000;41(2)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
112	HÃ¤user, W.; Bernardy, K.; UÃ§eyler, N.; Sommer, C. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. Jama.2009;301(2)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
113	Jung, A. C.; Staiger, T.; Sullivan, M. The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. J Gen Intern Med.1997;12(6)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
114	HÃ¤user, W.: Wolfe, F.: TÃ¶lle, T.: UÃ§eyler, N.: Sommer, C. The role of antidepressants in the management of fibromyalgia syndrome: a systematic review and meta-analysis. CNS Drugs.2012;26(4)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
115	Perrot, S.: Javier, R. M.: Marty, M.: Le Jeunne, C.: Laroche, F. Is there any evidence to support the use of anti-depressants in painful rheumatological conditions? Systematic review of pharmacological and clinical studies. Rheumatology (Oxford).2008;47(8)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
116	Choy, E.: Marshall, D.: Gabriel, Z. L.: Mitchell, S. A.: Gylee, E.: Dakin, H. A. A systematic review and mixed treatment comparison of the efficacy of pharmacological treatments for fibromyalgia. Semin Arthritis Rheum.2011;41(3)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
117	HÃ¤user, W.: Petzke, F.: ÃœÃ§eyler, N.: Sommer, C. Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. Rheumatology (Oxford).2011;50(3)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
118	Rossy, L. A.; Buckelew, S. P.; Dorr, N.; Hagglund, K. J.; Thayer, J. F.; McIntosh, M. J.; Hewett, J. E.; Johnson, J. C. A meta-analysis of fibromyalgia treatment interventions. Ann Behav Med.1999;21(2)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
119	NÃ¼esch, E.; HÃ¤user, W.; Bernardy, K.; Barth, J.; JÃ¼ni, P. Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis. Ann Rheum Dis.2013;72(6)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
120	Perrot, S.; Russell, I. J. More ubiquitous effects from non-pharmacologic than from pharmacologic treatments for fibromyalgia syndrome: a meta-analysis examining six core symptoms. Eur J Pain.2014;18(8)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
121	Derry, S.: Gill, D.: Phillips, T.: Moore, R. A. Milnacipran for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev.2012;3(3)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
122	HÃ¤user, W.: UrrÃºtia, G.: Tort, S.: UÃ§eyler, N.: Walitt, B. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. Cochrane Database Syst Rev.2013;0(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;

123	Moore, R. A.: Derry, S.: Aldington, D.: Cole, P.: Wiffen, P. J. Amitriptyline for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev.2012;12(0)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
124	Sultan, A.: Gaskell, H.: Derry, S.: Moore, R. A. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials. BMC Neurol.2008;8(0)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
125	UÃ§eyler, N.: HÃ¤user, W.: Sommer, C. A systematic review on the effectiveness of treatment with antidepressants in fibromyalgia syndrome. Arthritis Rheum.2008;59(9)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
126	Lunn, M. P. T.: Hughes, R. A. C.: Wiffen, P. J. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database of Systematic Reviews.2014;0(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
127	Lino, P. A.: Martins, C. C.: Miranda, G.: de Souza, E. Silva M. E.: de Abreu, M. Use of antidepressants in dentistry: A systematic review. Oral Dis.2018;24(7)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
128	VanderWeide, L. A.: Smith, S. M.: Trinkley, K. E. A systematic review of the efficacy of venlafaxine for the treatment of fibromyalgia. J Clin Pharm Ther.2015;40(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
129	Mikockaâ€• Walus, A.: Prady, S. L.: Pollok, J.: Esterman, A. J.: Gordon, A. L.: Knowles, S.: Andrews, J. M. Adjuvant therapy with antidepressants for the management of inflammatory bowel disease. Cochrane Database of Systematic Reviews.2019;0(4)	Exclusion reason: Ineligible outcomes;
130	KleinstÃ¤uber, M.: WitthÃ¶ft, M.: Steffanowski, A.: van Marwijk, H.: Hiller, W.: Lambert, M. J. Pharmacological interventions for somatoform disorders in adults. Cochrane Database of Systematic Reviews.2014;0(11)	Exclusion reason: Ineligible outcomes;
131	Franco, J. V. A.; Turk, T.; Jung, J. H.; Xiao, Y. T.; Iakhno, S.; Tirapegui, F. I.; Garrote, V.; Vietto, V. Pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome: a Cochrane systematic review. BJU Int.2020;125(4)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
132	Ruepert, L.: Quartero, A. O.: de Wit, N. J.: van der Heijden, G. J.: Rubin, G.: Muris, J. W. M. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Database of Systematic Reviews.2011;0(8)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
133	Humble, S. R.; Dalton, A. J.; Li, L. A systematic review of therapeutic interventions to reduce acute and chronic post-surgical pain after amputation, thoracotomy or mastectomy. Eur J Pain.2015;19(4)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
134	Pazin, C.: de Souza Mitidieri, A. M.: Silva, A. P.: Gurian, M. B.: Poli-Neto, O. B.: Rosa, E. Silva J. C. Treatment of bladder pain syndrome and interstitial cystitis: a systematic review. Int Urogynecol J.2016;27(5)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
135	Yang, M.: Zhou, M.: He, L.: Chen, N.: Zakrzewska, J. M. Non-antiepileptic drugs for trigeminal neuralgia. Cochrane Database Syst Rev.2011;0(1)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
136	Di, X. P.: Luo, D. Y.: Jin, X.: Zhao, W. Y.: Li, H.: Wang, K. J. Efficacy and safety comparison of pharmacotherapies for interstitial cystitis and bladder pain syndrome: a systematic review and Bayesian network meta-analysis. Int Urogynecol J.2021;0(0)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
137	Leo, R. J.: Dewani, S. A systematic review of the utility of antidepressant pharmacotherapy in the treatment of vulvodynia pain. J Sex Med.2013;10(10)	Exclusion reason: Ineligible study design;

138	Telang, S.; Walton, C.; Olten, B.; Bloch, M. H. Meta-analysis: Second generation antidepressants and headache. J Affect Disord.2018;236(0)	Exclusion reason: Ineligible outcomes;
139	Huertas-Ceballos, A.: Logan, S.: Bennett, C.: Macarthur, C. Pharmacological interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood. Cochrane Database Syst Rev.2008;0(1)	Exclusion reason: Children/adolescents;
140	Anghelescu, B. A.; Todoran, R.; Terroba-Chambi, C.; Bruno, V. Antidepressants Effects on Pain in Parkinson Disease: A Systematic Review. Clin Neuropharmacol.2021;44(6)	Exclusion reason: Ineligible comparator;
141	Nguyen, T. M.: Eslick, G. D. Systematic review: the treatment of noncardiac chest pain with antidepressants. Aliment Pharmacol Ther.2012;35(5)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
142	Weijenborg, P. W.: de Schepper, H. S.: Smout, A. J.: Bredenoord, A. J. Effects of antidepressants in patients with functional esophageal disorders or gastroesophageal reflux disease: aÂ systematic review. Clin Gastroenterol Hepatol.2015;13(2)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
143	de Oliveira Filho, G. R.; Kammer, R. S.; Dos Santos, H. C. Duloxetine for the treatment acute postoperative pain in adult patients: A systematic review with meta-analysis. J Clin Anesth.2020;63(0)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
144	Burgstaller, J. M.; Jenni, B. F.; Steurer, J.; Held, U.; Wertli, M. M. Treatment efficacy for non-cardiovascular chest pain: a systematic review and meta-analysis. PLoS One.2014;9(8)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
145	Kaminski, A.: Kamper, A.: Thaler, K.: Chapman, A.: Gartlehner, G. Antidepressants for the treatment of abdominal pain-related functional gastrointestinal disorders in children and adolescents. Cochrane Database Syst Rev.2011;2011(7)	Exclusion reason: Children/adolescents;
146	Nishishinya, B.: UrrÃºtia, G.: Walitt, B.: Rodriguez, A.: Bonfill, X.: Alegre, C.: Darko, G. Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy. Rheumatology (Oxford).2008;47(12)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
147	Lunn, M. P.: Hughes, R. A.: Wiffen, P. J. Duloxetine for treating painful neuropathy or chronic pain. Cochrane Database Syst Rev.2009;0(4)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
148	Derry, S.: Phillips, T.: Moore, R. A.: Wiffen, P. J. Milnacipran for neuropathic pain in adults. Cochrane Database Syst Rev.2015;2015(7)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
149	Briley, M.; Moret, C. Treatment of comorbid pain with serotonin norepinephrine reuptake inhibitors. CNS Spectr.2008;13(7 Suppl 11)	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
150	Bae S, Alboog A, Esquivel KS, Abbasi A, Zhou J, Chui J. Efficacy of perioperative pharmacological and regional pain interventions in adult spine surgery: a network meta-analysis and systematic review of randomised controlled trials. Br J Anaesth. 2022 Jan;128(1):98-117	Exclusion reason: Overlap with another eligible review on the same topic that had more trials;
151	Maniker RB, Damiano J, Ivie RMJ, Pavelic M, Woodworth GE. Perioperative Breast Analgesia: a Systematic Review of the Evidence for Perioperative Analgesic Medications. Curr Pain Headache Rep. 2022 Apr;26(4):299-321.	Overlap with most recent and updated review on the same topic
152	Farag HM, Yunusa I, Goswami H, Sultan I, Doucette JA, Eguale T. Comparison of Amitriptyline and US Food and Drug Administration-Approved Treatments for Fibromyalgia: A	Direct effects not provided

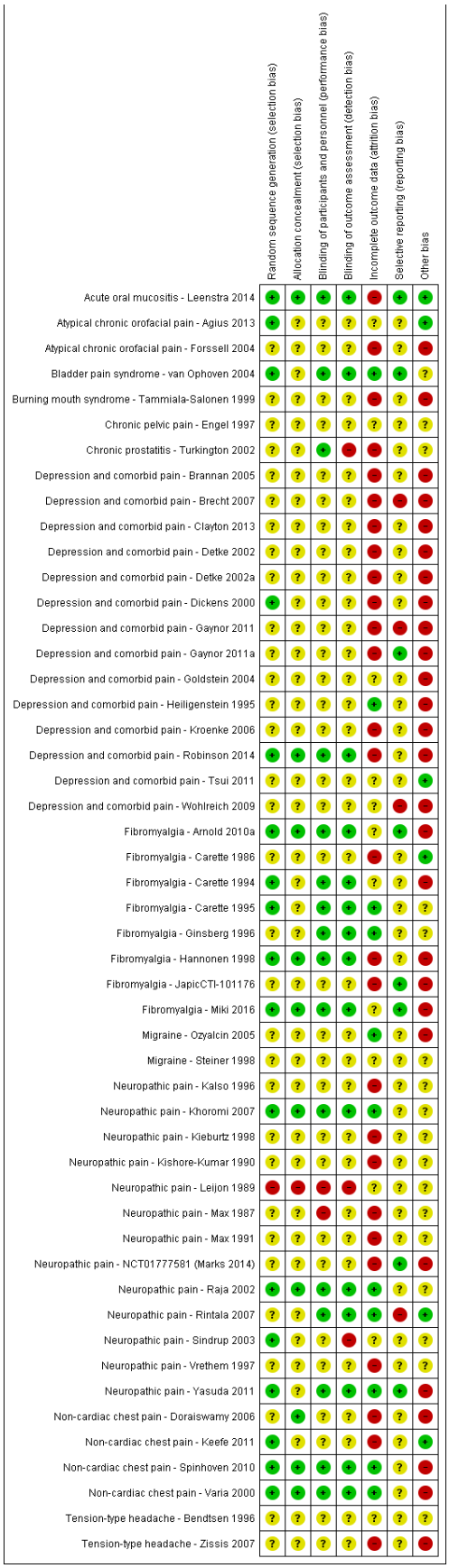
	Systematic Review and Network Meta-analysis. JAMA Netw Open. 2022 May 2;5(5):e2212939.	
153	Allen, C., Walker, A. M., Premji, Z. A., Beauchemin-Turcotte, M.-E., Wong, J., Soh, S., Hawboldt, G. S., Shinkaruk, K. S., & Archer, D. P. (2022). Preventing persistent postsurgical pain: A systematic review and component network meta-analysis. European Journal of Pain, 26, 771– 785	Ineligible outcomes
154	Baradwan S, Alshahrani MS, Alkhamis WH, Allam HS, AlSghan R, Ghazi A, Ragab B, Elmazzaly SMM, Aboshama RA, Ismail RA, Dahshan SA, Al-Touny AA, Daghash NH, Abdelhakim AM, Abbas AM, Fouda AA, Ezzat Abdelfattah L. Preoperative duloxetine on postoperative pain after laparoscopic gynecological surgeries: A systematic review and meta-analysis of randomized controlled trials. J Gynecol Obstet Hum Reprod. 2022 Mar;51(3):102305.	Overlap with most recent and updated review on the same topic
155	Lambarth A, Zarate-Lopez N, Fayaz A. Oral and parenteral anti-neuropathic agents for the management of pain and discomfort in irritable bowel syndrome: A systematic review and meta-analysis. Neurogastroenterol Motil. 2022 Jan;34(1):e14289.	Incomplete selection of trials
156	Tan HL, Smith JG, Hoffmann J, Renton T. A systematic review of treatment for patients with burning mouth syndrome. Cephalalgia. 2022 Feb;42(2):128-161. doi: 10.1177/03331024211036152	Ineligible comparator
157	Jackson JL, Cogbill E, Santana-Davila R, Eldredge C, Collier W, Gradall A, Sehgal N, Kuester J. A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache. PLoS One. 2015 Jul 14;10(7):e0130733.	Concerns over trial selection and data extraction
158	Alberti FF, Becker MW, Blatt CR, Ziegelmann PK, da Silva Dal Pizzol T, Pilger D. Comparative efficacy of amitriptyline, duloxetine and pregabalin for treating fibromyalgia in adults: an overview with network meta-analysis. Clin Rheumatol. 2022 Jul;41(7):1965-1978.	Ineligible study design

Supplementary file 3. Methodological quality of included reviews (AMSTAR-2)

Author (year)	1	2*	3	4*	5	6	7*	8	9*	10	11*	12	13*	14	15*	16	Overall confidence
Wang (2022)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Roberts (2022)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Ferreira (2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Farag (2021)	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Critically low
Ford (2021)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Do (2021)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No	No	No	Critically low
Imamura (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Franco (2019)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Christophorou (2019)	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Ford (2019)	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Critically low
Caruso (2019)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Critically low
Perez-Lopes (2019)	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	No	No	No	Yes	Critically low
Welsch (2018) [SNRI]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Low
Welsch (2018) [Mirtazapine]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Jackson (2017)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Gebhardt (2016)	Yes	No	Yes	No	No	No	No	Yes	No	No	Yes	Yes	No	No	Yes	Yes	Critically low
Alviar (2016)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Moore (2015)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Critically low
Walitt (2015)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Banzi (2015)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Low
Finnerup (2015)	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Atluri (2015)	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Critically low
Banzi (2015)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Low
Cheong (2014)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	High
Tort (2012)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Critically low
Richards (2011)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High

Items marked with an * are considered critical; A "yes" was given to all items related to meta-analysis for reviews that did not conduct meta-analysis for simplicity. This did not affect the overall rating of a review. 1. Research question/inclusion criteria included the components of PICO; 2. Methods were established a priori; 3. Selection of study design; 4. Comprehensive literature search; 5. Study selection in duplicate; 6. Data extraction in duplicate; 7. List of excluded studies with justification; 8. Included studies described in detail; 9. Risk of bias was assessed using satisfactory methods; 10. Sources of funding of trials were reported; 11. Appropriate meta-analysis methods were used (if applicable); 12. Impact of risk of bias was assessed in the meta-analyses (if applicable); 13. Risk of bias was accounted for when interpreting/discussing the results; 14. Heterogeneity explored and/or discussed satisfactorily; 15. Publication bias was assessed (if applicable); 16. Sources of conflicts of interests for the review were reported.

Risk of bias of individual trials assessed when a review (i) did not assess risk of bias, (ii) assessed risk of bias but did not use the Cochrane Risk of Bias tool, or (iii) did not factor in industry sponsorship in their risk of bias assessment.



Supplementary file 4. Trials with industry ties (n = 69).

Trial reference	Antidepressant class	Review it appears on
Chappell AS, Ossanna MJ, Liu-Seifert H, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. Pain 2009;146:253-60. doi:10.1016/j.pain.2009.06.024	SNRI	Ferreira (2021)
Chappell AS, Desaiah D, Liu-Seifert H, et al. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. Pain Pract 2011;11:33-41. doi:10.1111/j.1533-2500.2010.00401.x	SNRI	Ferreira (2021)
Dickens C, Jayson M, Sutton C, Creed F. The relationship between pain and depression in a trial using paroxetine in sufferers of chronic low back pain. Psychosomatics 2000;41:490-9. doi:10.1176/appi.psy.41.6.490	SSRI	Ferreira (2021) Gebhardt (2016)
Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin 2011;27:2361-72. doi:10.1185/03007995.2011.633502	SNRI	Ferreira (2021)
Goodkin K, Gullion CM, Agras WS. A randomized, double-blind, placebo-controlled trial of trazodone hydrochloride in chronic low back pain syndrome. J Clin Psychopharmacol 1990;10:269-78. doi:10.1097/00004714-199008000-00006	SARI	Ferreira (2021)
Jenkins DG, Ebbutt AF, Evans CD. Tofranil in the treatment of low back pain. J Int Med Res 1976;4(Suppl):28-40.	TCA	Ferreira (2021)
Katz J, Pennella-Vaughan J, Hetzel RD, Kanazi GE, Dworkin RH. A randomized, placebo-controlled trial of bupropion sustained release in chronic low back pain. J Pain 2005;6:656-61. doi:10.1016/j.jpain.2005.05.002	NDRI	Ferreira (2021)
Konno S, Oda N, Ochiai T, Alev L. Randomized, Double-blind, Placebo-controlled Phase III Trial of Duloxetine Monotherapy in Japanese Patients With Chronic Low Back Pain. Spine (Phila Pa 1976) 2016;41:1709-17. doi:10.1097/BRS.0000000000001707	SNRI	Ferreira (2021)
Marks DM, Pae CU, Patkar AA. A double-blind, placebo-controlled, parallel-group pilot study of milnacipran for chronic radicular pain (sciatica) associated with lumbosacral disc disease. Prim Care Companion CNS Disord 2014;16:16. doi:10.4088/PCC.14m01658	SNRI	Ferreira (2021) Caruso (2019)
Skljarevski V, Ossanna M, Liu-Seifert H, et al. A double-blind, randomized trial of duloxetine versus placebo in the management of chronic low back pain. Eur J Neurol 2009;16:1041-8. doi:10.1111/j.1468-1331.2009.02648.x	SNRI	Ferreira (2021)
Skljarevski V, Zhang S, Desaiah D, et al. Duloxetine versus placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. J Pain 2010;11:1282-90. doi:10.1016/j.jpain.2010.03.002	SNRI	Ferreira (2021)
Skljarevski V, Desaiah D, Liu-Seifert H, et al. Efficacy and safety of duloxetine in patients with chronic low back pain. Spine (Phila Pa 1976) 2010;35:E578-85. doi:10.1097/BRS.0b013e3181d3cef6	SNRI	Ferreira (2021)
Uchio Y, Enomoto H, Alev L, et al. A randomized, double-blind, placebo-controlled Phase III trial of duloxetine in Japanese patients with knee pain due to osteoarthritis. J Pain Res 2018;11:809-21. doi:10.2147/JPR.S164128	SNRI	Ferreira (2021)
Wang G, Bi L, Li X, et al. Efficacy and safety of duloxetine in Chinese patients with chronic pain due to osteoarthritis: a randomized, double-blind,	SNRI	Ferreira (2021)

placebo-controlled study. Osteoarthritis Cartilage 2017;25:832-8. doi:10.1016/j.joca.2016.12.025		
Tammiala-Salonen, T., & Forssell, H. (1999). Trazodone in burning mouth pain: A placebo-controlled, double-blind study. Journal of Orofacial Pain, 13(2), 83–88.	SARI	Farag (2021)
Forssell H, Tasmuth T, Tenovuo O, Hampf G, Kalso E. Venlafaxine in the treatment of atypical facial pain: a randomized controlled trial. J Orofac Pain 2004;18:131–137.	SNRI	Do (2021)
Foster HE Jr, Hanno PM, Nickel JC, Payne CK, Mayer RD, Burks DA, Yang CC, Chai TC, Kreder KJ, Peters KM, Lukacz ES, FitzGerald MP, Cen L, Landis JR, Propert KJ, Yang W, Kusek JW, Nyberg LM; Interstitial Cystitis Collaborative Research Network. Effect of amitriptyline on symptoms in treatment naïve patients with interstitial cystitis/painful bladder syndrome. J Urol. 2010 May;183(5):1853-8.	TCA	Imamura (2010)
Gao Y, Ning G, Jia WP, Zhou ZG, Xu ZR, Liu ZM, Liu C, Ma JH, Li Q, Cheng LL, Wen CY, Zhang SY, Zhang Q, Desaiah D, Skljarevski V. Duloxetine versus placebo in the treatment of patients with diabetic neuropathic pain in China. Chin Med J 2010;123:3184–92.	SNRI	Caruso (2019)
Vollmer TL, Robinson MJ, Risser RC, Malcolm SK. A randomized, double-blind, placebo-controlled trial of duloxetine for the treatment of pain in patients with multiple sclerosis. Pain Pract 2014;14:732–44.	SNRI	Caruso (2019)
Wernicke JF, Pritchett YL, D'Souza DN, Waninger A, Tran P, Iyengar S, Raskin J. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology 2006;67:1411–20.	SNRI	Caruso (2019)
Yasuda H, Hotta N, Nakao K, Kasuga M, Kashiwagi A. Kawamori R Superiority of duloxetine to placebo in improving diabetic neuropathic pain: results of a randomized controlled trial in Japan. J Diabetes Investig 2011;2:132–9.	SNRI	Caruso (2019)
Raskin J, Pritchett YL, Wang F, D'Souza DN, Waninger AL, Iyengar S, Wernicke JF. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Med 2005;6:346–56.	SNRI	Caruso (2019)
Gao Y, Guo X, Han P, Li Q, Yang G, Qu S, Yue L,Wang CN, Skljarevski V, Duenas H, Raskin J, Gu L. Treatment of patients with diabetic peripheral neuropathic pain in China: a double-blind randomized trial of duloxetine vs. placebo. Int J Clin Pract 2015;69:957–66.	SNRI	Caruso (2019)
Allen R, Sharma U, Barlas S. Clinical experience with desvenlafaxine in treatment of pain associated with diabetic peripheral neuropathy. J Pain Res 2014;7:339–51.	SNRI	Caruso (2019)
Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. PAIN 2005;116:109–18.	SNRI	Caruso (2019)
Kuiken SD, Tytgat GNJ, Boeckxstaens GEE. The selective serotonin reuptake inhibitor fluoxetine does not change rectal sensitivity and symptoms in patients with irritable bowel syndrome: A double-blind, randomized, placebo-controlled study. Clin Gastroenterol Hepatol. 2003;1:219–28.	SSRI	Ford (2019)
Turkington D, Grant JB, Ferrier IN, Rao NS, Linsley KR, Young AH. A randomized controlled trial of fluvoxamine in prostatodynia, a male somatoform pain disorder. Journal of Clinical Psychiatry. 2002;63(9):778-81.	SSRI	Franco (2019)
JapicCTI-101176 2010. https://www.clinicaltrials.jp/cti-user/trial/ShowDirect.jsp?japicId=JapicCTI-101176	Atypical	Welsch (2018)
Miki K, Murakami M, Oka H, Onozawa K, Yoshida S, Osada K. Efficacy of mirtazapine for the treatment of fibromyalgia without concomitant	Atypical	Welsch (2018)

depression: a randomized, double-blind, placebo-controlled phase IIa study in Japan. Pain. 2016;157(9):2089-2096. doi:10.1097/j.pain.0000000000000622		
Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, Goldstein DJ. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis Rheum. 2004 Sep;50(9):2974-84. doi: 10.1002/art.20485.	SNRI	Welsch (2018)b
Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, Wernicke JF. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain. 2005 Dec 15;119(1-3):5-15. doi: 10.1016/j.pain.2005.06.031. Epub 2005 Nov 17.	SNRI	Welsch (2018)b
Arnold LM, Clauw D, Wang F, Ahl J, Gaynor PJ, Wohlreich MM. Flexible dosed duloxetine in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. J Rheumatol. 2010 Dec;37(12):2578-86. doi: 10.3899/jrheum.100365. Epub 2010 Sep 15.	SNRI	Welsch (2018)b
Arnold LM, Gendreau RM, Palmer RH, Gendreau JF, Wang Y. Efficacy and safety of milnacipran 100 mg/day in patients with fibromyalgia: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2010 Sep;62(9):2745-56. doi: 10.1002/art.27559.	SNRI	Welsch (2018)b
Arnold LM, Zhang S, Pangallo BA. Efficacy and safety of duloxetine 30 mg/d in patients with fibromyalgia: a randomized, double-blind, placebo-controlled study. Clin J Pain. 2012 Nov-Dec;28(9):775-81. doi: 10.1097/AJP.0b013e3182510295.	SNRI	Welsch (2018)b
Chappell AS, Bradley LA, Wiltse C, Detke MJ, D'Souza DN, Spaeth M. A six-month double-blind, placebo-controlled, randomized clinical trial of duloxetine for the treatment of fibromyalgia. Int J Gen Med. 2008 Nov 30;1:91-102. doi: 10.2147/ijgm.s3979.	SNRI	Welsch (2018)b
Murakami M, Osada K, Mizuno H, Ochiai T, Alev L, Nishioka K. A randomized, double-blind, placebo-controlled phase III trial of duloxetine in Japanese fibromyalgia patients. Arthritis Res Ther. 2015 Aug 22;17(1):224. doi: 10.1186/s13075-015-0718-y.	SNRI	Welsch (2018)b
Bateman L, Palmer RH, Trugman JM, Lin Y. Results of switching to milnacipran in fibromyalgia patients with an inadequate response to duloxetine: a phase IV pilot study. J Pain Res. 2013 Apr 26;6:311-8. doi: 10.2147/JPR.S43395.	SNRI	Welsch (2018)b
Branco JC, Zachrisson O, Perrot S, Mainguy Y; Multinational Coordinator Study Group. A European multicenter randomized double-blind placebo-controlled monotherapy clinical trial of milnacipran in treatment of fibromyalgia. J Rheumatol. 2010 Apr;37(4):851-9. doi: 10.3899/jrheum.090884.	SNRI	Welsch (2018)b
Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. Clin Ther. 2008 Nov;30(11):1988-2004. doi: 10.1016/j.clinthera.2008.11.009. Erratum in: Clin Ther. 2009 Feb;31(2):446.	SNRI	Welsch (2018)b
Matthey A, Cedraschi C, Piguet V, Besson M, Chabert J, Daali Y, Courvoisier D, Montagne A, Dayer P, Desmeules JA. Dual reuptake inhibitor milnacipran and spinal pain pathways in fibromyalgia patients: a randomized, double-blind, placebo-controlled trial. Pain Physician. 2013 Sep-Oct;16(5):E553-62.	SNRI	Welsch (2018)b

Mease PJ, Clauw DJ, Gendreau RM, Rao SG, Kranzler J, Chen W, Palmer RH. The efficacy and safety of milnacipran for treatment of fibromyalgia. a randomized, double-blind, placebo-controlled trial. J Rheumatol. 2009 Feb;36(2):398-409. doi: 10.3899/jrheum.080734.	SNRI	Welsch (2018)b
Russell JI, Mease PJ, Smith TR, Kajdasz DK, Wohlreich MM, Detke MJ, Walker DJ, Chappell AS, Arnold LM. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. Pain. 2008 Jun;136(3):432-444. doi: 10.1016/j.pain.2008.02.024	SNRI	Welsch (2018)b
Staud_R, Lucas_YE, Price_DD, Robinson_ME. Dual reuptake inhibitor milnacipran and spinal pain pathways in fibromyalgia patients: a randomized, double-blind, placebo-controlled trial. Journal of Pain 2015;16:750-9.	SNRI	Welsch (2018)b
Vitton O, Gendreau M, Gendreau J, Kranzler J, Rao SG. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. Hum Psychopharmacol. 2004 Oct;19 Suppl 1:S27-35. doi: 10.1002/hup.622.	SNRI	Welsch (2018)b
Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine, 60mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. J Clin Psychiatry. 2002;63:308–315	SNRI	Gebhardt (2016)
Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. J Psychiatr Res. 2002;36:383–390.	SNRI	Gebhardt (2016)
Brannan SK, Mallinckrodt CH, Brown EB, et al. Duloxetine 60 mg once-daily in the treatment of painful physical symptoms in patients with major depressive disorder. J Psychiatr Res. 2005;39:43–53	SNRI	Gebhardt (2016)
Robinson M, Oakes TM, Raskin J, et al. Acute and long-term treatment of late-life major depressive disorder: duloxetine versus placebo. Am J Geriatr Psychiatry. 2014;22:34–45.	SNRI	Gebhardt (2016)
Kroenke K, Messina N 3rd, Benattia I, Graepel J, Musgnung J. Venlafaxine extended release in the short-term treatment of depressed and anxious primary care patients with multisomatoform disorder. J Clin Psychiatry. 2006 Jan;67(1):72-80.	SNRI	Gebhardt (2016)
Wohlreich MM, Sullivan MD, Mallinckrodt CH, et al. Duloxetine for the treatment of recurrent major depressive disorder in elderly patients: treatment outcomes in patients with comorbid arthritis. Psychosomatics. 2009;50:402–412.	SNRI	Gebhardt (2016)
Brecht S, Courtecuisse C, Debieuvre C, et al. Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: a randomized controlled trial. J Clin Psychiatry. 2007;68:1707–1716.	SNRI	Gebhardt (2016)
Gaynor PJ, Gopal M, Zheng W, et al. A randomized placebo-controlled trial of duloxetine in patients with major depressive disorder and associated painful physical symptoms. Curr Med Res Opin. 2011;27:1849–1858.	SNRI	Gebhardt (2016)
Gaynor PJ, Gopal M, Zheng W, et al. Duloxetine versus placebo in the treatment of major depressive disorder and associated painful physical symptoms: a replication study. Curr Med Res Opin. 2011;27:1859–1867.	SNRI	Gebhardt (2016)
Clayton AH, Kornstein SG, Dunlop BW, et al. Efficacy and safety of desvenlafaxine 50 mg/d in a randomized, placebo-controlled study of perimenopausal and postmenopausal women with major depressive disorder. J Clin Psychiatry. 2013;74:1010–1017.	SNRI	Gebhardt (2016)
Goldstein DJ, Lu Y, Detke MJ, Wiltse C, Mallinckrodt C, Demitrack MA. Duloxetine in the treatment of depression: a double-blind placebo-	SNRI and SSRI	Gebhardt (2016)

controlled comparison with paroxetine. J Clin Psychopharmacol. 2004 Aug;24(4):389-99.		
Heiligenstein JH, Ware JE Jr, Beusterien KM, et al. Acute effects of fluoxetine versus placebo on functional health and well-being in late-life depression. Int Psychogeriatr. 1995;7(suppl):125–137.	SSRI	Gebhardt (2016)
Zissis NP, Harmoussi S, Vlaikidis N, Mitsikostas D, Thomaidis T, Georgiadis G, Karageorgiou K. A randomized, double-blind, placebo-controlled study of venlafaxine XR in out-patients with tension-type headache. Cephalalgia. 2007 Apr;27(4):315-24. doi: 10.1111/j.1468-2982.2007.01300.x.	SNRI	Banzi (2015) [tension-type headache]
Ozyalcin SN, Talu GK, Kiziltan E, Yucel B, Ertas M, Disci R. The efficacy and safety of venlafaxine in the prophylaxis of migraine. Headache. 2005 Feb;45(2):144-52. doi: 10.1111/j.1526-4610.2005.05029.x.	SNRI	Banzi (2015) [migraine]
Nørregaard J, Volkmann H, Danneskiold-Samstøe B. A randomized controlled trial of citalopram in the treatment of fibromyalgia. Pain. 1995 Jun;61(3):445-449. doi: 10.1016/0304-3959(94)00218-4.	SSRI	Walitt (2015)
Wolfe F, Cathey MA, Hawley DJ. A double-blind placebo controlled trial of fluoxetine in fibromyalgia. Scand J Rheumatol. 1994;23(5):255-9. doi: 10.3109/03009749409103725.	SSRI	Walitt (2015)
Arnold LM, Hess EV, Hudson JI, Welge JA, Berno SE, Keck PE Jr. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. Am J Med. 2002 Feb 15;112(3):191-7. doi: 10.1016/s0002-9343(01)01089-0.	SSRI	Walitt (2015)
GlaxoSmithKline. Treatment of fibromyalgia: a randomized, double blind, placebo-controlled study of paroxetine, a selective serotonin re-uptake inhibitor. Study ID 29060/433. http://www.gsk-clinicalstudyregister.com/.	SSRI	Walitt (2015)
Patkar AA, Masand PS, Krulewicz S, Mannelli P, Peindl K, Beebe KL, Jiang W. A randomized, controlled, trial of controlled release paroxetine in fibromyalgia. Am J Med. 2007 May;120(5):448-54. doi: 10.1016/j.amjmed.2006.06.006.	SSRI	Walitt (2015)
Carette S, Bell MJ, Reynolds WJ, Haraoui B, McCain GA, Bykerk VP, Edworthy SM, Baron M, Koehler BE, Fam AG, et al. Comparison of amitriptyline, cyclobenzaprine, and placebo in the treatment of fibromyalgia. A randomized, double-blind clinical trial. Arthritis Rheum. 1994 Jan;37(1):32-40. doi: 10.1002/art.1780370106.	TCA	Moore (2015)
Doraiswamy PM, Varia I, Hellegers C, Wagner HR, Clary GL, Beyer JL, Newby LK, O'Connor JF, Beebe KL, O'Connor C, Krishnan KR. A randomized controlled trial of paroxetine for noncardiac chest pain. Psychopharmacol Bull. 2006;39(1):15-24.	SSRI	Atluri (2014)
Varia I, Logue E, O'connor C, Newby K, Wagner HR, Davenport C, Rathey K, Krishnan KR. Randomized trial of sertraline in patients with unexplained chest pain of noncardiac origin. Am Heart J. 2000 Sep;140(3):367-72. doi: 10.1067/mhj.2000.108514.	SSRI	Atluri (2014)
Spinhoven P, Van der Does AJ, Van Dijk E, et al. Heart-focused anxiety as a mediating variable in the treatment of noncardiac chest pain by cognitive-behavioral therapy and paroxetine. J Psychosom Res 2010; 69:227–35.	SSRI	Atluri (2014)
Ash G, Dickens CM, Creed FH, Jayson MI, Tomenson B. The effects of dothiepin on subjects with rheumatoid arthritis and depression. Rheumatology (Oxford). 1999 Oct;38(10):959-67. doi: 10.1093/rheumatology/38.10.959.	TCA	Richards (1999)
Hannonen P, Malminiemi K, Yli-Kerttula U, Isomeri R, Roponen P. A randomized, double-blind, placebo-controlled study of moclobemide and amitriptyline in the treatment of fibromyalgia in females without	MAOi	Tort (2012)

psychiatric disorder. Br J Rheumatol. 1998 Dec;37(12):1279-86. doi: 10.1093/rheumatology/37.12.1279.		

Supplementary file 5. GRADE criteria and ratings for each review.

GRADE criterion	Description
Limitations in study design	Risk of bias assessment for randomised controlled trials was determined independently by two reviewers using the Cochrane risk of bias tool which considers random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases e.g. pharmaceutical company sponsorship. A trial was considered unclear risk when ***two or more*** items were judged as unclear risk. A trial was considered high risk when one or more items were judged as high risk. In cases where more than one trial contributed to an effect estimate, when more than ***50% of participants in the comparison were from trials at high overall risk of bias*** we downgraded one level for limitations in study design. ***Trials with unclear risk or high risk of bias were downgraded.***
Inconsistency	We downgraded ***one level*** if we identified important and non-explained heterogeneity in the ***I^2 test (> 50%)***. This criterion was not applicable where only one trial was included in a comparison. We did not downgrade for inconsistency if point estimates across studies were similar.
Indirectness	We downgraded for ***one level if <50% of participants in the comparison*** was considered to be similar (e.g. had the same condition). We did not downgrade for differences in interventions and comparators as we grouped interventions according to antidepressant class and all included trials had placebo as the comparator.
Imprecision	**Dichotomous outcomes:** A) When the total number of events was < 300, we downgraded the evidence by one level. OR B) When the 95% confidence interval around the pooled or best estimate of effect included ***appreciable benefit and harm,*** we downgraded by one level. **Continuous outcomes:** A) When the total sample size was < 400, we downgraded the evidence by one level. OR B) When the 95% confidence interval included appreciable benefit ***and*** harm, we downgraded the evidence by one level.
Publication bias	Assessed using funnel plot analysis/ Egger's regression test for ten or more studies. If this information was provided by the review, we adopted these results. When there were <10 studies in a comparison, this criterion was not applicable.

Outcome	Point estimate (95% CI)	Trials (participants)	GRADE (assessment by the review)	Comments	GRADE (our assessment)	Comments
Wang (2022) – postoperative pain						
SNRI – Pain 24h (continuous)	-7.3 (-12.9 to -1.7)	16 (1128)	Moderate	**Risk of bias:** 9/16 (58%) trials at low RoB **Inconsistency:** I2 = 93% *(downgraded)* **Indirectness:** 13/16 (81%) had major surgery **Imprecision:** >400 participants **Publication bias:** No evidence	Moderate	No changes required
SSRI – Pain 24h (continuous)	0 (-7.1 to 7.1)	1 (114)	Not reported	GRADE was done combining data from SNRI and SSRI trials	Moderate	**Risk of bias:** 1/1 (100%) trial at low RoB **Inconsistency:** N/A (1 trial only – homogenous population) **Indirectness:** Only one trial, homogenous population **Imprecision:** n <400 *(downgraded)* **Publication bias:** N/A
Roberts (2022) – Aromatase inhibitor therapy-induced pain in breast cancer						
SNRI – Pain (continuous)	-6.3 (-9.7 to -2.9)	1 (255)	Not reported	Review did not report certainty of evidence for this outcome and comparison	Low	**Risk of bias:** High *(downgraded)* **Inconsistency:** N/A (1 trial only) **Indirectness:** N/A (1 trial only – homogenous population) **Imprecision:** n <400 *(downgraded)* **Publication bias:** N/A
Ferreira (2021) Back pain						
SNRI – Pain (continuous)	-5.3 (-7.3 to -3.3)	4 (1415)	Moderate	**Risk of bias:** 4/4 trials at high RoB (downgraded) **Inconsistency:** I2 = 0% **Indirectness:** N/A **Imprecision:** not downgraded **Publication bias:** N/A	Moderate	No changes required
SSRI – Pain (continuous)	1.5 (-5.4 to 8.5)	3 (170)	Low	**Risk of bias:** 3/3 trials at high RoB (downgraded)	Low	**Risk of bias:** High *(downgraded)*

				Inconsistency: 0% **Indirectness:** N/A **Imprecision:** not downgraded **Publication bias:** downgraded (small study effect)		**Inconsistency:** I^2 = 0% (not downgraded) **Indirectness:** Not downgraded **Imprecision:** n <400 *(downgraded)* **Publication bias:** N/A The certainty of evidence remains low and consistent what the review provided even if applying different criteria for imprecision (based on sample size) and publication bias (not assessing it as < 10 trials)
NDRI – Pain (continuous)	-1 (-12.2 to 10.2)	1 (44)	Low	**Risk of bias:** 1/1 trial at high RoB (downgraded) **Inconsistency:** 0% **Indirectness:** N/A **Imprecision:** not downgraded **Publication bias:** downgraded (small study effect)	Low	**Risk of bias:** 1/1 trial at high RoB (downgraded) **Inconsistency:** 0% **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A The certainty of evidence remains low and consistent what the review provided even if applying different criteria for imprecision (based on sample size) and publication bias (not assessing it as < 10 trials)
SARI – Pain (continuous)	-5.4 (-22.9 to 12.1)	1 (40)	Low	**Risk of bias:** 1/1 trial at high RoB (downgraded) **Inconsistency:** 0% **Indirectness:** N/A **Imprecision:** not downgraded **Publication bias:** downgraded (small study effect)	Low	**Risk of bias:** 1/1 trial at high RoB (downgraded) **Inconsistency:** 0% **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A The certainty of evidence remains low and consistent what the review provided even if applying different

						criteria for imprecision (based on sample size) and publication bias (not assessing it as < 10 trials)
Tetracyclics – Pain (continuous)	-4.5 (-20.4 to 11.4)	1 (34)	Low	**Risk of bias:** 1/1 trial at high RoB (downgraded) **Inconsistency:** 0% **Indirectness:** N/A **Imprecision:** not downgraded **Publication bias:** downgraded (small study effect)	Low	**Risk of bias:** 1/1 trial at high RoB (downgraded) **Inconsistency:** 0% **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A The certainty of evidence remains low and consistent what the review provided even if applying different criteria for imprecision (based on sample size) and publication bias (not assessing it as < 10 trials)
TCA – Pain (continuous)	-10.3 (-18.8 to -1.9)	7 (591)	Very low	**Risk of bias:** 5/7 trials at high RoB (downgraded) **Inconsistency:** I2 = 92% (downgraded) **Indirectness:** N/A **Imprecision:** not downgraded **Publication bias:** downgraded (small study effect)	Very low	**Risk of bias:** 5/7 trials at high RoB (downgraded) **Inconsistency:** I2 = 92% (downgraded) **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A The certainty of evidence remains very low and consistent what the review provided even if applying different criteria for imprecision (based on sample size) and publication bias (not assessing it as < 10 trials)
Ferreira (2021) Knee osteoarthritis						
SNRI – Pain (continuous)	-9.6 (-12.3 to -6.9)	8 (1941)	Low	**Risk of bias:** 6/8 trials at high RoB (downgraded) **Inconsistency:** I2 = 68% (downgraded)	Low	No changes required

				Indirectness: N/A **Imprecision:** not downgraded **Publication bias:** not downgraded		
Ferreira (2021) – Sciatica						
SNRI – Pain (continuous	-17.8 (-45.5 to 9.9)	3 (96)	Very low	**Risk of bias:** 3/3 trials at high RoB (downgraded) **Inconsistency:** I2=77% (downgraded) **Indirectness:** N/A **Imprecision:** 95% CI includes appreciable benefit (downgraded) **Publication bias:** Downgraded (small study effect)	Very low	**Risk of bias:** 3/3 trials at high RoB (downgraded) **Inconsistency:** I2=77% (downgraded) **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A Applying the criteria from this overview would not change the certainty evidence, which is very low. The only difference is that we did not downgrade for publication bias.
TCA – Pain (continuous)	-16 (-31.5 to -0.4)	2 (114)	Very low	**Risk of bias:** 2/2 trials with at least 2 unclear bias domains (downgraded) **Inconsistency:** I2 = 71% (downgraded) **Indirectness:** N/A **Imprecision:** 95% CI includes appreciable benefit (downgraded) **Publication bias:** Downgraded (small study effect)	Very low	**Risk of bias:** 2/2 trials with at least 2 unclear bias domains (downgraded) **Inconsistency:** I2 = 71% (downgraded) **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A Applying the criteria from this overview would not change the certainty evidence, which is very low. The only difference is that we did not downgrade for publication bias.
Farag (2021) Burning mouth syndrome						
SARI – Pain (continuous)	-1.6 (-6.8 to 3.6)	1 (37)	Low	**Risk of bias:** 1/1 trial with unclear attrition and reporting bias; and industry tes (downgraded) **Inconsistency:** N/A	Low	**Risk of bias:** 1/1 trials with at least 2 unclear bias domains (downgraded) **Inconsistency:** N/A **Indirectness:** N/A

				Indirectness: N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A		**Imprecision:** n < 400 (downgraded) **Publication bias:** N/A The one included trial for this outcome has 2 'unclear' bias domains* and the outcome has a sample size <400. Our criteria for determining the certainty of evidence agrees with that reported by the review: low certainty evidence. *Upon reassessing bias, we classified randomisation, allocation concealment and blinding of personnel and outcomes as unclear as well. The study also appeared to have been conducted by industry (it was the pharmaceutical company that created and managed the randomisation schedule), which further strengthens our decision to downgrade for bias.
Ford (2021) Functional dyspepsia						
TCA – Pain (continuous)	-2.3 (-7.3 to 2.8)	3 (293)	Not reported	Review did not report certainty of evidence for this outcome and comparison	Moderate	**Risk of bias:** all trials were at low RoB (not downgraded) **Inconsistency:** $I^2 = 0\%$ **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A
SSRI – Pain (continuous)	1.3 (-5.9 to 8.5)	2 (291)	Not reported	Review did not report certainty of evidence for this outcome and comparison	Low	**Risk of bias:** all trials were at low RoB (not downgraded) **Inconsistency:** $I^2 = 54\%$ (downgraded) **Indirectness:** N/A **Imprecision:** n < 400 (downgraded)

						Publication bias: N/A
Atypical – Pain (continuous)	1.7 (-21.2 to 24.6)	1 (34)	Not reported	Review did not report certainty of evidence for this outcome and comparison	Low	**Risk of bias:** 1/1 trial with >2 unclear domains (downgraded) **Inconsistency:** N/A **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A
Do (2021) - Atypical chronic orofacial pain						
TCA – Pain (continuous)	MD: -15.7 (-32.4 to 1.1)	1 (42)	Not reported	Review did not report certainty of evidence for this outcome and comparison	Low	**Risk of bias:** 1/1 trial with >2 unclear domains (downgraded) **Inconsistency:** N/A **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A
SNRI – Pain (continuous)	-13 (-26.1 to 0.1)	1 (36)	Not reported	Review did not report certainty of evidence	Low	**Risk of bias:** 1/1 trial at high RoB (downgraded) **Inconsistency:** N/A **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A In the review, the trial is rated as low risk of bias, however it is unclear how allocation concealment was ensured, and some participants were excluded from the analysis. The study also appeared to have been conducted by industry (it was the pharmaceutical company that created and managed the randomisation schedule), which further strengthens our decision to downgrade for bias.
Imamura (2020) – Bladder pain syndrome						

TCA – Pain (continuous)	-12.7 (-33.1 to 7.6)	2 (279)	Low	**Risk of bias:** 1/2 trials at high risk of bias (downgraded) **Inconsistency:** Not downgraded **Indirectness:** N/A **Imprecision:** downgraded **Publication bias:** N/A	Very low	**Risk of bias**: 1/2 (50%) studies at high risk of bias. Pain outcome in Foster 2010 not analysed using intention to treat principles. (downgraded) **Inconsistency:** I2 = 89% (downgraded) **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** Not applicable
Ford (2019) Irritable bowel syndrome						
TCA – Abdominal pain not improving (dichotomous)	0.6 (0.4 to 0.8)	4 (184)	Not reported	Review did not report certainty of evidence	Low	**Risk of bias:** 3/4 trials at high RoB (downgraded) **Inconsistency:** I2=35% (not downgraded) **Indirectness:** N/A **Imprecision:** < 300 events (downgraded) **Publication bias:** N/A
SSRI – Abdominal pain not improving (dichotomous)	0.6 (0.3 to 1.3)	3 (167)	Not reported	Review did not report certainty of evidence	Very low	**Risk of bias:** 3/3 trials at high RoB (downgraded) **Inconsistency:** I2=86% (downgraded) **Indirectness:** N/A **Imprecision:** < 300 events (downgraded) **Publication bias:** N/A
Caruso (2019) – Neuropathic pain						
SNRI - Pain intensity (continuous)	-6.8 (-8.7 to -4.8)	12 (3010)	Not reported	Review did not report certainty of evidence	Moderate	**Risk of bias**: >50% trials at high RoB (downgraded) **Inconsistency**: I2 = 60% but point estimates across studies were similar in magnitude and direction (not downgraded)

						Indirectness: We did not downgrade for indirectness as all conditions included in the review fit in the current classification of neuropathic pain (Scholz et al. Pain. 2019 Jan; 160(1): 53–59) **Imprecision:** n > 400 (not downgraded) **Publication bias:** No evidence upon forest plot inspection in RevMan
Perez-Lopes (2019) – Vulvodynia						
TCA – Pain (continuous)	8.2 (-11.8 to 28.2)	1 (58)	Not reported	Review did not report certainty of evidence	Low	**Risk of bias**: Trial at high risk of bias (attrition bias) (downgraded) **Inconsistency**: N/A **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A
Christophorou (2019) – Acute oral mucositis						
TCA – Pain (continuous)	-44 (-67 to -21)	1 (140)	Not reported	Review did not report certainty of evidence for this outcome (pain in people with acute oral mucositis)	Low	**Risk of bias**: Trial at high risk of bias (attrition bias) (downgraded) **Inconsistency**: N/A **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A
Franco (2019) – Chronic prostatitis						
SSRI – Pain (continuous)	-45 (-77.6 to -12.4)	1 (42)	Not reported	Review did not report certainty of evidence for this outcome and comparison	Low	**Risk of bias**: Trial at high risk of bias (attrition bias and industry funding) (downgraded) **Inconsistency**: N/A **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A
Welsch (2018a) – Fibromyalgia (SNRI)						

SNRI – 50% pain reduction (dichotomous)	1.4 (1.3 to 1.6)	15 (6918)	Low	**Risk of bias**: Not downgraded **Inconsistency**: Not downgraded **Indirectness:** Participants with major medical diseases and mental disorders except major depression excluded in > 50% of studies (downgraded) **Imprecision:** n < 400 (downgraded) **Publication bias:** Industry funding (downgraded)	Moderate	**Risk of bias:** 13/15 studies at high RoB per the review; the other 2 studies at low RoB were sponsored by pharmaceutical companies, which is a criterion to downgrade the evidence in our overview (downgraded) **Inconsistency:** I2 = 0% **Indirectness:** N/A **Imprecision:** n > 300 events (not downgraded) **Publication bias:** Not downgraded. We did not downgrade for indirectness as all trials recruited a similar population (despite some trials excluding people with certain comorbidities as noted by the review authors. Our assessment also differed from the authors on the publication bias domain. There is no evidence of publication bias upon funnel plot inspection, and we considered industry sponsorship to be part of the risk of bias domain, hence we did not downgrade for publication bias. In addition to the inspection of funnel plot which did not indicate the presence of publication bias, we note that the Cochrane review only found two trials awaiting classification, one that recruited 10 participants (completed in 2019) and another one

						whose recruitment status (planned recruitment: 150 participants) is unknown. We did not consider these two trials to provide compelling evidence of publication bias that would justify downgrading the evidence.
Welsch (2018b) – Fibromyalgia (Atypical)						
Atypical – Pain (dichotomous) 50% pain reduction	1.3 (0.9 to 1.9)	3 (591)	Low	**Risk of bias:** 169/591 (28.5%) of participants from studies at high RoB **Inconsistency:** I2 = 0% **Indirectness:** Downgraded as participants with inflammatory arthritis and depressive symptoms were excluded from >50% of trials **Imprecision:** Not downgraded **Publication bias:** Downgraded	Low	**Risk of bias:** All studies at high risk of bias (downgraded). **Inconsistency:** I2 = 0% **Indirectness:** Not downgraded **Imprecision:** < 300 events (downgraded) **Publication bias:** N/A We changed the risk of bias rating for risk of bias as we considered all studies to be at high risk of bias, including Miki 2016 (considered to be low risk of bias by the review) as it was an industry-funded trial
Jackson (2017) – Chronic tension type headache						
TCA - Headache frequency (days per month - continuous)	-4.8 (-6.6 to -3)	4 (197)	High	An explanation on the rationale for the GRADE rating was not provided	Low	**Risk of bias:** All trials providing data for the 8-week time point are at high RoB (downgraded) **Inconsistency:** I2 = 0% **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A
Gebhardt (2016) - Depression and comorbid chronic pain						
SNRI – Pain (continuous)	-6.4 (-7.7 to -5.1)	11 (3520)	Not reported	Review did not report certainty of evidence	Low	**Risk of bias:** 11/11 trials at high RoB (downgraded). **Inconsistency:** I2 = 0%

						Indirectness: Most studies conducted in participants with major depressive disorder and pain (not downgraded) **Imprecision:** n > 400 (not downgraded) **Publication bias:** Funnel plot suggests presence of publication bias (downgraded)
SSRI – Pain (continuous)	-5.9 (-10.1 to -1.7)	4 (947)	Not reported	Review did not report certainty of evidence	Low	**Risk of bias:** All trials at high RoB (downgraded) **Inconsistency:** I2 = 54% **Indirectness:** Most studies conducted in participants with major depressive disorder and pain (not downgraded) **Imprecision:** n >400 **Publication bias:** N/A
Alviar (2016) – Phantom limb pain						
TCA – Pain (continuous)	0 (-17.6 to 17.6)	1 (39)	Not reported	Review did not report certainty of evidence	Low	**Risk of bias:** Bias assessment in the review indicates that the trial is at low risk of bias. However, the trial made some ad hoc post-randomisation exclusions (downgraded) **Inconsistency:** N/A **Indirectness:** N/A **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A
Moore (2015) – Fibromyalgia						
TCA – 50% pain reduction (dichotomous)	2.1 (1.2 to 3.6)	4 (275)	Very low	The only information provided in the review to justify the "very low" classification was 'the small number of studies and participants'	Very low	**Risk of bias:** All trials are at high RoB (downgraded) **Inconsistency:** I2 = 56% (downgraded) **Indirectness:** N/A **Imprecision:** N < 300 events (downgraded) **Publication bias:** N/A

Banzi (2015) – Chronic migraine						
SNRI – Migraine Frequency (continuous)	-1.4 (-2.8 to -0.1)	1 (49)	Low	**Risk of bias:** Trial is at high RoB (downgraded) **Inconsistency:** Not downgraded **Indirectness:** Not downgraded **Imprecision:** downgraded **Publication bias:** N/A	Low	**Risk of bias:** Trial is at high RoB (downgraded) **Inconsistency:** I2 = 0% **Indirectness:** Not downgraded **Imprecision:** N < 300 events (downgraded) **Publication bias:** N/A
SSRI – Migraine Frequency (continuous)	-1.4 (-2.7 to -0.1)	1 (33)	Low	**Risk of bias:** All trials are at high RoB (downgraded) **Inconsistency:** Not downgraded **Indirectness:** Not downgraded **Imprecision:** downgraded **Publication bias:** N/A	Low	**Risk of bias:** All trials are at high RoB (downgraded) **Inconsistency:** I2 = 0% **Indirectness:** Not downgraded **Imprecision:** N < 300 events (downgraded) **Publication bias:** N/A
Banzi (2015) – Chronic tension-type headache						
SNRI – Headache frequency (continuous)	-2.3 (-7.3 to 2.7)	1 (59)	Low	**Risk of bias:** Downgraded **Inconsistency:** Not downgraded **Indirectness:** Not downgraded **Imprecision:** Downgraded **Publication bias:** Not downgraded	Low	**Risk of bias:** 1/1 trial at high risk of bias (downgraded) **Inconsistency:** Not downgraded **Indirectness:** Not downgraded **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A
SSRI - Headache frequency (continuous)	-0.2 (-3.9 to 3.5)	1 (68)	Low	**Risk of bias:** Downgraded **Inconsistency:** Not downgraded **Indirectness:** Not downgraded **Imprecision:** Downgraded **Publication bias:** Not downgraded	Low	**Risk of bias:** 1/1 trial at high risk of bias (downgraded) **Inconsistency:** Not downgraded **Indirectness:** Not downgraded **Imprecision:** n < 400 (downgraded) **Publication bias:** N/A
Finnerup (2015) – Neuropathic pain						
TCA - Pain reduction (30% or 50%)	3.4 (2.1 to 5.5)	15 (948)	Moderate	**Risk of bias:** 67% of trials had at one concern that would increase risk of bias (downgraded) **Inconsistency:** High statistical heterogeneity noted, but authors did not	Low	**Risk of bias:** All trials are at high RoB (downgraded) **Inconsistency:** I2 = 72% but point estimates across studies were similar in magnitude and direction (not downgraded)

				downgrade as most studies had effects in the same direction (favouring TCAs) **Indirectness:** Authors noted that included trials included a range of different conditions, but certainty of evidence was not downgraded for indirectness **Imprecision:** Authors noted *moderate* imprecision, with 33% of trials having NNTs with '*very wide 95% CIs*', but unsure **Publication bias:** Not assessed for this comparison individually. However, funnel plots containing data from all trials included in the review revealed significant publication bias. This review also upgraded the certainty of evidence for magnitude of effect size.		**Indirectness:** We did not downgrade for indirectness as all conditions included in the review fit in the current classification of neuropathic pain (*Scholz et al. Pain. 2019 Jan; 160(1): 53–59*) **Imprecision:** N > 300 events (not downgraded) **Publication bias:** Funnel plot suggests publication bias (downgraded)
Walitt (2015) - Fibromyalgia						
SSRI – Pain reduction (30%)	RR: 1.4 (1 to 2)	6 (343)	Very low	**Risk of bias:** 50% of participants from studies at high RoB (downgraded) **Inconsistency:** Not downgraded **Indirectness:** Downgraded as some trials did not include participants with inflammatory rheumatic diseases and/or depressive disorders **Imprecision:** Total number of participants <400 (downgraded) **Publication bias:** Not downgraded	Low	**Risk of bias:** All studies at high RoB (downgraded) **Inconsistency:** I^2 = 4% (Not downgraded) **Indirectness:** We did not downgrade for indirectness as all trials recruited a similar population (despite some trials excluding people with certain comorbidities as noted by the review authors. (not downgraded) **Imprecision:** Total number of participants <300 events (downgraded) **Publication bias:** Not downgraded
Atluri (2014) – Non-cardiac chest pain						

SSRI – Pain (continuous)	-3.8 (-9.8 to 2.3)	4 (184)	Moderate	**Risk of bias:** Not downgraded **Inconsistency:** Not downgraded **Indirectness:** Not downgraded **Imprecision:** Downgraded **Publication bias:** Not downgraded	Low	**Risk of bias:** ¾ trials at high risk of bias **Inconsistency:** I2 = 0% **Indirectness:** N/A **Imprecision:** N < 400 participants (downgraded) **Publication bias:** N/A
Cheong (2014) – Chronic pelvic pain						
SSRI – Pain (continuous)	0 (-6 to 6)	1 (23)	Low	Review did not report certainty of evidence for this outcome and comparison	Low	**Risk of bias:** Trial at high risk of bias (downgraded) **Inconsistency:** N/A **Indirectness:** N/A **Imprecision:** N < 400 participants (downgraded) **Publication bias:** N/A
Richards (2011) – Rheumatoid arthritis						
TCA – Pain > 6 weeks (mixed outcome measures)	Meta-analysis could not be conducted. Conflicting evidence of benefit of antidepressants versus placebo	7 (482)	Very low	**Risk of bias:** 6/7 trials at high risk of bias (downgraded) **Inconsistency:** N/A (data not pooled) **Indirectness:** different drugs, populations and most trials were conducted in the pre-biologics era, which is now standard of care for rheumatoid arthritis) **Imprecision:** trials with wide 95% CIs (downgrade) **Publication bias:** N/A	Very low	No changes required.
Tort (2012) – Fibromyalgia						
MAOI – Pain (continuous)	MD: -14.5 (-27.1 to -2)	2 (121)	Low	**Risk of bias:** Both trials at high risk of bias (downgraded) **Inconsistency:** Not downgraded **Indirectness:** N/A **Imprecision:** both trials with n < 50 participants per arm **Publication bias:** N/A	Very low	**Risk of bias:** Both trials at high risk of bias (downgraded) **Inconsistency:** I2 = 58% (downgraded) **Indirectness:** N/A **Imprecision:** N < 400 participants (downgraded) **Publication bias:** N/A

Supplementary file 6. Description of how data for our primary outcome (pain) from each review were handled

Wang (2022)

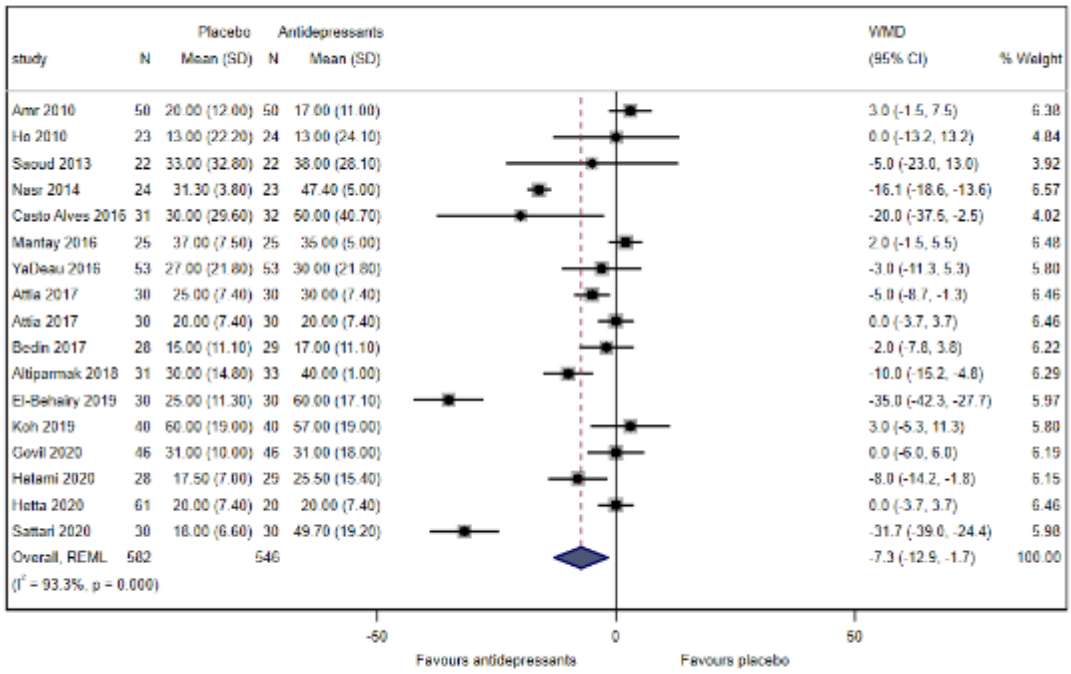
Eligible studies
All studies included in the 24h follow-up were included.

Data extracted from review or re-analysed?
Data were extracted from the review

Data conversions
Pain outcomes were converted to a 0-100 scale

Meta-analysis procedures
We used data from figure 2a, which presents data from SNRIs and SSRIs separately.

Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator



Other follow-up time-points presented in the review
Data from other follow-up times presented in the review largely agreed with the time point that we chose presented in the manuscript. Data can be found in Figure 2b in the review, and eFigures 1-5.

<u>SNRIs</u>
Pain at ≤ 6 hours
MD (95% CI): -8.2 (-11.5 to -4.9); 14 trials (n = 942)
Pain at 12 hours
MD (95% CI): -6.8. -12.8 to -0.7); 11 trials (n = 755)
Pain at 48 hours
MD (95% CI): -7.8 (-13 to -2.7); 12 trials (n = 821)
Pain at 10 days-1 month
MD (95% CI): -8.2 (-12.5 to -4); 6 trials (n = 453)
Pain at 6 months:

MD (95% CI): -13 (-18.7 to -7.3); 2 trials (n = 147)

SSRIs

Pain at ≤ 6 hours

MD (95% CI): -1.5 (-9.9 to 6.9); 2 trials (n = 1126)

Pain at 48 hours

MD (95% CI): 0 (-5.7 to 5.7); 1 trial (n = 114)

Pain at 10 days-1 month

MD (95% CI): -0.4 (-4.5 to 3.7); 1 trial (n = 361)

Pain at 6 months

MD (95% CI): -1.4 (-6.6 to 3.8); 1 trial (n = 361)

Roberts (2022)

Eligible studies Only one study included in the review was eligible 1. Henry NL, Unger JM, Schott AF, Fehrenbacher L, Flynn PJ, Prow DM, et al. Randomized, multicenter, placebo-controlled clinical trial of duloxetine versus placebo for aromatase inhibitor-associated arthralgias in early-stage breast cancer: SWOG S1202. Journal of Clinical Oncology 2018;36(4):326-32.
Data extracted from review or re-analysed? Data were extracted from the review.
Data used Pain outcomes were converted to a 0-100 scale The following data were used **Data:** *average pain* outcome **Means**: change scores from baseline to week 12 in supplementary file 3 **Standard deviations**: are from baseline scores in supplementary file 1
Meta-analysis procedures No meta-analysis was conducted since there was only one study available. Data were extracted from Analysis 2.1. Comparison 2: Treatment of aromatase inhibitor-induced musculoskeletal symptoms (AIMSS), Outcome 1: Pain

Ferreira (2021)

Eligible studies
All studies included in the 3-month follow-up (end of treatment) were included.

Data extracted from review or re-analysed?
Data were extracted from the review

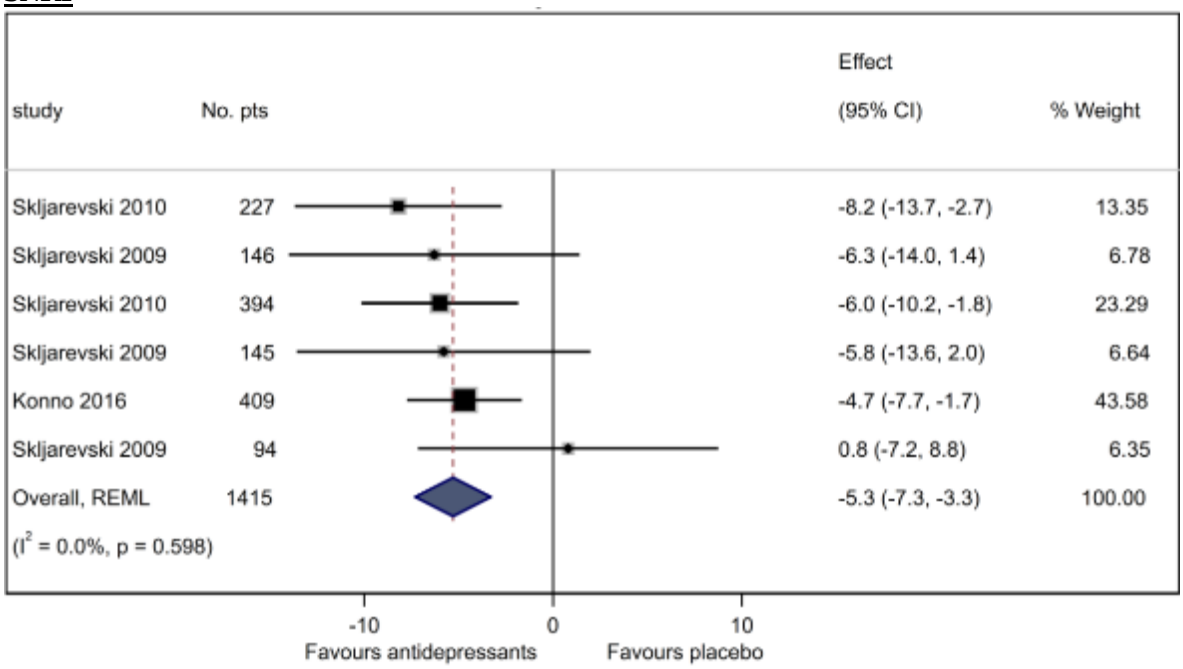
Data used
No data conversions were required

Meta-analysis procedures
No changes were made to the meta-analyses presented in the review.

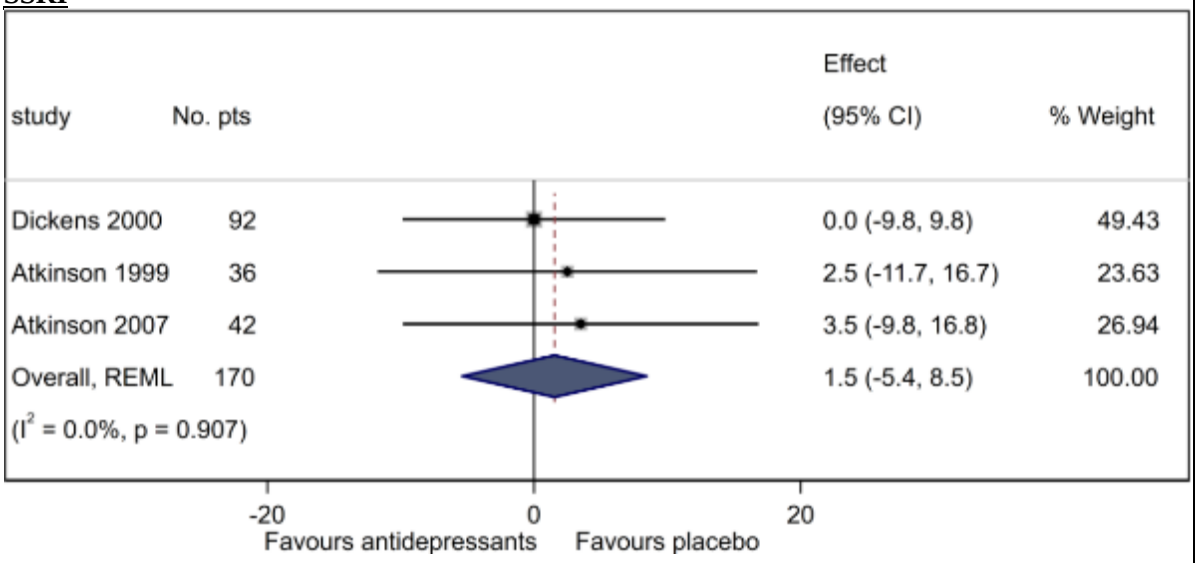
Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator

BACK PAIN

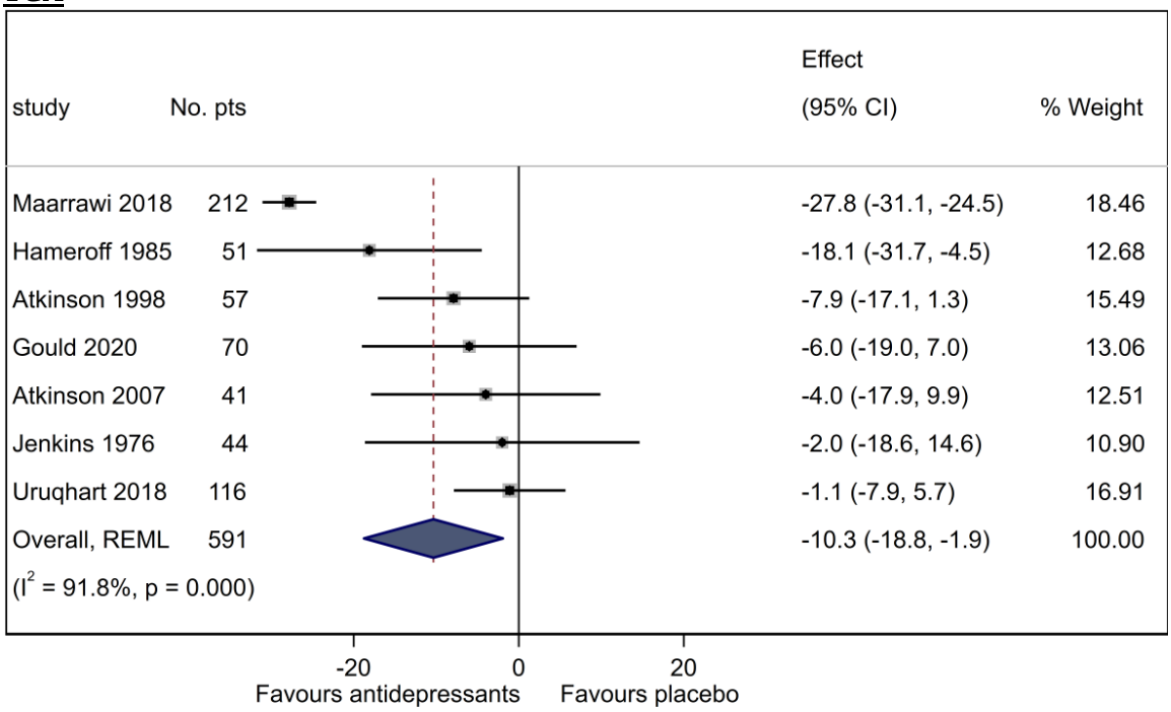
SNRI



SSRI

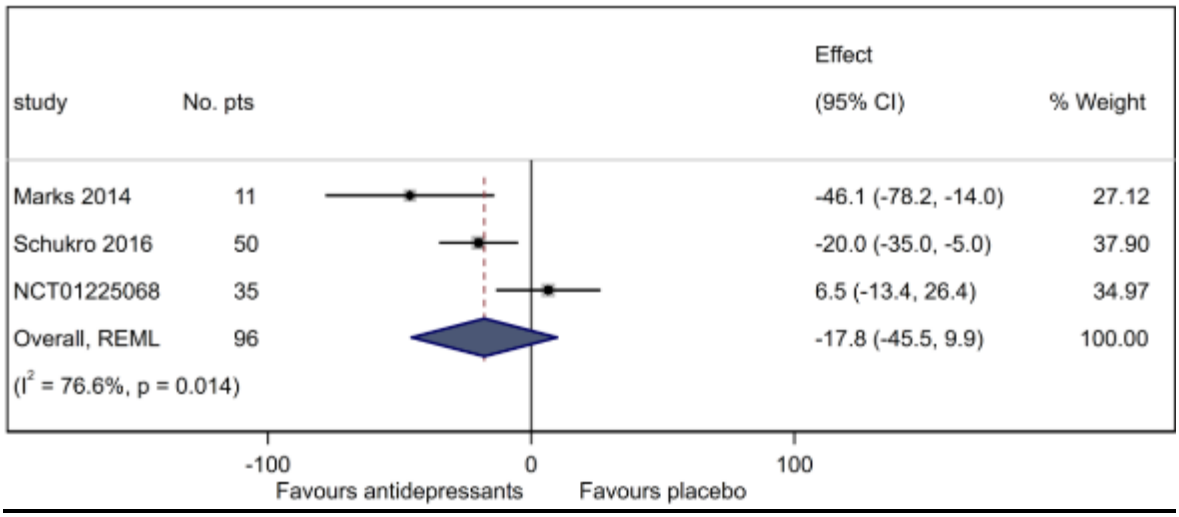


TCA

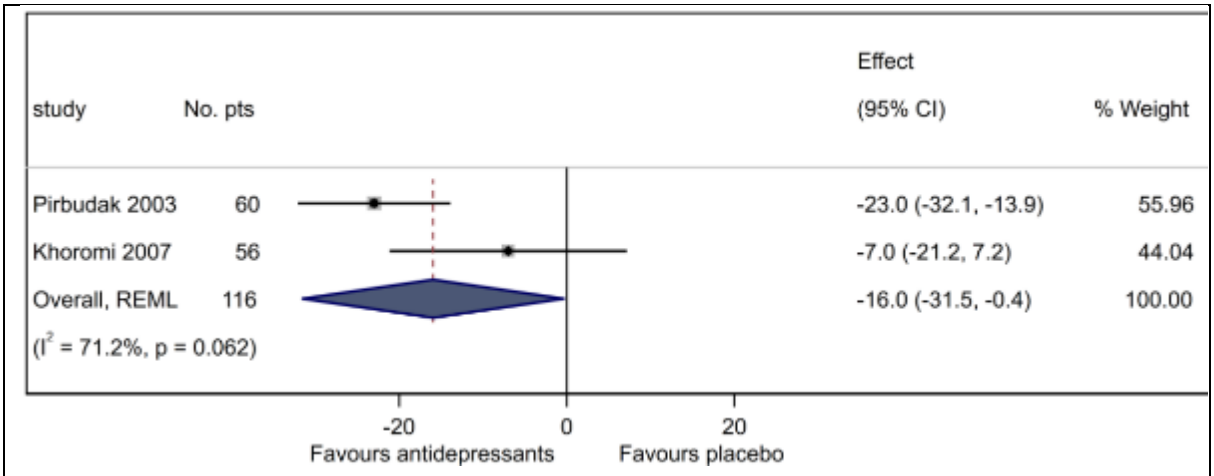


SCIATICA

SNRI

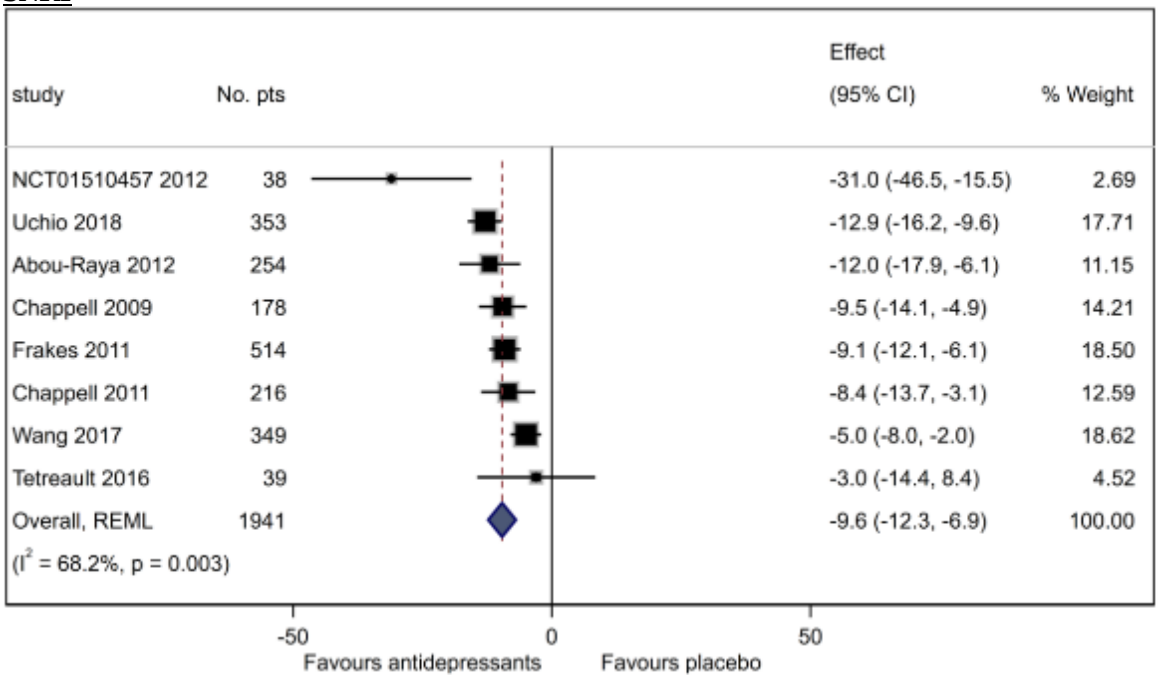


TCA



KNEE OSTEOARTHRITIS

SNRI



Other follow-up time-points presented in the review

BACK PAIN

SNRI

Pain ≤2 weeks

MD (95% CI): −3.67 (−5.91 to −1.42); 3 trials (n = 1068)

SSRI

Pain ≤2 weeks

MD (95% CI): −4.30 (−14.06 to 5.46); 1 trial (n = 92)

TCA

Pain ≤2 weeks

MD (95% CI): −0.86 (−5.40 to 3.68); 3 trials (n = 145)

Pain 3-12 months

MD (95% CI): −7.81 (−15.63 to 0.01); 1 trial (n = 118)

SCIATICA
SNRI
Pain ≤2 weeks
MD (95% CI): −18.60 (−31.87 to −5.33); 1 trial (n = 50)

TCA
Pain ≤2 weeks
MD (95% CI): −7.55 (−18.25 to 3.15); 2 trials (n = 94)

Pain 3-12 months
MD (95% CI): −27.0 (−36.11 to −17.89); 1 trial (n = 60)

OSTEOARTHRITIS
SNRI
Pain ≤2 weeks
MD (95% CI): −4.66 (−6.28 to −3.04); 4 trials (n = 1328)

Farag (2021)

Eligible studies Only one study included in the review was eligible 1. Tammiala-Salonen T, Forssell H. Trazodone in burning mouth pain: A placebo-controlled, double-blind study. Journal of Orofacial Pain, 1999;13(2):83–88.
Data extracted from review or re-analysed? Data were extracted from the review.
Data used • Pain scores were converted to a 0-100 scale
Meta-analysis procedures Meta-analysis was not performed as only one study was included in the comparison. In the review, authors re-analysed the data from the trial because results reported in the trial did not take into account a significant baseline difference between the groups on the primary outcome.

Ford (2021)

Eligible studies

Randomised-placebo controlled trials included in the review that assessed pain as an outcome were considered.

1. van Kerkhoven LA, Laheij RJ, Aparicio N, et al. Effect of the antidepressant venlafaxine in functional dyspepsia: a randomized, double-blind, placebo-controlled trial. Clin Gastroenterol Hepatol 2008;**6**:746-52.
2. Braak B, Klooker TK, Wouters MM, et al. Randomised clinical trial: the effects of amitriptyline on drinking capacity and symptoms in patients with functional dyspepsia, a double-blind placebo-controlled study. Aliment Pharmacol Ther 2011;**34**:638-48.
3. Tan VP, Cheung TK, Wong WM, et al. Treatment of functional dyspepsia with sertraline: A double-blind randomized placebo-controlled pilot study. World J Gastroenterol 2012;**18**:6127-33.
4. Talley NJ, Locke GR, Saito YA, et al. Effect of amitriptyline and escitalopram on functional dyspepsia: A multi-center, randomized, controlled study. Gastroenterology 2015;149:340-49.
5. Tack J, Ly HG, Carbone F, et al. Mirtazapine in patients with functional dyspepsia patients and weight loss. Clin Gastroenterol Hepatol 2016;**14**:385-92.
6. Cheong PK, Ford AC, Cheung CKY, et al. Low-dose imipramine for refractory functional dyspepsia: A randomised, double-blind, placebo-controlled trial. The lancet Gastroenterology & hepatology 2018;**3**:837-44
7. Kaosombatwattana U, Pongprasobchai S, Limsrivilai J, et al. Efficacy and safety of nortriptyline in functional dyspepsia in Asians: A randomized double-blind placebo-controlled trial. J Gastroenterol Hepatol 2018;**33**:411-17.

However, van Kerkhoven (2008) and Kaosombatwattana (2018) did not measure pain outcomes and were therefore not included in our analysis

Data extracted from review or re-analysed?
Data were re-analysed as described below.

Data used
We extracted the following data from each study:

SSRI

- **Talley 2015 (SSRI)**: We extracted post-treatment scores for upper abdominal pain (0-3) (Table 3)
- **Tan 2012**: Pain was measured with SF-36's bodily pain subscale (0-100).

TCA

- **Braak 2011**: Study measures lower and upper abdominal pain (scale: 0-5). We extracted data for upper abdominal pain as it was the most common measure extracted by other studies within this comparison. Data were extracted from Figure 6 using Webplotdigitizer.
- **Talley 2015 (TCA)**: We extracted post-treatment scores for upper abdominal pain (0-3) (Table 3)
- **Tack 2016**: We extracted data for epigastric pain (Supplementary Figure 2c). We extracted values for the 8-week follow-up (end of treatment).

Atypical

- **Cheong 2018**: We extracted data for epigastric pain (Table 2) at 12 weeks (end of treatment)

Extracted data were converted to a 0-100 scale

Meta-analysis procedures

Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator.

We fit two separate (SSRI and TCA; there was only one study for atypical antidepressants thus data were not pooled) models. We had to estimate standard deviations for a series of studies. Details are below:

SSRI

- **Talley 2015 (SSRI)**: Data from this study consisted of post-treatment means and 95% CI. We entered that data into Revman calculator to estimate standard deviations for each treatment. Data are shown in the forest plot below.
- **Tan 2012**: A common SD was estimated with the Cochrane calculator using p-value, t-value, sample size (between-groups tab); as higher scores in the SF36 subscales represent better health states, final mean values were reported as negative to ensure direction of effect is consistent with the meaning of the scale.

TCA

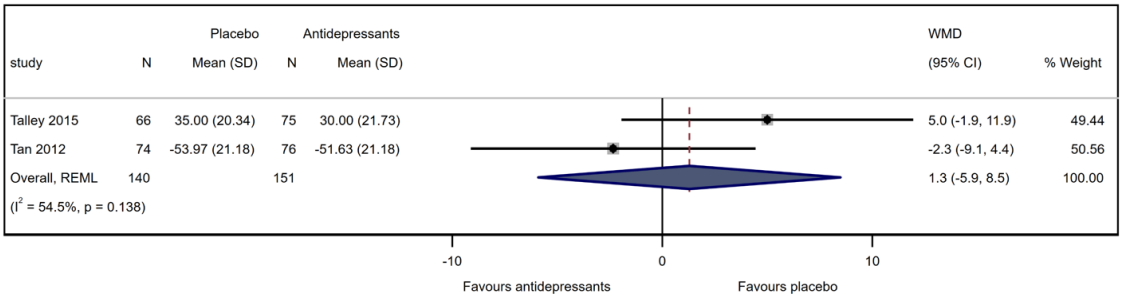
- **Braak 2011**: We estimated the standard deviation using the reported standard error (SE = 0.3 for both treatment arms). We used the Cochrane calculator (within-group tabs) for this procedure.
- **Talley 2015 (TCA)**: Data from this study consisted of post-treatment means and 95% CI. We entered that data into the calculator in Revman to estimate standard deviations for each treatment. Data are shown in the forest plot below.
- **Tack 2016**: The team agreed that the variability measures shown in Supplementary Figure 2c were standard errors instead of standard deviations. SEs were thus converted into SDs using the Cochrane calculator.

Atypical

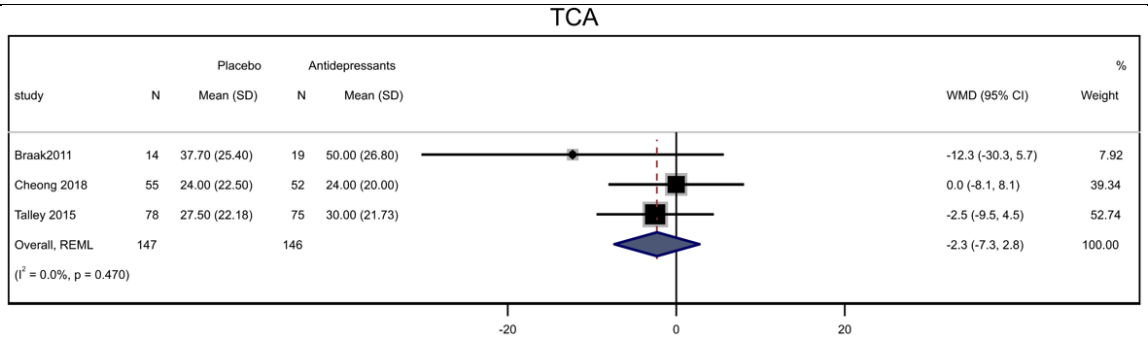
- **Cheong 2018**: Data were extracted table 2. No specific procedures were required.

FOREST PLOTS

SSRI



TCA



These findings are in contrast with the findings from the review, which showed TCAs to significantly reduce "symptoms of functional dyspepsia". We highlight here that we specifically extracted ***pain*** outcomes, whereas "***symptoms of functional dyspepsia***" could include pain but also more common symptoms in this condition such as post-prandial fullness and early satiety.

Do (2021)

Eligible studies

Two studies included in the review were included in this overview.

1. Agius AM, Jones NS, Muscat R. A randomized controlled trial comparing the efficacy of low-dose amitriptyline, amitriptyline with pindolol and surrogate placebo in the treatment of chronic tension-type facial pain. Rhinology 2013;51:143–153.
2. Forssell H, Tasmuth T, Tenovuo O, Hampf G, Kalso E. Venlafaxine in the treatment of atypical facial pain: a randomized controlled trial. J Orofac Pain 2004;18:131–137.

Data extracted from review or re-analysed?

Data were re-analysed from the two included trials.

Data used

- Pain outcomes from Agius 2013 were converted from 0-10 to a 0-100 scale.
- Data from Agius were extracted from Table 6 in the trial
- Data from Forssell 2004 were extracted from Figure 2 at 4 weeks (end of treatment)

Meta-analysis procedures

No meta-analysis was performed as only one trial of TCA and SNRI were found.

Imamura (2020)

Eligible studies

Two studies were included

- Foster HE Jr, Hanno_PM, Nickel_JC, Payne_CK, Mayer_RD, Burks_DA, et al. Effect of amitriptyline on symptoms in treatment naive patients with interstitial cystitis/painful bladder syndrome. Journal of Urology 2010;183(5):1853-8.
- van Ophoven A, Hertle L. Safety and efficacy of amitriptyline for the treatment of interstitial cystitis: results of a placebo-controlled trial and a prospective long-term observational study (Abstract number 109). Neurourology and Urodynamics 2005;24(5/6):572-3.

Data extracted from review or re-analysed?

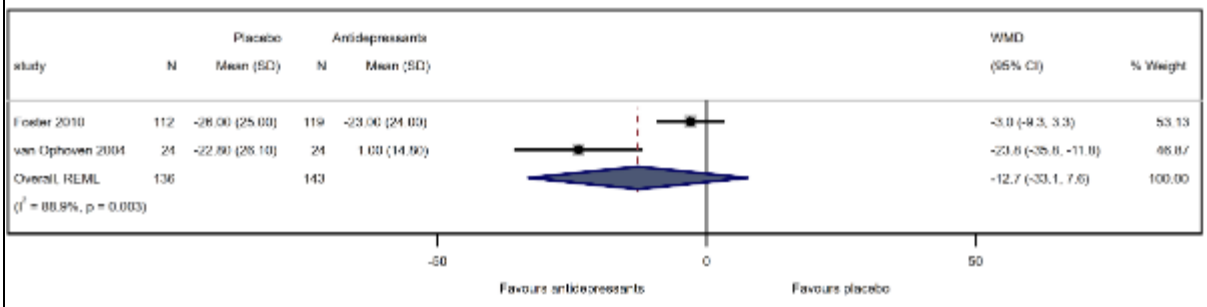
Data were re-analysed from the two included trials.

Data used

- We extracted data from the pairwise meta-analysis column in Table 5 ("Results of the meta-analyses for pain").

Meta-analysis procedures

- Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator.
- To investigate heterogeneity of the pairwise comparison, we requested the data from the two eligible trials so we could pool the data ourselves.
- Data sent by the authors matched the data from Table 5 (see forest plot below)
- Forest plot revealed high heterogeneity (89%). That information was used to downgrade the evidence for inconsistency.



Ford (2019)

Eligible studies

Eligible trials were those included in the comparison antidepressants versus placebo on abdominal pain (7 trials)

1. Heefner JD, Wilder RM, Wilson ID. Irritable colon and depression. Psychosomatics. 1978 Sep;19(9):540-7.
2. Vij JC, Jiloha RC, Kumar N, et al. Effect of antidepressant drug (doxepin) on irritable bowel syndrome patients. Indian J Psychiatry. 1991;33:243–6.
3. Vahedi H, Merat S, Rashidioon A, Ghoddoosi A, Malekzadeh R. The effect of fluoxetine in patients with pain and constipation-predominant irritable bowel syndrome: a double-blind randomized-controlled study. Aliment Pharmacol Ther. 2005 Sep 1;22(5):381-5.
4. Ghadir MR, Habibinejad H, Heidari A, et al. Doxepin is more effective than nortriptyline and placebo for the treatment of diarrhea-predominant irritable bowel syndrome: a randomized triple-blind placebo-controlled trial. Tehran Univ Med J. 2011;69:352–8.
5. Kuiken SD, Tytgat GN, Boeckxstaens GE. The selective serotonin reuptake inhibitor fluoxetine does not change rectal sensitivity and symptoms in patients with irritable bowel syndrome: a double blind, randomized, placebo-controlled study. Clin Gastroenterol Hepatol. 2003 May;1(3):219-28.
6. Tabas G, Beaves M, Wang J, Friday P, Mardini H, Arnold G. Paroxetine to treat irritable bowel syndrome not responding to high-fiber diet: a double-blind, placebo-controlled trial. Am J Gastroenterol. 2004 May;99(5):914-20.
7. Vahedi H, Merat S, Momtahen S, Kazzazi AS, Ghaffari N, Olfati G, Malekzadeh R. Clinical trial: the effect of amitriptyline in patients with diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2008 Apr;27(8):678-84.

Data extracted from review or re-analysed?

Data were extracted from the review.

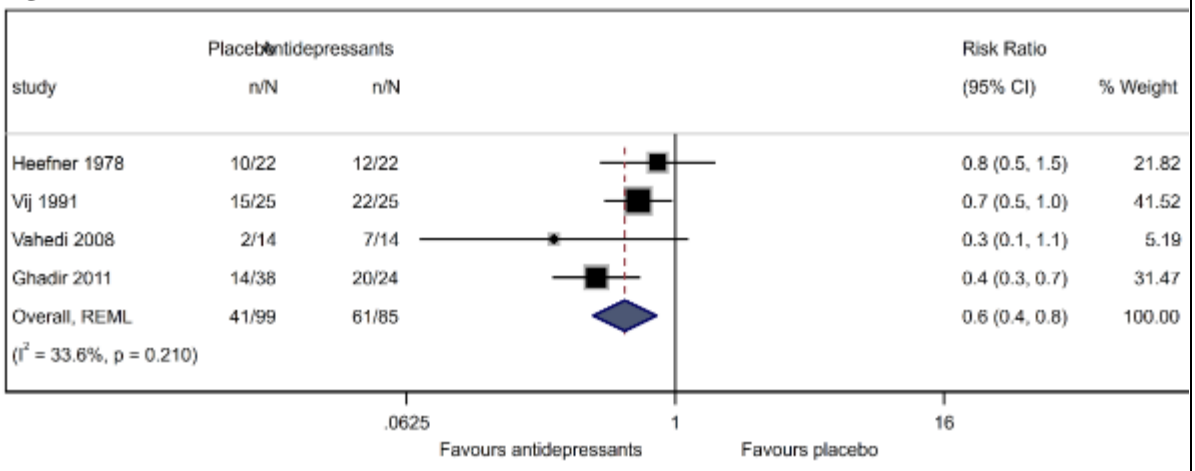
Data used

- We used data presented in Figure 3 (forest plot of antidepressant versus placebo on abdominal pain)
- No conversions were required

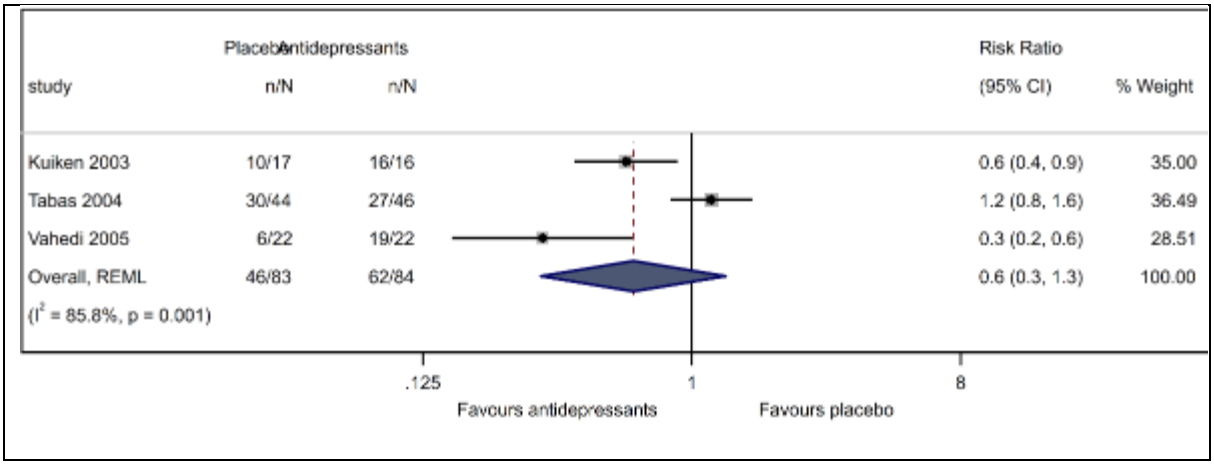
Meta-analysis procedures

Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator.

TCA



SSRI


Placebo
Antidepressants
Risk Ratio
study
n/N
n/N
(95% CI)
% Weight
Kuiken 2003
10/17
16/16
0.6 (0.4, 0.9)
35.00
Tabas 2004
30/44
27/46
1.2 (0.8, 1.6)
36.49
Vahedi 2005
6/22
19/22
0.3 (0.2, 0.6)
28.51
Overall, REML
46/83
62/84
0.6 (0.3, 1.3)
100.00
(I² = 85.8%, p = 0.001)
.125
1
8
Favours antidepressants
Favours placebo

Caruso (2019)

Eligible studies

This review included trials investigating the efficacy of SNRI and TCA antidepressants. Compared to the Finnerup (2015) review, also included in our overview and that also had data for SNRI and TCA antidepressants, Caruso (2019) had more trials of SNRI (12 vs 10) and fewer trials of TCA (6 vs 14 [15 comparisons]). For that reason, we only present data for SNRI antidepressants for the Caruso (2019) review.

Upon closer examination of this review, we identified that some SNRI trials were conducted in populations not typically considered to have neuropathic pain. These were:

- Hyer L, Scott C, Mullen CM, McKenzie LC, Robinson JS. Randomized double-blind placebo trial of duloxetine in perioperative spine patients. J Opioid Manag 2015;11:147–55.
- Forssell H, Tasmuth T, Tenovuo O, Hampf G, Kalso E. Venlafaxine in the treatment of atypical facial pain: a randomized controlled trial. J Orofac Pain 2004;18:131–7.

Hyer (2015) investigated the use of duloxetine in patients undergoing spine surgery. Back pain is typically classified as musculoskeletal pain unless there is evidence of a neuropathic pain component.[1] There is no evidence from the Hyer (2015) trial that the participants had neuropathic pain.

The Forssell (2004) trial investigated the efficacy of venlafaxine for orofacial pain. Orofacial pain is classified as distinct type of chronic pain.[1]

REFERENCE

1. Treede RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. Pain. 2015 Jun;156(6):1003-1007.

Other information:
The clinical trial registry NCT01777581 included in Caruso (2019) is published as a complete study as the following reference:

- Marks DM, Pae CU, Patkar AA. A double-blind, placebo-controlled, parallel-group pilot study of milnacipran for chronic radicular pain (sciatica) associated with lumbosacral disc disease. Prim Care Companion CNS Disord. 2014 Aug 14;16(4):10.4088/PCC.14m01658.

Data extracted from review or re-analysed?
Data were re-analysed from all the eligible trials.

Data used
Data from 12 trials were used in our overview (see references below).

References:

1. Allen R, Sharma U, Barlas S. Clinical experience with desvenlafaxine in treatment of pain associated with diabetic peripheral neuropathy. J Pain Res. 2014 Jun 23;7:339-51.
2. Gao Y, Ning G, Jia WP, Zhou ZG, Xu ZR, Liu ZM, Liu C, Ma JH, Li Q, Cheng LL, Wen CY, Zhang SY, Zhang Q, Desaiah D, Skljarevski V. Duloxetine versus placebo in the treatment of patients with diabetic neuropathic pain in China. Chin Med J (Engl). 2010 Nov;123(22):3184-92.
3. Gao Y, Guo X, Han P, Li Q, Yang G, Qu S, Yue L, Wang CN, Skljarevski V, Dueñas H, Raskin J, Gu L. Treatment of patients with diabetic peripheral neuropathic pain in China: a double-blind randomised trial of duloxetine vs. placebo. Int J Clin Pract. 2015 Sep;69(9):957-66.

4. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain. 2005 Jul;116(1-2):109-18. doi: 10.1016/j.pain.2005.03.029.
5. Marks DM, Pae CU, Patkar AA. A double-blind, placebo-controlled, parallel-group pilot study of milnacipran for chronic radicular pain (sciatica) associated with lumbosacral disc disease. Prim Care Companion CNS Disord. 2014 Aug 14;16(4):10.4088/PCC.14m01658.
6. Raskin J, Pritchett YL, Wang F, D'Souza DN, Waninger AL, Iyengar S, Wernicke JF. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Med. 2005 Sep-Oct;6(5):346-56.
7. Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. Pain. 2004 Aug;110(3):697-706. doi: 10.1016/j.pain.2004.05.010. Erratum in: Pain. 2005 Jan;113(1-2):248.
8. Simpson DA. Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. J Clin Neuromuscul Dis. 2001 Dec;3(2):53-62. doi: 10.1097/00131402-200112000-00002.
9. Vollmer TL, Robinson MJ, Risser RC, Malcolm SK. A randomized, double-blind, placebo-controlled trial of duloxetine for the treatment of pain in patients with multiple sclerosis. Pain Pract. 2014 Nov;14(8):732-44. doi: 10.1111/papr.12127.
10. Wernicke JF, Pritchett YL, D'Souza DN, Waninger A, Tran P, Iyengar S, Raskin J. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology. 2006 Oct 24;67(8):1411-20. doi: 10.1212/01.wnl.0000240225.04000.1a.
11. Yasuda H, Hotta N, Nakao K, Kasuga M, Kashiwagi A, Kawamori R. Superiority of duloxetine to placebo in improving diabetic neuropathic pain: Results of a randomized controlled trial in Japan. J Diabetes Investig. 2011 Apr 7;2(2):132-9. doi: 10.1111/j.2040-1124.2010.00073.x.
12. Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Fadul CE, Knox C, Le-Lindqwister N, Gilman PB, Shapiro CL; Alliance for Clinical Trials in Oncology. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA. 2013 Apr 3;309(13):1359-67. doi: 10.1001/jama.2013.2813.

Meta-analysis procedures

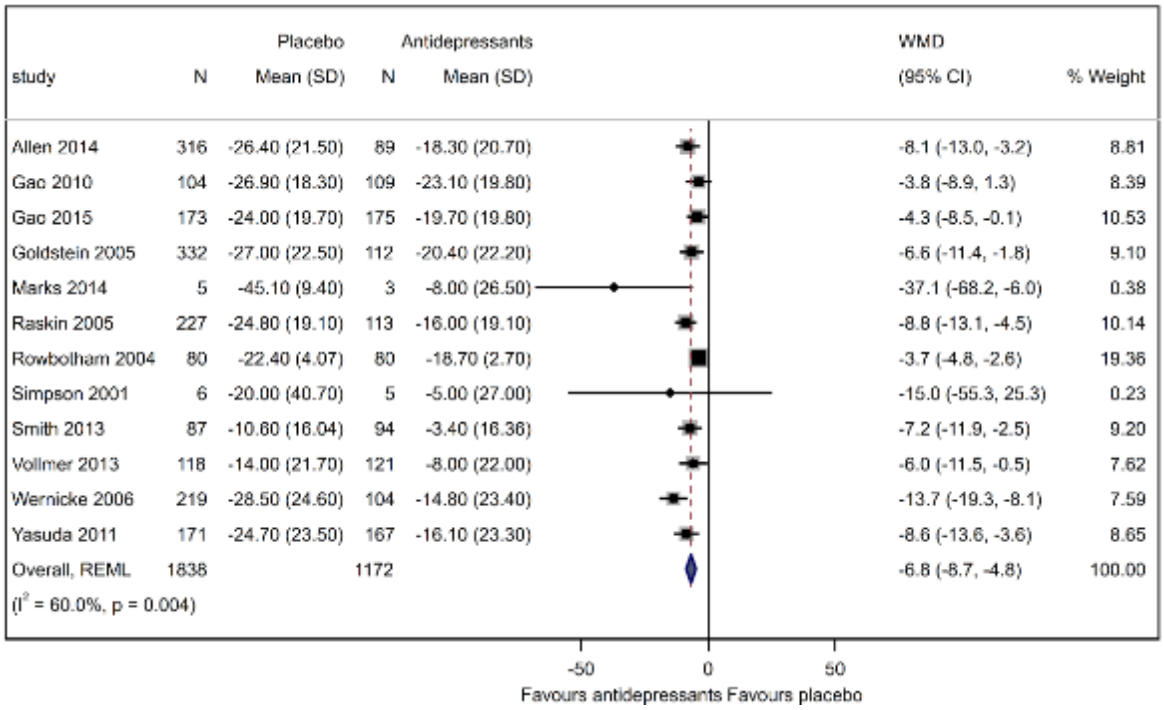
We were able to check the data pooled by the author (Supplementary file – "pain (continuous)" outcome against the data from each eligible study. All studies measured pain using similar outcome measures but in different scales (either 0-10 or 0-100).

Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator.

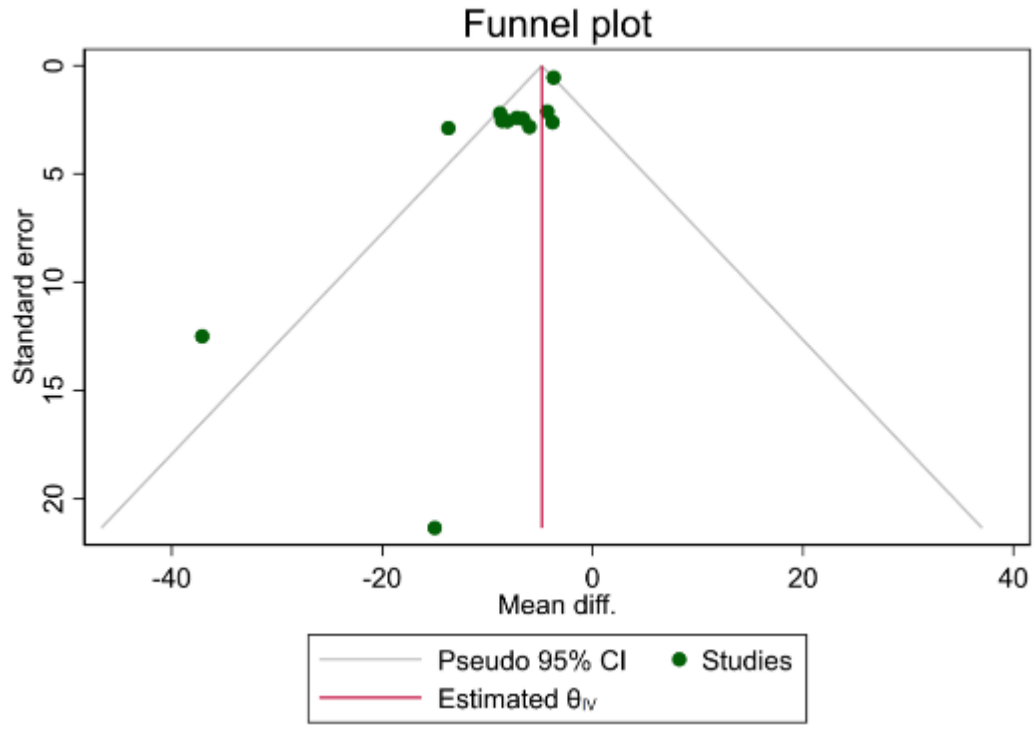
A few minor discrepancies in the data extracted by the review in relation to the data reported by the trials were noted. They made no difference in the overall interpretation of the findings. They are:

- Gao 2010: Estimated standard deviations reported by the review (using SE values reported in the trial) for the duloxetine (1.93) and placebo (1.87) do not match those generated by the Cochrane SD calculator of 1.83 (18.3 on a 0-100 scale) and 1.98 (19.8 on a 0-100 scale). We have therefore used our estimated SDs.
- Smith 2013: SDs were imputed, but values do not appear to be right. Using the within group 95%CI provided by the study and estimated SDs with the Cochrane SD calculator yield different SD values for both groups. Using within-group 95%Cis reported in the trial results in a SD (duloxetine) of 1.60 and SD (placebo) of 1.63. The Cochrane SD imputation tool results in an estimated SD of 1.63. These SDs reproduce the between-group mean differences and 95% CI reported in the paper (-0.72; 95%CI -1.19 to -0.25). Sample sizes were also slightly different in our interpretation; 87 in the duloxetine group (vs 88) and 94

(vs 99) in the placebo group. That is because 1 and 5 participants in the duloxetine and placebo group, respectively, were excluded from the primary analysis due to lack of data.



There was no evidence of publication bias per our observation of the funnel plot (see below)



Perez-Lopez (2019)

Eligible studies

One study included in the review was eligible:

- Foster DC, Kotok MB, Huang LS, Watts A, Oakes D, Howard FM, Poleshuck EL, Stodgell CJ, Dworkin RH. Oral desipramine and topical lidocaine for vulvodynia: a randomized controlled trial. Obstet Gynecol. 2010 Sep;116(3):583-593

Data extracted from review or re-analysed?

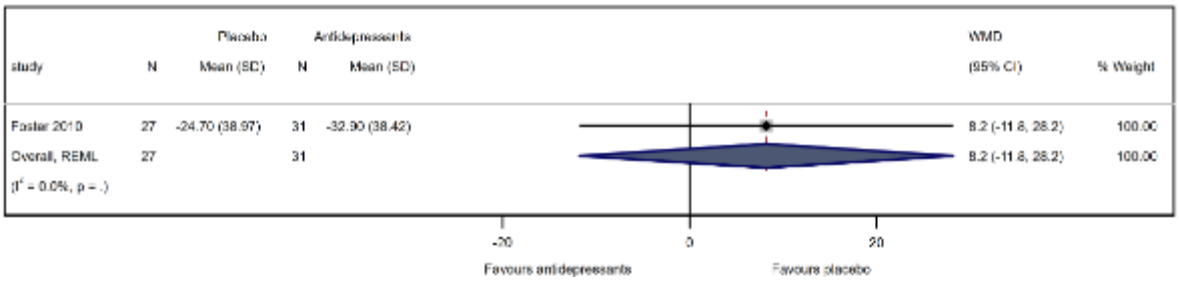
Data were re-analysed from the eligible trial.

Data used

- We used data from the desipramine tablets (n = 27) and placebo groups (n = 31) only. We extracted data from the primary outcome (Tampon test) at week 12 (end of treatment) in Figure 2A.
- Data were on a 0-100 scale therefore did not require any conversions.

Meta-analysis procedures

- Meta-analysis was not performed as only one study was eligible.
- We used Webplotdigitizer (https://apps.automeris.io/wpd/) to obtain the values for the point estimates and standard errors for each group at week 12 in Figure 2A.
- We used standard errors to estimate SDs using the RevMan calculator



Christophorou (2019)

Eligible studies Only one trial in the review was eligible: 1. Leenstra JL, Miller RC, Qin R, Martenson JA, Dornfeld KJ, Bearden JD, Puri DR, Stella PJ, Mazurczak MA, Klish MD, Novotny PJ, Foote RL, Loprinzi CL. Doxepin rinse versus placebo in the treatment of acute oral mucositis pain in patients receiving head and neck radiotherapy with or without chemotherapy: a phase III, randomized, double-blind trial (NCCTG-N09C6 [Alliance]). J Clin Oncol. 2014 May 20;32(15):1571-7.
Data extracted from review or re-analysed? Data were re-analysed from the eligible trial.
Data used • We used data from the area under the curve (AUC) for the mean mouth and throat pain reduction between the groups reported as the study's primary outcome and primary endpoint (before crossover). Sample size available for the primary analysis was 140 (69 for the doxepin arm, 71 for the placebo arm). • Data were reported on a 0-10 scale and was therefore converted to a 0-100 scale.
Meta-analysis procedures • No specific meta-analysis procedures were required

Franco (2019)

Eligible studies

Only one trial from this review was included:

1. Turkington D, Grant JB, Ferrier IN, Rao NS, Linsley KR, Young AH. A randomized controlled trial of fluvoxamine in prostatodynia, a male somatoform pain disorder. J Clin Psychiatry. 2002 Sep;63(9):778-81.

Other trials of antidepressants were not included for the following reasons:

- Lee 2005: The outcome measures used in the trial did not measure pain specifically or separately from other symptoms.
- Giannantoni 2014: The outcome measures used in the trial did not measure pain specifically or separately from other symptoms.
- Zhang 2017: Did not compare antidepressants (duloxetine and sertraline) to placebo and the outcome measures used in the trial did not measure pain specifically or separately from other symptoms.

References:

1. Giannantoni A, Porena M, Gubbiotti M, Maddonni S, Di Stasi SM. The efficacy and safety of duloxetine in a multidrug regimen for chronic prostatitis/chronic pelvic pain syndrome. Urology. 2014 Feb;83(2):400-5.
2. Lee RA, West RM, Wilson JD. The response to sertraline in men with chronic pelvic pain syndrome. Sex Transm Infect. 2005 Apr;81(2):147-9.
3. Zhang M, Li H, Ji Z, Dong D, Yan S. Clinical study of duloxetine hydrochloride combined with doxazosin for the treatment of pain disorder in chronic prostatitis/chronic pelvic pain syndrome: An observational study. Medicine (Baltimore). 2017 Mar;96(10):e6243.

Data extracted from review or re-analysed?

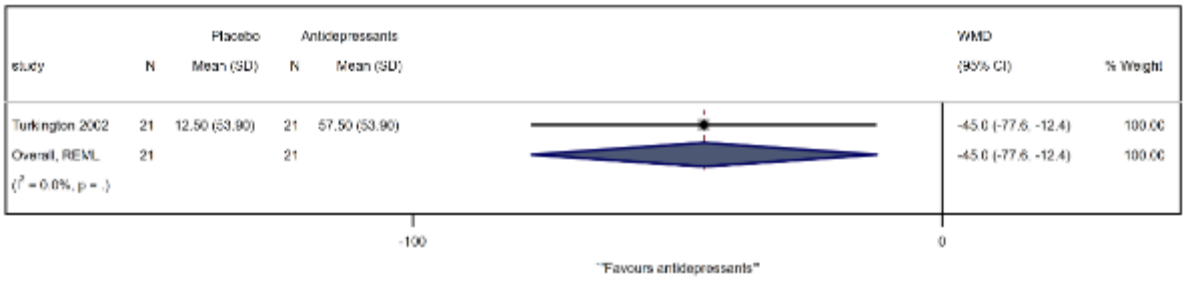
Data were re-analysed from the eligible trial.

Data used

- We used the p-value for the between-group difference (in Table 3) to calculate the t-value. The t-value was then used to calculate the standard error which, in combination with each group's sample size, was used to estimate a common standard deviation of 5.3916312
- Post-treatment means for each group are displayed in the study's Table 3.
- Data were converted from a 0-10 to 0-100 scale

Meta-analysis procedures

- Meta-analysis was not performed as only one study was included. A forest plot is reported below with the data converted into a 0-100 scale.



Welsch (2018a) - SNRI

Eligible studies

All studies included in the review were eligible for this overview

Data used

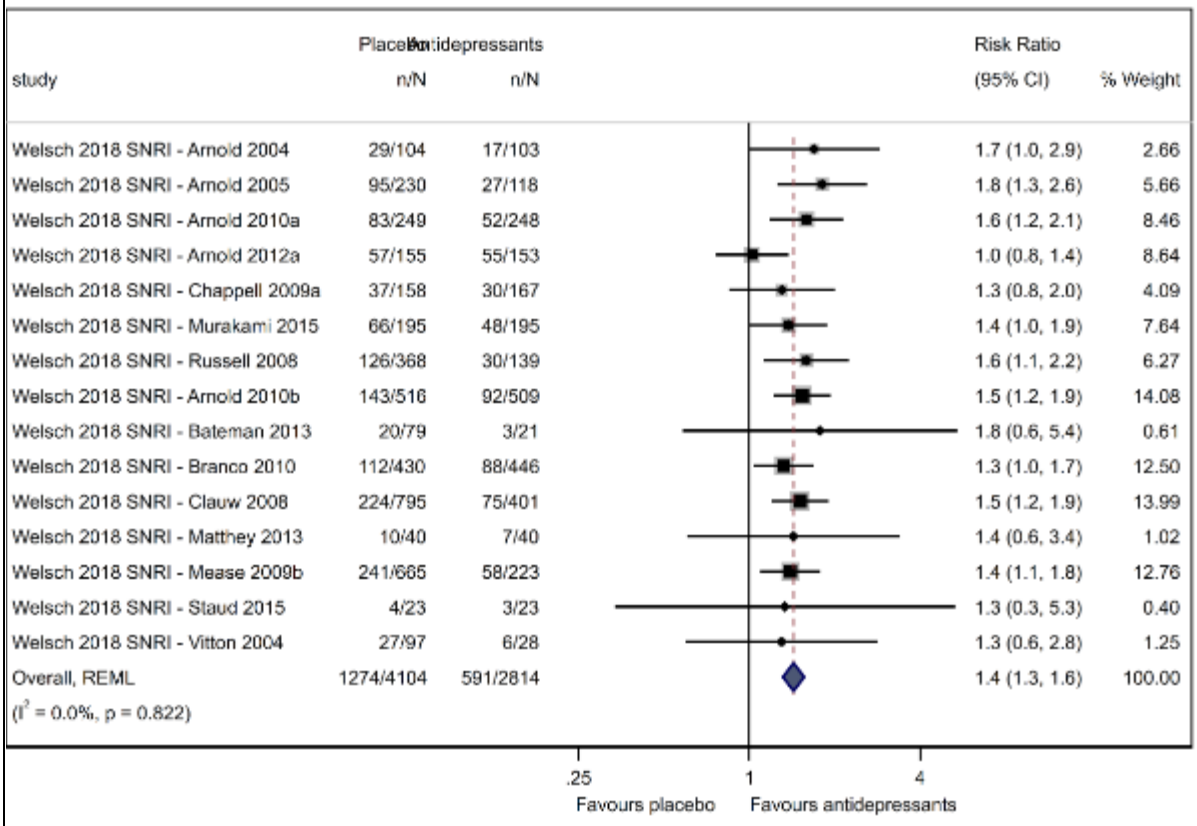
- We extracted data from the review's primary outcome (pain relief 50% or greater). The data is available under "*Analysis 1.1. Comparison 1: SNRIs versus placebo in parallel and crossover design trials, Outcome 1: Self-reported pain relief of 50% or greater*".
- We only extracted this outcome was it was the only pain outcome part of the list of primary outcomes of the review.

Data extracted from review or re-analysed?

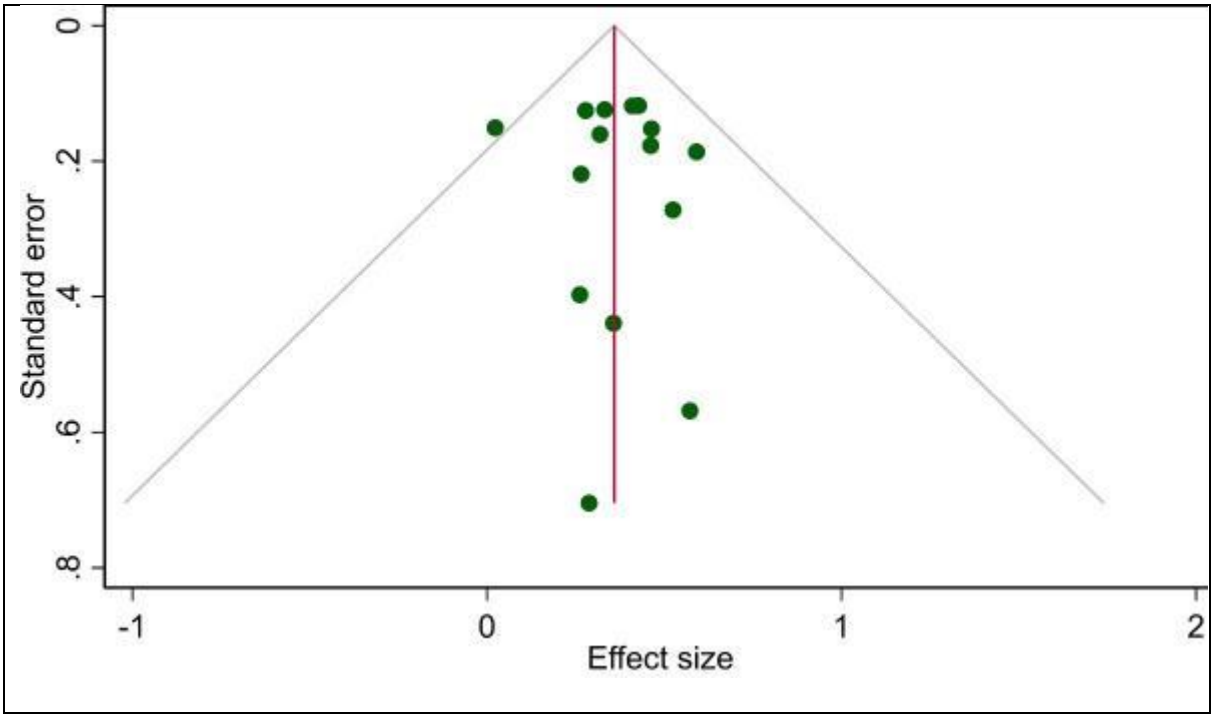
Data extracted from the review.

Meta-analysis procedures

- Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator. The pooled estimate is reported as risk ratio (95% CI)



Visual inspection of the funnel plot did not suggest the presence of publication bias. Studies with smaller sample sizes


Standard error
0
.2
.4
.6
.8
-1
0
1
2
Effect size

Welsch (2018b) - Mirtazapine

Eligible studies

All studies included in the review were eligible for this overview

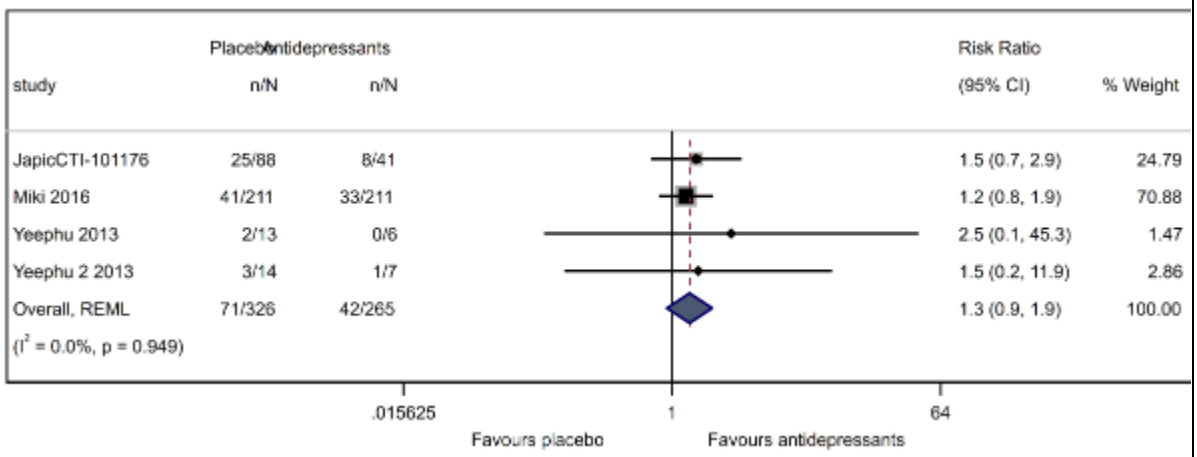
Data used

- We extracted data from the review's primary outcome (pain relief 50% or greater). The data is available under "*Analysis 1.1. Comparison 1: Mirtazapine versus placebo at the end of treatment, Outcome 1: Participant-reported pain relief of 50% or greater*".

We only extracted this outcome was it was the only pain outcome part of the list of primary outcomes of the review.

Meta-analysis procedures

- Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator. The pooled estimate is reported as risk ratio (95% CI)



Jackson (2017)

Eligible studies

Eligible trials from this review were those that compared an antidepressant to placebo and had data for the review's primary outcome (headache frequency). No trial of tricyclics had data for the review's primary outcome. Thus, we presented data from the outcome with the most studies, and listed other outcomes here

TCA:

1. Morland 1979
2. Indaco 1988
3. Bendtsen 1996
4. Holroyd 2001

Tetracyclics

1. Bendtsen 2007
2. Langemark 1990

References:

1. Mørland TJ, Storli OV, Mogstad TE. Doxepin in the prophylactic treatment of mixed 'vascular' and tension headache. Headache. 1979 Nov;19(7):382-3.
2. Indaco A, Carrieri PB. Amitriptyline in the treatment of headache in patients with Parkinson's disease: a double-blind placebo-controlled study. Neurology. 1988 Nov;38(11):1720-2.
3. Langemark M, Loldrup D, Bech P, Olesen J. Clomipramine and mianserin in the treatment of chronic tension headache. A double-blind, controlled study. Headache. 1990 Feb;30(3):118-21
4. Bendtsen L, Jensen R, Olesen J. A non-selective (amitriptyline), but not a selective (citalopram), serotonin reuptake inhibitor is effective in the prophylactic treatment of chronic tension-type headache. J Neurol Neurosurg Psychiatry. 1996 Sep;61(3):285-90.
5. Holroyd KA, O'Donnell FJ, Stensland M, Lipchik GL, Cordingley GE, Carlson BW. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. JAMA. 2001 May 2;285(17):2208-15.
6. Bendtsen L, Buchgreitz L, Ashina S, Jensen R. Combination of low-dose mirtazapine and ibuprofen for prophylaxis of chronic tension-type headache. Eur J Neurol. 2007 Feb;14(2):187-93.

Data extracted from review or re-analysed?

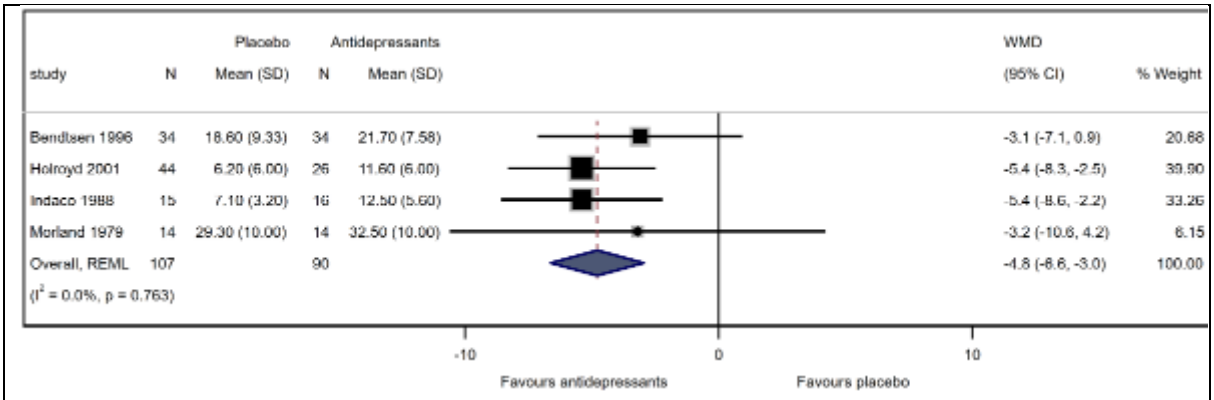
Data were extracted from the review.

Data used

TCA VS PLACEBO – HEADACHE FREQUENCY

For the comparison TCA vs placebo, we extracted data from the review's primary outcome – headache frequency (Figure 1). The International Headache Society (IHS) recommends headache frequency to be the primary outcome measure in trials of prophylactic treatment of tension-type headache.[1]

In table 2, we reported data from the 8-week follow-up, as this was the time point closest to the end of treatment in most studies (Bendtsen 1996 = 8 weeks; Morland = 9 weeks). The other two studies from this comparison had a treatment duration of 12 weeks (closest to the 12-week follow-up) and 26 weeks (closest to the 24 week follow-up). 8 weeks was also the follow-up time point with the most studies.



Data from the other time points were similar (extracted directly from the review):

Headache frequency:
4 weeks
MD (95% CI): -6.17 (-8.12 to -4.21); 2 trials (n = 117)
12 weeks
MD (95% CI): -3.81 (-5.36 to -2.26); 3 trials (n = 362)
24 weeks
MD (95% CI): -5 (-7.91 to -2.09); 1 trials (n = 70)

TRICYCLICS VS PLACEBO
Data on headache frequency was not available for this comparison. The secondary outcomes reported by the review in Online appendix 3 are reported below

Headache Index (summarised as standardised mean difference)
8 weeks
-0.16 (-0.77 to 0.45); 1 trial (n = 41)

Headache severity (summarised as standardised mean difference)
4 weeks
-0.07 (-0.57 to 0.42); 1 trial (n = 41)
8 weeks
-0.01 (-0.49 to 0.32); 2 trials (n = 111)

Use of acute medications (doses/month)
8 weeks
3.8 (-5.7 to 13.2)

50% headache improvement (RR)
4 weeks
1.2 (0.54 to 2.5); 1 trial (n = 64)
8 weeks
1.1 (0.68 to 1.8)

REFERENCE

1. Bendtsen L, Bigal ME, Cerbo R, Diener HC, Holroyd K, Lampl C, Mitsikostas DD, Steiner TJ, Tfelt-Hansen P; International Headache Society Clinical Trials Subcommittee. Guidelines for controlled trials of drugs in tension-type headache: second edition. Cephalalgia. 2010 Jan;30(1):1-16.

Meta-analysis procedures

- Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator. The pooled estimate is reported as risk ratio (95% CI)

Gebhardt (2016)

Eligible studies

- 14 of the 19 trials included in the review were included in our overview.

Included trials

1. Brannan SK, Mallinckrodt CH, Brown EB, Wohlreich MM, Watkin JG, Schatzberg AF. Duloxetine 60 mg once-daily in the treatment of painful physical symptoms in patients with major depressive disorder. J Psychiatr Res. 2005 Jan;39(1):43-53.
2. Brecht S, Courtecuisse C, Debieuvre C, Croenlein J, Desaiah D, Raskin J, Petit C, Demyttenaere K. Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: a randomized controlled trial. J Clin Psychiatry. 2007 Nov;68(11):1707-16.
3. Clayton AH, Kornstein SG, Dunlop BW, Focht K, Musgnung J, Ramey T, Bao W, Ninan PT. Efficacy and safety of desvenlafaxine 50 mg/d in a randomized, placebo-controlled study of perimenopausal and postmenopausal women with major depressive disorder. J Clin Psychiatry. 2013 Oct;74(10):1010-7.
4. Detke MJ, Lu Y, Goldstein DJ, Hayes JR, Demitrack MA. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. J Clin Psychiatry. 2002 Apr;63(4):308-15.
5. Detke MJ, Lu Y, Goldstein DJ, McNamara RK, Demitrack MA. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. J Psychiatr Res. 2002 Nov-Dec;36(6):383-90.
6. Gaynor PJ, Gopal M, Zheng W, Martinez JM, Robinson MJ, Marangell LB. A randomized placebo-controlled trial of duloxetine in patients with major depressive disorder and associated painful physical symptoms. Curr Med Res Opin. 2011 Oct;27(10):1849-58.
7. Gaynor PJ, Gopal M, Zheng W, Martinez JM, Robinson MJ, Hann D, Marangell LB. Duloxetine versus placebo in the treatment of major depressive disorder and associated painful physical symptoms: a replication study. Curr Med Res Opin. 2011 Oct;27(10):1859-67.
8. Goldstein DJ, Lu Y, Detke MJ, Wiltse C, Mallinckrodt C, Demitrack MA. Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. J Clin Psychopharmacol. 2004 Aug;24(4):389-99. [**NB: The trial referenced in the review is Goldstein 2002, but the description of the trial in the review's supplementary file indicates that the authors made a mistake and were referring to Goldstein 2004 instead. Also, Goldstein 2002 does not report pain outcomes.]**
9. Kroenke K, Messina N 3rd, Benattia I, Graepel J, Musgnung J. Venlafaxine extended release in the short-term treatment of depressed and anxious primary care patients with multisomatoform disorder. J Clin Psychiatry. 2006 Jan;67(1):72-80.
10. Robinson M, Oakes TM, Raskin J, Liu P, Shoemaker S, Nelson JC. Acute and long-term treatment of late-life major depressive disorder: duloxetine versus placebo. Am J Geriatr Psychiatry. 2014 Jan;22(1):34-45.
11. Wohlreich MM, Sullivan MD, Mallinckrodt CH, Chappell AS, Oakes TM, Watkin JG, Raskin J. Duloxetine for the treatment of recurrent major depressive disorder in elderly patients: treatment outcomes in patients with comorbid arthritis. Psychosomatics. 2009 Jul-Aug;50(4):402-12.
12. Dickens C, Jayson M, Sutton C, Creed F. The relationship between pain and depression in a trial using paroxetine in sufferers of chronic low back pain. Psychosomatics. 2000 Nov-Dec;41(6):490-9.
13. Tsui JI, Herman DS, Kettavong M, Anderson BJ, Stein MD. Escitalopram is associated with reductions in pain severity and pain interference in opioid dependent patients with depressive symptoms. Pain. 2011 Nov;152(11):2640-2644.
14. Heiligenstein JH, Ware JE Jr, Beusterien KM, Roback PJ, Andrejasich C, Tollefson GD. Acute effects of fluoxetine versus placebo on functional health and well-being in late-life depression. Int Psychogeriatr. 1995;7 Suppl:125-37.

Excluded trials

1. Detke MJ, Wiltse CG, Mallinckrodt CH, McNamara RK, Demitrack MA, Bitter I. Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Neuropsychopharmacol. 2004 Dec;14(6):457-70. **[There are no pain outcomes to be extracted]**
2. Perahia DG, Wang F, Mallinckrodt CH, Walker DJ, Detke MJ. Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Psychiatry. 2006 Sep;21(6):367-78. **[There are no pain outcomes to be extracted]**
3. Robinson MJ, Sheehan D, Gaynor PJ, Marangell LB, Tanaka Y, Lipsius S, Ohara F, Namiki C. Relationship between major depressive disorder and associated painful physical symptoms: analysis of data from two pooled placebo-controlled, randomized studies of duloxetine. Int Clin Psychopharmacol. 2013 Nov;28(6):330-8. **[Pooled analysis of 2 other included trials; Gaynor 2011 and Gaynor 2011a]**
4. Hameroff SR, Weiss JL, Lerman JC, Cork RC, Watts KS, Crago BR, Neuman CP, Womble JR, Davis TP. Doxepin's effects on chronic pain and depression: a controlled study. J Clin Psychiatry. 1984 Mar;45(3 Pt 2):47-53. **[Hameroff was the only TCA trial included in this review, and it was included in the Ferreira 2021 back pain review]**
5. Onghena P, De Cuyper H, Van Houdenhove B, Verstraeten D. Mianserin and chronic pain: a double-blind placebo-controlled process and outcome study. Acta Psychiatr Scand. 1993 Sep;88(3):198-204. **[Issues with study design – crossover trial with no wash-out period]**

Data extracted from review or re-analysed?

We extracted data from the included trials

Data used

SNRI vs placebo comparison

- Detke 2002: Overall pain (Figure 3)
- Detke 2002a: Overall pain (Figure 3A)
- Goldstein 2004: Overall pain (Table 3)
- Brannan 2005: BPI Average pain (Table 2)
- Kroenke 2006: PHQ-15 Pain subscale (Table 2)
- Brecht 2007: BPI Average pain (Table 2)
- Wohlreich 2009: Overall pain (Table 5)
- Gaynor 2011: BPI Average pain (Table 2)
- Gaynor 2011a: BPI Average pain (Table 2)
- Clayton 2013: VAS-PI (Table 2)
- Robinson 2014: BPI Average pain (Table 2)

SSRI vs placebo comparison

- Dickens 2000: VAS day 56 (Table 4)
- Tsui 2011: Pain severity (results)
- Heiligenstein 1995: SF-36 Bodily pain subscale (Table 3)
- Goldstein 2004: Overall pain (Table 3)

Meta-analysis procedures

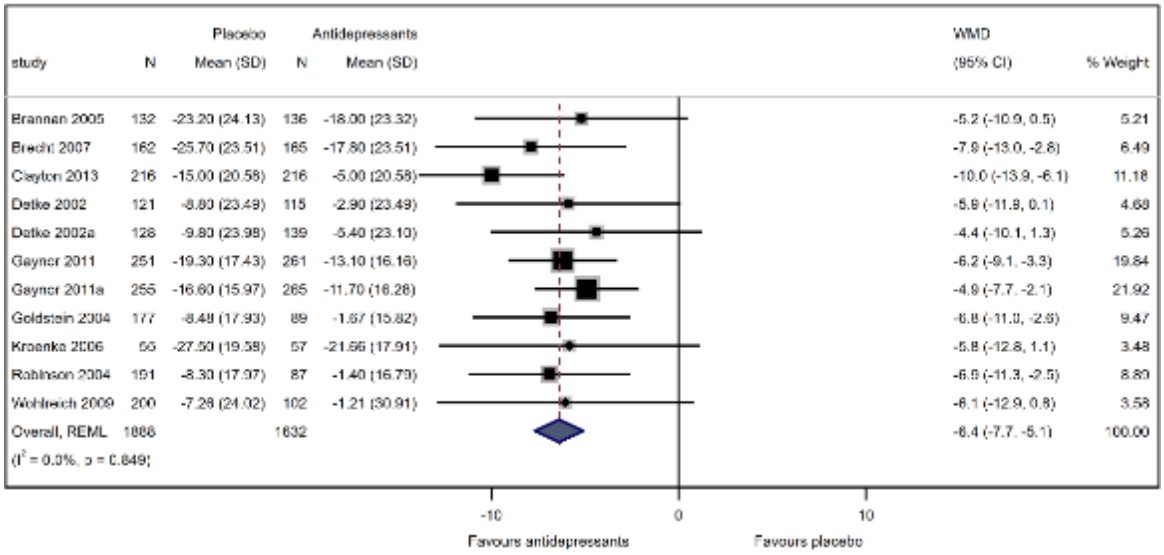
Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator. The pooled estimate is reported as risk ratio (95% CI)

SNRI vs placebo comparison

- Detke 2002: Used Webplotdigitizer to extract change scores from fig 3a; estimated SDs using the Cochrane calculator (from p-value in Fig 3a)
- Detke 2002a: Imputed SD from baseline as no other variability measure was reported for the primary analysis

- Goldstein 2004: Converted medians (IQR) to means (SD) using Wan's conversion formula; combined duloxetine 40 + 80 mg groups in Revman
- Brannan 2005: SD estimated via SE and sample size using the Cochrane calculator
- Kroenke 2006: None
- Brecht 2007: Reported the adjusted mean differences between the groups
- Wohlreich 2009: For each treatment (duloxetine or placebo), we combined the arthritis and no arthritis groups in Revman
- Gaynor 2011: Estimated SDs via SEs and sample size using the Cochrane calculator
- Gaynor 2011a: Estimated SDs via SEs and sample size using the Cochrane calculator
- Clayton 2013: Estimated SDs via SEs and sample size using the Cochrane calculator
- Robinson 2014: Estimated SDs via SEs and sample size using the Cochrane calculator

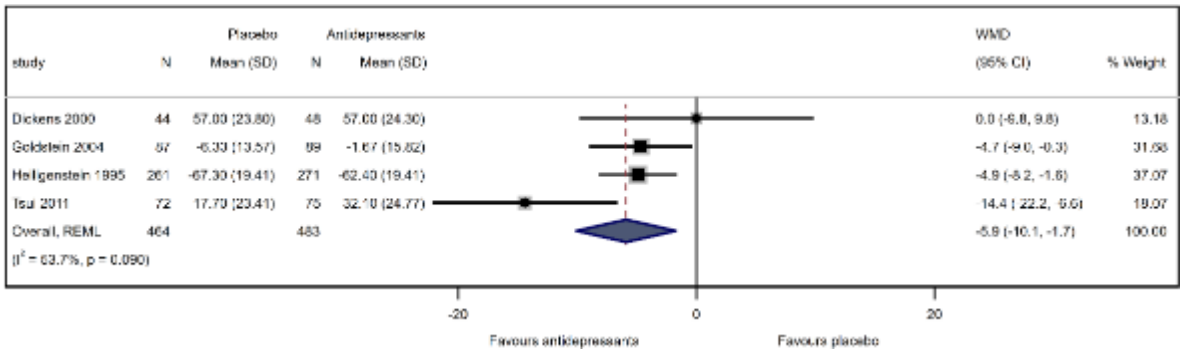
SNRI



SSRI vs placebo comparison

- Dickens 2000: No estimation was required
- Tsui 2011: No estimation was required
- Heiligenstein 1995: Changed the direction of the effect to match the other trials (i.e. pain =0 is no pain; pain = 100 is the worst possible pain)
- Goldstein 2004: Converted medians (IQR) to means (SD) using Wan's conversion

SSRI



Reference:

Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014 Dec 19;14:135.

Alviar (2016)

Eligible studies

Only one trial from this review was eligible for our overview:

- Robinson LR, Czerniecki JM, Ehde DM, Edwards WT, Judish DA, Goldberg ML, Campbell KM, Smith DG, Jensen MP. Trial of amitriptyline for relief of pain in amputees: results of a randomized controlled study. Arch Phys Med Rehabil. 2004 Jan;85(1):1-6.

Data extracted from review or re-analysed?

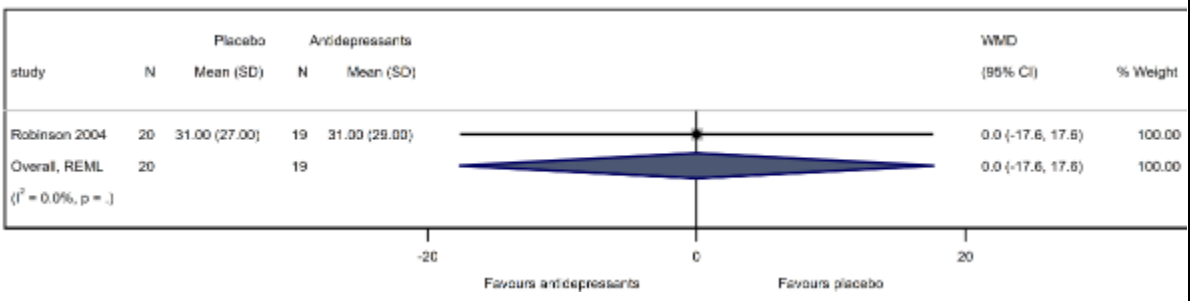
Data were re-analysed by extracting data from the eligible trial.

Data used

- We extracted data from the study's primary outcome (average pain intensity) (Table 3 in Robinson 2004)
- Data were converted to a 0-100 scale

Meta-analysis procedures

- Meta-analysis was not conducted as only one study was available. The forest plot below shows the data extracted from the trial.



Walitt (2015)

Eligible studies

- Trials that had data for the review's primary outcome (At least 30% pain reduction) were included
  1. Anderberg 2000
  2. Norregaard 1995
  3. Arnold 2002
  4. GSK 2005
  5. Patkar 2007
  6. Wolfe 1994

REFERENCES

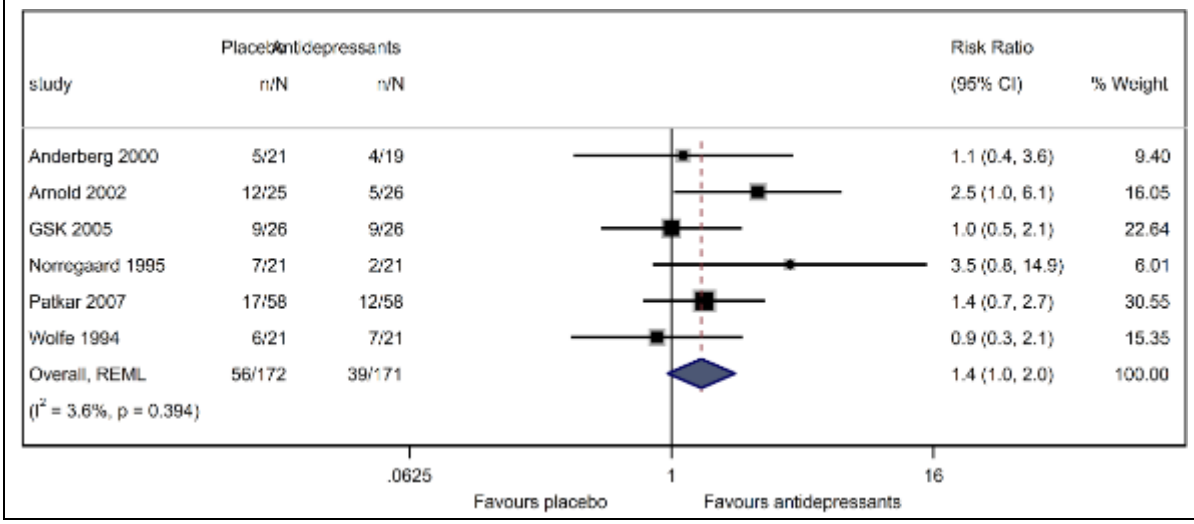
1. Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in patients with fibromyalgia--a randomized, double-blind, placebo-controlled study. Eur J Pain. 2000;4(1):27-35.
2. Arnold LM, Hess EV, Hudson JI, Welge JA, Berno SE, Keck PE Jr. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. Am J Med. 2002 Feb 15;112(3):191-7.
3. GlaxoSmithKline. Treatment of fibromyalgia: a randomized, double blind, placebo-controlled study of paroxetine, a selective serotonin re-uptake inhibitor. Study ID 29060/433. http://www.gsk-clinicalstudyregister.com/.
4. Nørregaard J, Volkmann H, Danneskiold-Samstøe B. A randomized controlled trial of citalopram in the treatment of fibromyalgia. Pain. 1995 Jun;61(3):445-449.
5. Patkar AA, Masand PS, Krulewicz S, Mannelli P, Peindl K, Beebe KL, Jiang W. A randomized, controlled, trial of controlled release paroxetine in fibromyalgia. Am J Med. 2007 May;120(5):448-54.
6. Wolfe F, Cathey MA, Hawley DJ. A double-blind placebo controlled trial of fluoxetine in fibromyalgia. Scand J Rheumatol. 1994;23(5):255-9

Data used

- We used data for the outcome "*Analysis 1.1. Comparison 1 SSRI versus placebo, Outcome 1 At least 30% pain reduction*". This outcome was the only pain-related outcome listed in the review as a primary outcome. Other primary outcomes were global improvement (which were calculated as a function of the Fibromyalgia Impact Questionnaire), Fatigue, Sleep problems, Depression, and Tolerability (also extracted but as a secondary outcome in our review).

Meta-analysis procedures

- Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator. The pooled estimate is reported as risk ratio (95% CI)



Note: This finding contrasts with the findings reported originally by the Cochrane review. In that review, authors summarised the pooled effect as risk difference (RD) and 95%CI. They describe an effect of **0.1 (0.01 to 0.2)**. The result becomes not significant when data are summarised as risk ratios as we did. We followed guidance from the Cochrane Handbook (section 10.4.3 *Which effect measure for dichotomous outcomes?*) which recommends using risk ratios instead of risk differences.

Moore (2015)

Eligible studies

All studies that had data on pain at 50% (the only primary outcome listed in the review) with data.

Data extracted from review or re-analysed?

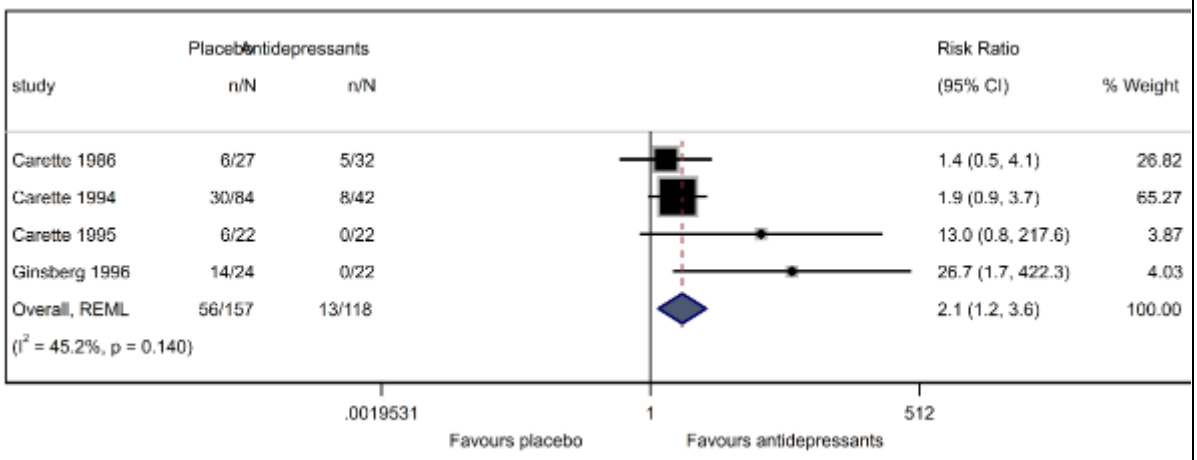
Data were re-analysed

Data used

- We used data for the outcome "*Analysis 1.1. Comparison 1 Amitriptyline versus placebo, Outcome 1 Third-tier efficacy*". This outcome represented a pain relief of at least 50%. Other pain outcomes listed as primary outcomes (e.g. pain relief of at least 30% did not have any studies).

Meta-analysis procedures

- Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator. The pooled estimate is reported as risk ratio (95% CI)



Banzi (2015) [migraine]

Eligible studies

Two trials in the review had eligible data for the review's primary outcome (headache frequency) and were included in our overview

1. Steiner TJ, Ahmed F, Findley LJ, MacGregor EA, Wilkinson M. S-fluoxetine in the prophylaxis of migraine: a phase II double-blind randomized placebo-controlled study. Cephalalgia. 1998 Jun;18(5):283-6.
2. Ozyalcin SN, Talu GK, Kiziltan E, Yucel B, Ertas M, Disci R. The efficacy and safety of venlafaxine in the prophylaxis of migraine. Headache. 2005 Feb;45(2):144-52.

Data extracted from review or re-analysed?

Data were re-analysed

Data used

We extracted data from the two placebo-controlled trials that reported data on the review's primary outcome, headache frequency.

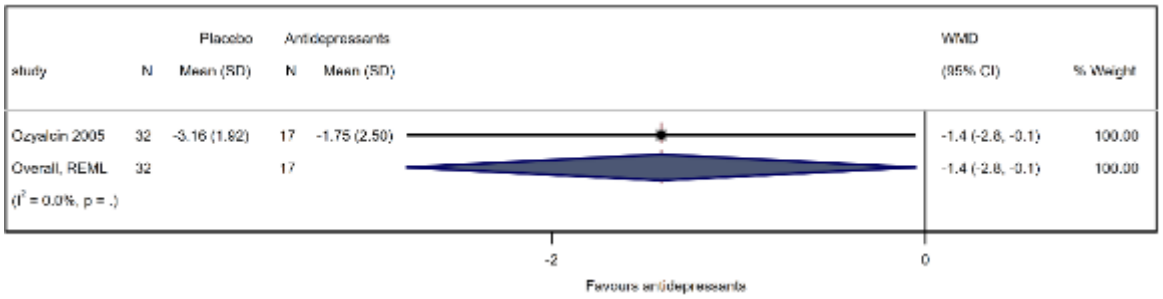
- For Steiner 1998, we extracted data from "Month 4" in Table 2. We chose this timepoint because it was the end of the treatment phase (1 month run-in period + 3 months of treatment). In the 1-month run-in period that preceded the treatment period, all participants were prescribed placebo and those who responded (defined by the trial as < 2 headache episodes during that month) were subsequently excluded from the study.
- For Ozyalcin 2005, we extracted data from the outcome "number of days with headache" in Table 2.

Meta-analysis procedures

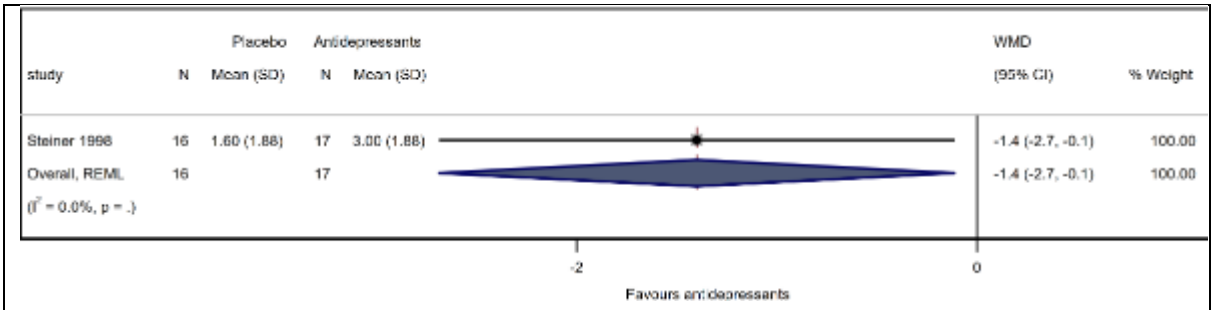
- Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator.
- For Steiner 1998, we used the Cochrane SD calculator to estimate a common standard deviation for both treatment groups. We used the between-group mean difference in headache frequency (-1.4 days) and between-group p-value at week 4 (p = 0.041) to estimate the t-score and, subsequently, a common standard deviation.
- For Ozyalcin, we combined data from the two active treatment groups (venlafaxine 75 and 150 mg). The study reported outcomes as medians (minimum-maximum). To estimate the mean and standard deviation for each group we used the method proposed by Wan et al.[1]
- Placebo group: Mean =1.75; SD = 2.5
- Venlafaxine 75 mg: Mean = 2.5; SD = 1.72
- Venlafaxine 150 mg: Mean = 3.75; SD = 1.94
- As data from table 2 represent *reduction* in days with headache, we added a negative sign to the mean values for each group.

Forest plots for both trials for headache frequency outcome

SNRI



SSRI



REFERENCE

1. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014 Dec 19;14:135.

Banzi (2015) [tension-type headache]

Eligible studies Two trials had data for the review's primary outcome and were therefore eligible for our overview. 1. Bendtsen L, Jensen R, Olesen J. A non-selective (amitriptyline), but not a selective (citalopram), serotonin reuptake inhibitor is effective in the prophylactic treatment of chronic tension-type headache. J Neurol Neurosurg Psychiatry. 1996 Sep;61(3):285-90. 2. Zissis NP, Harmoussi S, Vlaikidis N, Mitsikostas D, Thomaidis T, Georgiadis G, Karageorgiou K. A randomized, double-blind, placebo-controlled study of venlafaxine XR in out-patients with tension-type headache. Cephalalgia. 2007 Apr;27(4):315-24.
Data extracted from review or re-analysed? Data were extracted from the review.
Data used We used data reported in the "Analysis 1.1. Comparison 1 SSRIs or SNRIs versus placebo, Outcome 1 Headache frequency (number of headache days) (follow-up: 8 weeks)." Outcome.
Meta-analysis procedures Meta-analysis was not conducted as only one trial from each antidepressant class (SNRI or SSRI) was included.

Finnerup (2015)

Eligible studies

This review included trials investigating the efficacy of SNRI and TCA antidepressants. Compared to the Caruso (2019) review, also included in our overview and that also had data for SNRI and TCA antidepressants, Finnerup (2015) had fewer trials of SNRI (10 vs 12) and more trials of TCA with available data (6 vs 14 [15 comparisons]). For that reason, we only present data for TCA antidepressants for the Finnerup (2015) review.

The eligible studies with pain data available (supplied by the first author) are:

1. Eija K, Tiina T, J NP. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. Pain. 1996 Feb;64(2):293-302.
2. Khoromi S, Cui L, Nackers L, Max MB. Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. Pain. 2007 Jul;130(1-2):66-75. doi: 10.1016/j.pain.2006.10.029.
3. Kieburtz K, Simpson D, Yiannoutsos C, Max MB, Hall CD, Ellis RJ, Marra CM, McKendall R, Singer E, Dal Pan GJ, Clifford DB, Tucker T, Cohen B. A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. AIDS Clinical Trial Group 242 Protocol Team. Neurology. 1998 Dec;51(6):1682-8.
4. Kishore-Kumar R, Max MB, Schafer SC, Gaughan AM, Smoller B, Gracely RH, Dubner R. Desipramine relieves postherpetic neuralgia. Clin Pharmacol Ther. 1990 Mar;47(3):305-12.
5. Leijon G, Boivie J. Central post-stroke pain--a controlled trial of amitriptyline and carbamazepine. Pain. 1989 Jan;36(1):27-36.
6. Max MB, Culnane M, Schafer SC, Gracely RH, Walther DJ, Smoller B, Dubner R. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. Neurology. 1987 Apr;37(4):589-96.
7. Max MB, Kishore-Kumar R, Schafer SC, Meister B, Gracely RH, Smoller B, Dubner R. Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial. Pain. 1991 Apr;45(1):3-9.
8. Raja SN, Haythornthwaite JA, Pappagallo M, Clark MR, Travison TG, Sabeen S, Royall RM, Max MB. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology. 2002 Oct 8;59(7):1015-21.
9. Rintala DH, Holmes SA, Courtade D, Fiess RN, Tastard LV, Loubser PG. Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. Arch Phys Med Rehabil. 2007 Dec;88(12):1547-60.
10. Sindrup SH, Bach FW, Madsen C, Gram LF, Jensen TS. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. Neurology. 2003 Apr 22;60(8):1284-9.
11. Vrethem M, Boivie J, Arnqvist H, Holmgren H, Lindström T, Thorell LH. A comparison a amitriptyline and maprotiline in the treatment of painful polyneuropathy in diabetics and nondiabetics. Clin J Pain. 1997 Dec;13(4):313-23.
12. Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith L, Warsh J. Amitriptyline versus placebo in postherpetic neuralgia. Neurology. 1982 Jun;32(6):671-3.
13. PhRMA and FDA 1008-040 (2007) [Trial registry]
14. Österberg and Boivie, 2005 [Thesis]

The Vrethem 1997 trial had two arms (amitriptyline and maprotiline), which were assessed separately. This additional comparison means that this review had a total of 15 comparisons of an antidepressant to placebo.

Data extracted from review or re-analysed?

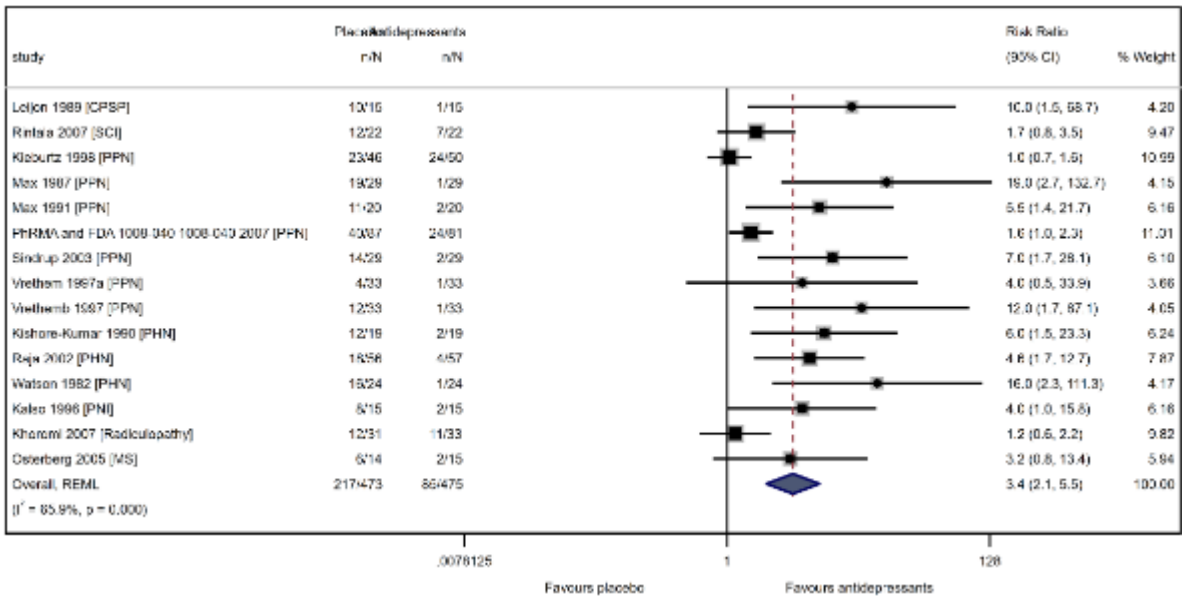
Data were re-analysed

Data used

All data used for this outcome was supplied by the review's lead author. The outcome of this review was pain reduction of 30% of 50% or at least moderate pain relief.

Meta-analysis procedures

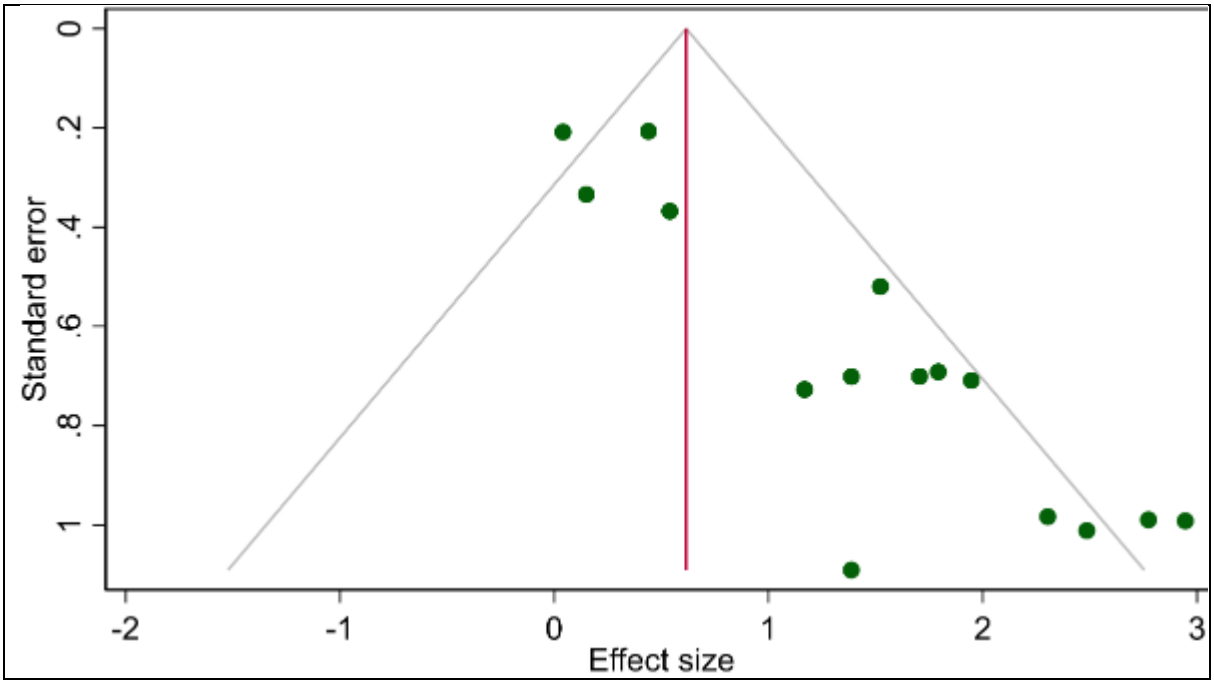
- Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator. The pooled estimate is reported as risk ratio (95% CI)
- We used number of events and sample size to compute risk ratios and 95% confidence intervals for each one of the 14 trials with available data.



We performed another sensitivity analysis where we only left the trials investigating amitriptyline (excluded trials investigating other TCAs). No change in heterogeneity was observed (65%).

Because point estimates across studies were similar in magnitude and direction and most studies pointed towards an effect of TCA compared to placebo, we considered that the amount of statistical heterogeneity found would not impact our confidence in the results. Guidance to support our decision can be found in the GRADE Handbook (section 5.2.2).

The funnel plot revealed an asymmetrical distribution, which led us to downgrade the certainty of evidence by publication bias. The Finnerup (2015) review did not downgrade the certainty of evidence for this outcome for publication bias.


Standard error
0
.2
.4
.6
.8
1
-2
-1
0
1
2
3
Effect size

Atluri (2015)

Eligible studies

All studies providing data for pain were eligible for this overview

1. Doraiswamy PM, Varia I, Hellegers C, Wagner HR, Clary GL, Beyer JL, Newby LK, O'Connor JF, Beebe KL, O'Connor C, Krishnan KR. A randomized controlled trial of paroxetine for noncardiac chest pain. Psychopharmacol Bull. 2006;39(1):15-24.
2. Keefe FJ, Shelby RA, Somers TJ, Varia I, Blazing M, Waters SJ, McKee D, Silva S, She L, Blumenthal JA, O'Connor J, Knowles V, Johnson P, Bradley L. Effects of coping skills training and sertraline in patients with non-cardiac chest pain: a randomized controlled study. Pain. 2011 Apr;152(4):730-741.
3. Spinhoven P, Van der Does AJ, Van Dijk E, Van Rood YR. Heart-focused anxiety as a mediating variable in the treatment of noncardiac chest pain by cognitive-behavioral therapy and paroxetine. J Psychosom Res. 2010 Sep;69(3):227-35.
4. Varia I, Logue E, O'connor C, Newby K, Wagner HR, Davenport C, Rathey K, Krishnan KR. Randomized trial of sertraline in patients with unexplained chest pain of noncardiac origin. Am Heart J. 2000 Sep;140(3):367-72.

Data extracted from review or re-analysed?

Data were re-analysed.

Authors of the review had originally pooled data using standardised mean differences (SMD) and re-expressed the SMD using the control group baseline standard deviation from the Keefe 2011 trial. Upon inspecting the data entered in the meta-analysis, we judged that the data were sufficiently similar to be pooled using mean differences. All 4 trials measured pain using the same scale; some reported outcomes as change scores, and some had reported outcomes as final scores.

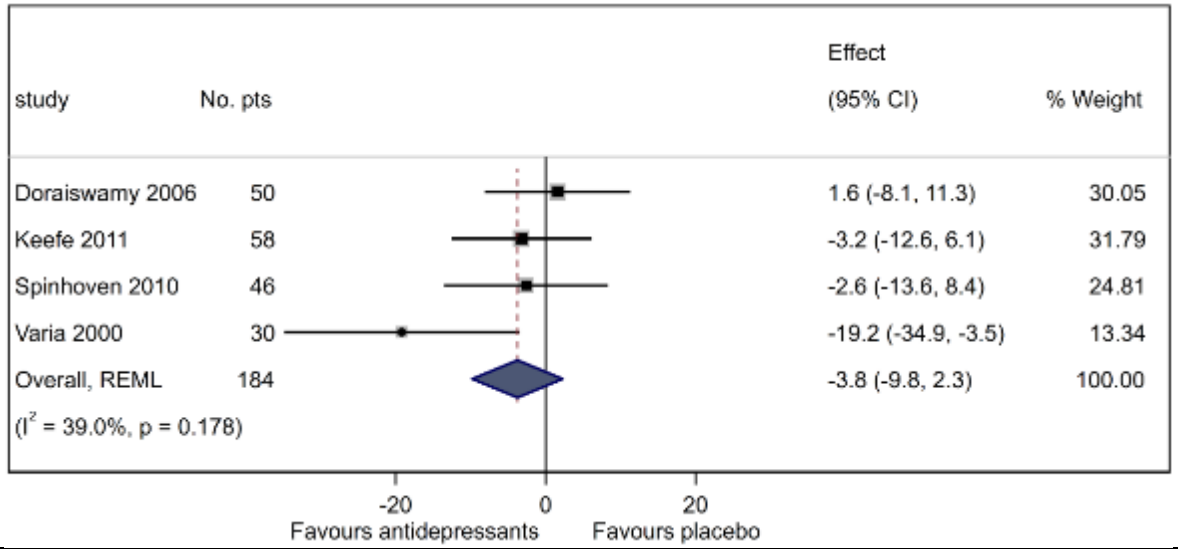
Data used

- Doraiswamy 2006: Figure 3 (data extracted using Webplot digitizer)
- Keefe 2011: Pain outcomes at 10 weeks extracted from table 1
- Spinhoven 2010: Pain outcomes extracted from Table 2
- Varia 2000: Pain outcomes extracted from Table 1

- We converted scores into a scale of 0-100 when needed

Meta-analysis procedures

- Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator. The pooled estimate is reported as risk ratio (95% CI)
- The pooled mean difference is only slightly different than the one reported in the review that was computed by re-expressing the SMD (-4.1, 95% CI -11.2 to 2.9)



Cheong (2014)

Eligible studies Only one study in this review was potentially eligible: 1. Engel CC Jr, Walker EA, Engel AL, Bullis J, Armstrong A. A randomized, double-blind crossover trial of sertraline in women with chronic pelvic pain. J Psychosom Res. 1998 Feb;44(2):203-7.
Data extracted from review or re-analysed? Data were re-analysed.
Data used We used data for the Composite Pain Intensity outcome (Table 1). This was the study's primary outcome. This outcome was measured on a 0-10 scale.
Meta-analysis procedures We converted data from a 0-10 scale into a 0-100 scale. No other meta-analytical procedures were required.

Richards (2011)

Eligible studies

Six trials included in the meta-analysis compared an antidepressant (tricyclic) to placebo).

1. Ash G, Dickens CM, Creed FH, Jayson MI, Tomenson B. The effects of dothiepin on subjects with rheumatoid arthritis and depression. Rheumatology (Oxford). 1999 Oct;38(10):959-67
2. Fowler PD, MacNeill A, Spencer D, Robinson ET, Dick WC. Imipramine, rheumatoid arthritis and rheumatoid factor. Curr Med Res Opin. 1977;5(3):241-6.
3. rank RG, Kashani JH, Parker JC, Beck NC, Brownlee-Duffeck M, Elliott TR, Haut AE, Atwood C, Smith E, Kay DR. Antidepressant analgesia in rheumatoid arthritis. J Rheumatol. 1988 Nov;15(11):1632-8.
4. Grace EM, Bellamy N, Kassam Y, Buchanan WW. Controlled, double-blind, randomized trial of amitriptyline in relieving articular pain and tenderness in patients with rheumatoid arthritis. Curr Med Res Opin. 1985;9(6):426-9.
5. Macfarlane JG, Jalali S, Grace EM. Trimipramine in rheumatoid arthritis: a randomized double-blind trial in relieving pain and joint tenderness. Curr Med Res Opin. 1986;10(2):89-93.
6. Saarialho-Kere U, Julkunen H, Mattila MJ, Seppälä T. Psychomotor performance of patients with rheumatoid arthritis: cross-over comparison of dextropropoxyphene, dextropropoxyphene plus amitriptyline, indomethacin, and placebo. Pharmacol Toxicol. 1988 Oct;63(4):286-92.

Data extracted from review or re-analysed?

Data were re-analysed

Data used

Of the 6 included trials, only two had some data that could potentially be pooled (Ash 1999 and MacFarlane 1986). The other 4 trials have several issues with their data (described below) which made it not feasible to extract those data. There is also marked heterogeneity with regards to the timepoints at which pain outcomes were collected (e.g. Sarrialho-Kere 1988 provided treatment for 2 weeks; Grace 1985 provided treatment for 32 weeks). We therefore agreed with the review authors that the effect of antidepressants in this review was not estimable.

1. Fowler 1977: treatment for 6 weeks; variability measures are not described in the study, and SDs cannot be estimated (p-values, t-values are not reported precisely)
2. Frank 1988: treatment for 32 weeks; Data in table 2 does not contain SDs, and p-values are for the 4-group comparison only (there are no p-values for the post-hoc drug vs placebo head-to-head comparison).
3. Grace 1985: treatment for 12 weeks; pain measured on a 0-4 scale. There are no variability measures or any other data that would allow us to estimate SDs (e.g p-values, t-values).
4. Sarrialho-Kere 1988: treatment for 2 weeks: data on pain for the amitriptyline vs placebo not available.

Meta-analysis procedures

Meta-analysis was not performed.

Tort (2012)

Eligible studies

Two studies that provided data for pain (the review's primary outcome were eligible

1. Ginsberg F, Joos E, Géczy J, Brahwyler J, Vandekerckhove J, Famaey J. A Pilot Randomized Placebo-Controlled Study of Pirlindole in the Treatment of Primary Fibromyalgia. J Musculoskelet Pain. 1998;6(2):5-17
2. Hannonen P, Malminiemi K, Yli-Kerttula U, Isomeri R, Roponen P. A randomized, double-blind, placebo-controlled study of moclobemide and amitriptyline in the treatment of fibromyalgia in females without psychiatric disorder. Br J Rheumatol. 1998 Dec;37(12):1279-86.

Data extracted from review or re-analysed?

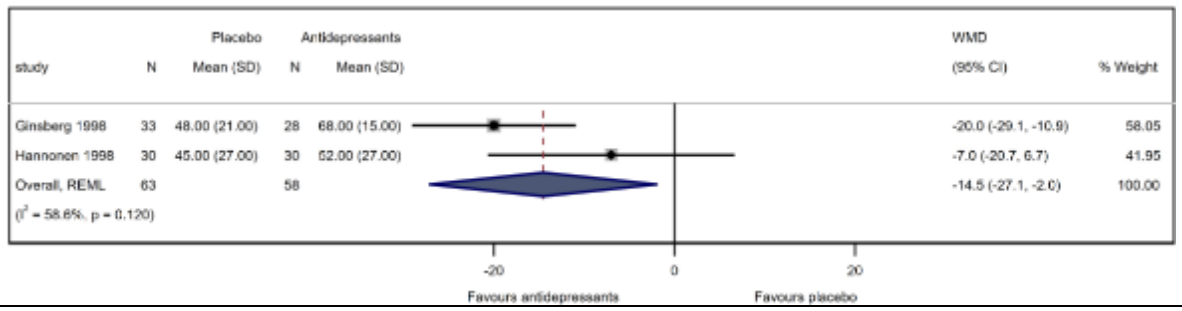
Data were extracted from the review.

Data used

- We used data from "Analysis 1.1. Comparison 1 MAOIs vs placebo (efficacy), Outcome 1 Pain (VAS).".
- Pooled estimates were presented on a 0-10 scale; we have converted them to a 0-100 scale.

Meta-analysis procedures

- Analysis method: random effects with a restricted maximum likelihood heterogeneity variance estimator. The pooled estimate is reported as risk ratio (95% CI)



Supplementary file 7. Citation matrix identifying the amount of overlap of trials between reviews. Overlaps are highlighted.

Trials	Wang (2022)	Roberts (2022)	Ferreira (2021)	Farag (2021)	Ford (2021)	Do (2021)	Imamura (2020)	Ford (2019)	Caruso (2019)	Perez-Lopez (2019)	Christophorou (2019)	Franco (2019)	Welsch (2018)	Welsch (2018)	Jackson (2017)	Gebhardt (2016)	Alviar (2016)	Walitt (2015)	Moore (2015)	Banzi (2015)	Banzi (2015)	Finnerup (2015)	Atluri (2015)	Nguyen (2012)	Cheong (2014)	Richards (2012)	Tort (2012)
Amr & Yousef 2010	x																										
Ho 2010	x																										
Saoud 2013	x																										
Nasr 2014	x																										
Casto-Alves 2016	x																										
Mantay 2016	x																										
YaDeau 2016	x																										
Attia 2017	x																										
Bedin 2017	x																										
Altiparmak 2018	x																										
El-Behairy 2019	x																										
Koh 2019	x																										
Govil 2020	x																										
Hatami 2020	x																										
Hetta 2020	x																										
Sattari 2020	x																										
Lunn 2015	x																										
Henry 2018		x																									
Gould 2020			x																								
Urquhart 2018			x																								
Maarrawi 2018			x																								
Konno 2016			x																								

Skljarevski. Spine (Phila 1976) 2010			x																							
Skljarevski. J Pain 2010			x																							
Skljarevski. Eur J Neurol 2009			x																							
Atkinson 2007			x																							
Katz 2005			x																							
Dickens 2000			x													x										
Atkinson 1999			x																							
Atkinson 1998			x																							
Goodkin 1990			x																							
Hameroff 1985			x																							
Jenkins 1976			x																							
Schukro 2016			x																							
Vanelderen 2015			x																							
NCT01225068 2014			x																							
Marks 2014			x						x																	
Khoromi 2007			x																				x			
Pirbudak 2003			x																							
Uchio 2018			x																							
Wang 2017			x																							
Tetreault 2016			x																							
Abou-Raya 2012			x																							
Chappell 2011			x																							
Frakes 2011			x																							
NCT01510457 2012			x																							
Chappell 2009			x																							
Tammiala-Salonen 1999				x																						

Talley 2015					x																						
Tan 2012					x																						
Braak 2011					x																						
Tack 2016					x																						
Cheong 2018					x																						
Agius 2013						x																					
Forssell 2004						x																					
Foster. 2010 J Urol 2010							x																				
van Ophoven 2005							x																				
Heefner 1978								x																			
Vij 1991								x																			
Vahedi 2005								x																			
Ghadir 2011								x																			
Kuiken 2003								x																			
Tabas 2004								x																			
Vahedi 2008								x																			
Allen 2014									x																		
Gao 2010									x																		
Gao 2015									x																		
Goldstein 2005									x																		
Raskin 2005									x																		
Rowbotham 2004									x																		
Simpson 2001									x																		
Vollmer 2014									x																		
Wernicke 2006									x																		
Yasuda 2011									x																		
Smith 2013									x																		

Foster. Obstet Gynecol 2010										x																	
Leenstra 2014											x																
Turkington 2002												x															
Arnold. Arthritis & Rheum 2004													x														
Arnold. Pain 2005													x														
Arnold. J Rheumatol 2010													x														
Arnold. Clin J Pain 2012													x														
Chappell. Int J Gen Med 2009													x														
Murakami 2015													x														
Russell 2008													x														
Arnold. Arthritis Rheum 2010													x														
Bateman 2013													x														
Branco 2010													x														
Clauw 2008													x														
Matthey 2013													x														
Mease. J Rheumatol 2009													x														
Staud 2015													x														
Vitton 2004													x														
JapiccCTI-101176														x													
Miki 2016														x													
Yeephu 2013														x													
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Bendtsen 2007															x												
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Brecht 2007																x											
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Gaynor 2011																x											
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Tsui 2011																x											
Robinson 2004																	x										
Anderberg 2000																		x									
GlaxoSmithKline 2005																		x									
Norregaard 1995																		x									
Arnold. Am J Med 2002																		x									
Patkar 2007																		x									
Wolfe 1994																		x									
Carette 1986																			x								

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Carette 1995																			x								
Ginsberg 1996																			x								
Ozyalcin 2005																				x							
Steiner 1988																				x							
Zissis 2007																					x						
Eija 1996																						x					
Kieburtz 1998																						x					
Kishore-Kumar 1990																						x					
Leijon 1989																						x					
Max 1987																						x					
Max 1991																						x					
Raja 2002																						x					
Rintala 2007																						x					
Sindrup 2003																						x					
Vrethem 1997																						x					
Watson 1982																						x					
PhRMA and FDA 1008-040 2007																						x					
Österberg and Boivie 2005																						x					
Doraiswamy 2006																							x				
Keefe 2011																							x				
Spinhoven 2010																							x				
Varia 2000																							x				
Lee 2010																								x			
Engel 1998																									x		
Ash 1999																										x	
Fowler 1977																										x	

Frank 1988																										x	
Grace 1985																										x	
Macfarlane 1986																										x	
Saarialho-Kere 1988																										x	
Sarzi 1988																										x	
Ginsberg 1998																											x
Hannonen 1998																											x

*Bendtsen 1996 appears in two reviews (Jackson 2017) and Banzi (2015), however each review uses a different comparison within the trial. In Jackson (2017) the comparison of interest is TCA vs placebo; in Banzi 2015, the comparison of interest is SSRI vs placebo. As there are no data overlap this trial is not counted in the calculation of overlap presented in the manuscript.

References to included trials:

1. Amr YM, Yousef AA. Evaluation of efficacy of the perioperative administration of Venlafaxine or gabapentin on acute and chronic postmastectomy pain. Clin J Pain. 2010 Jun;26(5):381-5.
2. Ho KY, Tay W, Yeo MC, Liu H, Yeo SJ, Chia SL, Lo NN. Duloxetine reduces morphine requirements after knee replacement surgery. Br J Anaesth. 2010 Sep;105(3):371-6.
3. Saoud A, Elkabarity R. Effect of perioperative duloxetine on postoperative pain relief following anterior cervical microdiscectomy and fusion. A pilot study. World Spinal Column J 2013.4:57e66
4. Nasr DA. Efficacy of perioperative duloxetine on acute and chronic postmastectomy pain. Ain-Shams J Anaesth. 2014.7:129-33
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14. Hatami M, Kheirati A, Behdad S, Javaheri A, Vaziribozorg S. The effect of preoperative administration of duloxetine on postoperative pain after laparoscopic myomectomy. Acta Med Iran. 2020;58:121e5
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18. Henry NL, Unger JM, Schott AF, Fehrenbacher L, Flynn PJ, Prow DM, Sharer CW, Burton GV, Kuzma CS, Moseley A, Lew DL, Fisch MJ, Moinpour CM, Hershman DL, Wade JL 3rd. Randomized, Multicenter, Placebo-Controlled Clinical Trial of Duloxetine Versus Placebo for Aromatase Inhibitor-Associated Arthralgias in Early-Stage Breast Cancer: SWOG S1202. J Clin Oncol. 2018 Feb 1;36(4):326-332.
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Supplementary file 8. Sensitivity analysis describing effect sizes and methodological quality of systematic reviews deemed ineligible due to overlap with a review with more trials (n = 57 reviews that were excluded after full-text reading for overlap with an included review).

8.1 Back pain & sciatica

Review	Trials	Effect sizes	Comments
INCLUDED REVIEW Ferreira BMJ. 2021 Jan 20;372:m4825	**Back pain** **SNRI** 1. Konno 2016 2. Skljarevski 2009 3. Skljarevski 2010 4. Skljarevski 2010b **TCA** 5. Hameroff 1985 6. Jenkins 1976 7. Atkinson 1998 (+ SSRI) 8. Atkinson 2007 (+ SSRI) 9. Gould 2020 10. Maarrawi 2018 11. Urquhart 2018 12. Pheasant 1982 13. Alcoff 1982 14. Schliessbach 2018 15. Hameroff 1982 **SSRI** 16. Dickens 2000 **NDRI** 17. Katz 2005 **SARI** 18. Goodkin 1990 **Tetracyclic** 19. Atkinson 1999 **Sciatica** **SNRI**	**Outcome: Pain intensity (0-100) (continuous)** **Back pain** **SNRI** MD: -5.3 (-7.3 to -3.3) (4 trials, n = 1415) **TCA** MD: -10.3 (-18.8 to -1.9) (7 trials, n = 591) **SSRI** MD: 1.5 (-5.4 to 8.5) (3 trials, n = 370) **NDRI** MD: -1 (-12.2 to 10.2) (1 trial, n = 44) **SARI** MD: -5.4 (-22.9 to 12.1) (1 trial, n = 40) **Tetracyclic** MD: -4.5 (-20.4 to 11.4) (1 trial, n = 34) **Sciatica** **SNRI**	

	20. Schukro 2016 21. Marks 2014 22. NCT01225068 2014 **TCA** 23. Vanelderen 2015 24. Khoromi 2007 25. Pirbudak 2003	MD: -17.8 (-45.5 to 9.9) (3 trials, n = 96) **TCA** MD: -16 (-31.5 to -0.4) (2 trials, n = 114)	
Kolber Can Fam Physician. 2021;67(1)	**SNRI** 1. Konno 2016 2. Skljarevski 2009 3. Skljarevski 2010 4. Skljarevski 2010b	**Outcome: ≥30% pain relief (dichotomous)** SNRI RR: 1.25 (95% CI 1.13 to 1.38) (4 trials, 1499)	Did not include trials of other antidepressants
Ferraro Syst Rev. 2021;10(1)	**SNRI** 1. Konno 2016 2. Skljarevski 2009 3. Skljarevski 2010 4. Skljarevski 2010b 5. Johnson 2011* 6. NCT03249558* 7. NCT03364075* **TCA** 8. Jenkins 1976 9. Atkinson 1998 (+ SSRI) 10. Atkinson 2007 (+ SSRI) 11. Gould 2020 12. Urquhart 2018 13. Pheasant 1982 14. Alcoff 1982 15. Schliessbach 2018 16. Treves 1991*	**Outcome: Pain intensity (0-100) (continuous)** **SNRI** MD: −5.74 (−7.74, −3.75) (6 trials, n = 1,499) **TCA** MD: -6.49 (-11.05 to -1.92) (5 trials, n = 351) **SSRI** MD: 2.34 (-3.8 to 8.49) (3 trials, n = 172) **Atypical** MD: -1.98 (−6.86, 2.89) (2 trials, n = 83)	SNRI comparison included 2 trials of sciatica included in the Ferreira 2021 review under 'sciatica' (Schukro 2016 and NCT01225068 2014) TCA comparison did not include two trials of amitriptyline (Marrawi 2018; Hameroff 1985) included in the Ferreira 2021 meta-analysis Classified a trial of imipramine (Schliessbach 2018) as being of a tetracyclic antidepressant

	SSRI 17. Dickens 2000 18. NCT00227292* **NDRI** 19. Katz 2005 **SARI** 20. Goodkin 1990 **Tetracyclic** 21. Atkinson 1999 *Johnson 2011 is an abstract only with no data; *NCT00227292, *NCT03249558 and *NCT03364075 had no data *Treves 1991 not truly placebo-controlled	**TeCA** MD: −0.31 (−5.36, 4.75) (2 trials, n = 136)	
Weng Osteoarthritis Cartilage. 2020;28(6)	**SNRI** 1. Konno 2016 2. Skljarevski 2009 3. Skljarevski 2010 4. Skljarevski 2010b	N/A	Combined trials of back pain and osteoarthritis in the same forest plot.
Chou Ann Intern Med.2017;166(7)	1. 10 trials identified from a 2010 Cochrane review (Urquhart 2010) 2. Farajirad 2013* 3. Mazza 2010* 4. Schukro 2016 5. Skljarevski 2009 6. Skljarevski 2010 7. Skljarevski 2010b *Farajirad 2013 and Mazza 2010 are not placebo-controlled	**Outcome: Pain intensity (no scale)** **SNRI** Data not pooled **TCA** SMD: -0.10 (-0.51 to 0.31) (4 trials) **SSRI** SMD: 0.11 (-0.17 to 0.39)	Data for SNRIs not pooled, less trials for the TCA comparison, and no data for other antidepressant classes as reported by Ferreira 2021 Did not pool data for sciatica

8.2 Knee osteoarthritis

Review	Trials	Effect sizes	Comments
INCLUDED REVIEW Ferreira BMJ. 2021 Jan 20;372:m4825	**SNRI** 1. NCT01510457 2012 2. Uchio 2018 3. Abou-Raya 2012 4. Chappell 2009 5. Frakes 2010 6. Chappell 2011 7. Wang 2017 8. Tetreault 2016	**Outcome: Pain intensity (0-100) (continuous)** MD: 9.6 (-12.3 to -6.9) (8 trials, n = 1941)	
Chen Clin J Pain.2021;37(11)	**SNRI** 1. Chappell 2009 2. Chappell 2011 3. Frakes 2011 4. Wang 2017 5. Uchio 2018 6. Abou-Raya	**Outcome: Pain intensity (0-10) (continuous)** MD: -0.74 (-0.92 to -0.57) (5 trials, n = 1695)	It is unclear in the review which time point authors extracted the data from, and why not all available trials had their data extracted (eg Abou-Raya 2012 is included in the review but not included in the meta-analysis).
Weng Osteoarthritis Cartilage. 2020;28(6)	**SNRI** 1. Chappell 2009 2. Chappell 2011 3. Frakes 2011 4. Wang 2017 5. Uchio 2018	N/A	Combined trials of back pain and osteoarthritis in the same forest plot.
Chen Intern Med J.2019;49(12)	**SNRI** 1. Chappell 2009 2. Chappell 2011 3. Frakes 2011 4. Wang 2017 5. Uchio 2018	**Outcome: Pain intensity (0-10) (continuous)** MD: -0.74 (-0.92 to -0.57) (5 trials, n = 1695)	It is unclear in the review which time point authors extracted the data from, and why not all available trials had their data extracted (eg Abou-Raya 2012 is included in the review but not included in the meta-analysis).
Osani Korean J Intern Med. 2019;34(5)	**SNRI** 1. Abou-Raya 2012 2. Chappell 2009	**Outcome: Pain intensity (no scale)** SMD: -0.38 (-0.48 to -0.28)	Included one trial of hand OA (Sofat 2017) which was presented separately

	3. Chappell 2011 4. Frakes 2011 5. Sofat 2017 6. Wang 2017 7. Uchio 2018	(5 trials, n = 1713)	

8.3 Bladder pain syndrome

Review	Trials	Effect sizes	Comments
INCLUDED REVIEW Imamura Cochrane *Database Syst Rev*. 2020;7:CD013325	**TCA** 1. Van Ophoven 2004 2. Foster 2010	**Outcome: Pain intensity (0-100)** MD: -12.7 (-33.1 to 7.6) (2 trials, n = 279)	
Di X Int Urogynecol J.2021;0(0)	**TCA** 1. Van Ophoven 2004	N/A	Only included Van Ophoven 2004 and only provided indirect effects of amitriptyline.
Santos Rev Bras Ginecol Obstet.2018;40(2)	**TCA** 1. Van Ophoven 2004 2. Foster 2010	Results were not pooled	
Pazin C Int Urogynecol J.2016;27(5)	Did not include any randomised trials assessing the efficacy of antidepressants for bladder pain syndrome	N/A	

8.4 Burning mouth syndrome

Review	Trials	Effect sizes	Comments
INCLUDED REVIEW Farag *Oral Dis*. Mar 12 2021	**SARI** 1. Tammiala-Salonen 1999	**Outcome: Pain intensity (0-100)** MD: -1.6 (-6.8 to 3.6) (1 trial, n = 37)	
McMillan Cochrane Database Syst Rev. 2016;0(11)	**SARI** 1. Tammiala-Salonen 1999	**Outcome: Pain intensity (0-10)** MD: 1.26 (-0.24 to 2.76) (1 trial, n = 37)	Same trial included in the Farag 2021 review. This review pooled final scores from the trial, whereas Farag 2021 analysed change scores given the important imbalance in pain levels at baseline reported by Tammiala-Salonen 1999. The effect of trazodone is not statistically significant, but favours the placebo group, whereas in Farag 2021 it favours the trazodone group.
Åšlebioda J Oral Rehabil .2020;47(11)	**SARI** 1. Tammiala-Salonen 1999	Results are presented descriptively only: "Antidepressants (eg trazodone) were tested in a study by Tammiala-Salonen and Forsell (1999). The authors did not observe statistically significant differences between the study group and controls in pain reduction."	
Liu Oral Dis.2018;24(3)	**SARI** 1. Tammiala-Salonen 1999	Results are presented descriptively only: "Other treatments: Benzydamine hydrochloride rinse, lycopene-enriched	

		extra virgin olive oil, *trazodone*, topical urea, and Hypericum perforatum all failed to achieve significant pain or symptom reduction vs placebo.	
Lino Oral Dis. 2018;24(7)	**SARI** 1. Tammiala-Salonen 1999 **SNRI** 2. Forssell 2004 (orofacial pain) **TCA** 3. Raigrodski 2001 (bruxism) 4. Raigrodski 2001b (bruxism)	Results are presented descriptively only "*Trazodone* and hypericum perforatum extract failed to relieve pain in burning mouth syndrome" "[Forssell 2004] found modest results in terms of statistical and clinical significance" "Clinical trials on patients with bruxism compared the use of amitriptyline. In these studies, the results indicated little utility of this therapeutic class in these cases"	Raigrodsky et al 2001 & Raigrodsky et al 2001 are likely the same study split into 2 different manuscripts. Only one of the reports reported on pain levels (Raigrodski AJ. Journal of Prosthodontics, 10: 73-77, 2001). This crossover trial had no wash-out period and for that reason we chose not to include it.

8.5 Fibromyalgia

Review	Trials	Effect sizes	Comments
INCLUDED REVIEW Welsch Cochrane Database Syst Rev.2018 28;2(2):CD010292.	**SNRI** 1. Arnold 2004 2. Arnold 2005 3. Arnold 2010a 4. Arnold 2012a 5. Chappell 2009a 6. Murakami 2015 7. Russell 2008 8. Arnold 2010b 9. Bateman 2013 10. Branco 2010 11. Clauw 2008 12. Matthey 2013 13. Mease 2009b 14. Staud 2015 15. Vitton 2004	**Outcome: Pain reduction ≥50% (dichotomous)** RR: 1.4 (1.3 to 1.6) (15 trials, n = 6918)	
Cording Cochrane Database Syst Rev.2015.10:CD008244	**SNRI** 1. Arnold 2010 2. Bateman 2013 3. Branco 2010 4. Clauw 2013 5. Mease 2009 6. Vitton 2004	**Outcome: Pain reduction ≥50% (dichotomous)** **Milnacipran 100 mg** RR: 1.57 (1.26 to 1.96) (2 trials, 1250) **Milnacipran 200 mg** Did not report outcomes of at least 50% of pain relief **Outcome: Pain reduction ≥30% (dichotomous)** **Milnacipran 200 mg** RR: 1.35 (1.18 to 1.54)	Outcomes of milnacipran 100 mg and 200 mg were reported separately. The included review (Welsch 2018) included more trials of milnacipran and all other trials of duloxetine. Results for milnacipran only in the Welsch 2018 review are consistent (not reported in this overview) **Outcome: Pain reduction ≥50% (dichotomous)** RR: 1.43 (1.31, 1.56) (8 trials, n = 4336)

		(3 trials, n = 1798)	
Lian Int J Neurosci.2020;130(1):71-82	**SNRI** 1. Arnold 2004 2. Arnold 2005 3. Arnold 2010 4. Arnold 2012 5. Chappell 2008 6. Russell 2008 **7.** Murakami 2015	**Outcome: Pain reduction ≥50% (dichotomous)** RR: 1.45 (1.27 to 1.66) (7 trials, n = 2585) **Outcome: Pain intensity (no scale)** SMD: -0.26 (-0.35 to -0.18) (7 trials, n = 2617)	Results are consistent with those from the Welsch 2018 Cochrane review for duloxetine only: RR: 1.43 (1.23 to 1.67) (7 trials, n = 2582) The negligible differences are due to the choice of statistical model (Welsch 2018 used an inverse variance random effects model; Lian 2020 used a Mantel-Haenszel fixed effects model) and the extra 2 events in the duloxetine group reported in Murakami 2015 (66 in Welsch 2018 vs 66 in Lian 2020)
Lee Rheumatol Int.2016;36(5):663-72	**SNRI** 1. Arnold 2005 2. Russell 2008 3. Clauw 2008 4. Branco 2010 5. Arnold 2010	Direct effects of SNRIs were not reported in the review	
VanderWeide J Clin Pharm Ther.2015;40(1)	**SNRI** 1. Dwight 1998* 2. Sayar 2003* 3. Evren 2004* 4. Diaz-Marsa 2011* **5.** Ziljstra 2002 *****All 4 trials are open label and therefore not eligible	Results are described descriptively for each trial individually	The only placebo-controlled trial by Ziljstra 2002 was excluded from Welsch 2018 as it was only available as an abstract.
Lunn Cochrane Database Syst Rev.2014;0(1): CD007115	**SNRI** 1. Arnold 2004 2. Arnold 2005	**Outcome: Pain reduction ≥50% at 12 weeks or less (all doses) (dichotomous)**	All trials were also included in the Welsch 2018 review. The review also pooled data stratified by dose.

	3. Arnold 2010 4. Arnold 2012 5. Chappell 2008 6. Russell 2008	RR: 1.5 (1.29 to 1.75) (5 trials, n = 1887) **Outcome: Pain reduction ≥50% at more than 12 weeks (all doses) (dichotomous)** RR: 1.4 (1.09 to 1.79) (2 trials, n = 845)	
INCLUDED REVIEW Welsch Cochrane Database Syst Rev. 2018 6;8(8):CD012708.	**Atypical (Mirtazapine)** 1. JapicCTI-101176 2. Miki 2016 3. Yeephu 2013	**Outcome: Pain reduction ≥50% (dichotomous)** RR: 1.3 (0.9 to 1.9) (3 trials, n = 591)	
Ottman Rheumatol Int. 2018 Dec;38(12):2217-2224	**Atypical (Mirtazapine)** 6. Samborski 2004* 7. Yeephu 2013 8. Miki 2016 9. Suttiruksa 2016 Samborski 2004 is an open-label trial	Results are presented descriptively for each trial only	Suttiruksa 2016 was not included in Welsch 2018. The trial included 40 participants. Using data from table 5 (means and SEs from each group), we combined estimates for both treatment arms (mirtazapine 15 mg + mirtazapine 30 mg) in RevMan 5.4. We estimated the between-group mean difference (95% CI) of mirtazapine vs placebo (0-100) to be: **-8.48 (-52.56 to 35.60).** We consider that this small trial would not have had any impact on the conclusion around the efficacy of mirtazapine for fibromyalgia (inconclusive evidence of no effect).

INCLUDED REVIEW Moore Cochrane Database Syst Rev. 2015 7:CD011824	**TCA** 1. Braz 2013 2. Carette 1986 3. Carette 1994 4. Carette 1995 5. de Zanette 2014 6. Ginsberg 1996 7. Goldenberg 1986 8. Goldenberg 1996 9. Hannonen 1998	**Outcome: ≥50% pain reduction (dichotomous)** RR: 2.9 (1 to 8.7) (4 trials, n = 275)	Data were re-analysed using a random effects model as described in supplementary file 6.
Moore Cochrane Database Syst Rev. 2012 12:CD008242	**TCA** 1. Carette 1986 2. Carette 1994 3. Carette 1995 4. Ginsberg 1996 5. Goldenberg 1986 6. Goldenberg 1996 7. Hannonen 1998	**Outcome: Second-tier efficacy eg ≥30% pain reduction (dichotomous)** RR: 2.9 (1.7 to 4.9) (4 trials, n not provided)	The effect estimate is the same as reported by Moore 2015. For reasons stated elsewhere, we re-analysed the data pooled from the 4 trials using a random-effects model due to the marked heterogeneity (>55%), which led to more imprecise estimates as seen above for Moore 2015.

8.6. Functional dyspepsia

Review	Trials	Effect sizes	Comments
INCLUDED REVIEW Ford Aliment Pharmacol Ther. 2021 Jan;53(1):8-21.	**SNRI** 1. van Kerkhoven 2008* **SSRI** 2. Tan 2012 3. Talley 2015 (also has a TCA arm) **TCA** 4. Braak 2011 5. Cheong 2018 6. Kaosombatwattana 2018* **Atypical** 7. Tack 2016 *Did not report pain outcomes	**Outcome measure: Pain intensity (continuous)** **SSRI** MD: 1.3 (-5.9 to 8.5) (2 trials, n = 291) **TCA** MD: -2.3 (-7.3 to 2.8) (3 trials, n = 293) **Atypical** MD: 1.7 (-21.2 to 24.6) (1 trial, n = 34)	
Ford Gut.2017;66(3)	**SNRI** 1. van Kerkhoven 2008 **SSRI** 2. Tan 2012 3. Talley 2015 (also has a TCA arm) **TCA** 4. Braak 2011 5. Wu 2011* **Atypical** 6. Tack 2016	N/A	As with the Ford 2021 review, this review did not report data on pain outcomes, but some of the included trials did report pain outcomes, which we extracted

	*Wu 2011 is a conference abstract that was subsequently published as full article as Cheong 2018 (included in the Ford 2021 review)		
Hojo Intern Med.2017;56(23)	**SNRI** 1. van Kerkhoven 2008 **SSRI** 2. Tan 2012 3. Talley 2015 (also has a TCA arm) **TCA** 4. Braak 2011 5. Otaka 2005* **Tetracyclic** 6. Tanum 1996* * Otaka 2005 does not contain a placebo-controlled comparison of amitriptyline * Tanum 1996 includes patients with 'functional gastrointestinal disorders', not functional dyspepsia	**Outcome measure: Not described (dichotomous)** **SNRI** RR: 1.02 (0.80-1.31) (1 trial, n = 160) **SSRI** RR: 1.01 (0.87 to 1.18) (1 trial, n = 193)	The SNRI trial (van Kerkhoven 2008) did not measure pain outcomes specifically

8.7 Irritable bowel syndrome

Review	Trials	Effect sizes	Comments
INCLUDED REVIEW Ford Am J Gastroenterol. 2019 Jan;114(1):21-39	**TCA** 1. Heefner 1978 2. Vij 1991 3. Vahedi 2008 4. Ghadir 2011 **SSRI** 5. Kuiken 2003 6. Tabas 2004 7. Vahedi 2005	**Outcome: Abdominal pain not improving (dichotomous)** **TCA** RR: 0.6 (0.4 to 0.8) (4 trials, n = 184) **SSRI** RR: 0.6 (0.3 to 1.3) (3 trials, n = 167)	
Xie PLoS One.2015;10(8)	**TCA** 1. Talley 2008 (also has a SSRI arm) **SSRI** 2. Creed 2003* 3. Talley 2008 4. Ladabaum 2010 *Not a placebo-controlled trial	**Outcome: Improvement in the degree of abdominal pain (continuous)** **TCAs** MD: -37.9 (-63.89 to -11.91) (1 trial, n = 34) **SSRI*** MD: -6.26 (-20.37 to 7.85) (2 trials, n = 78) *The SSRI pooled estimate excludes the non-placebo-controlled trial, converted all data into a common 0-100 scale, and reported the sample size that provided data at follow-up at week 8 in Ladabaum 2010 (n = 45 instead of n = 54 as reported in the review)	Pooled data on pain presented in the review (eg Figure 5) used mean differences to summarise findings; studies presented data in different scales (e.g. 0-10 and 0-100) but the authors of the systematic review did not conduct the appropriate conversions so that all data could be on the same scale. Outcomes for TCA and SSRIs from these extra two trials match those reported in our overview.

8.8 Musculoskeletal pain

Review	Methodological quality	Trials	Effect sizes	Comments
van den Driest Fam Pract.2017;34(2)		**TCA** 1. Farajirad 2013* 2. Schreiber 2001* 3. Kalita 2014* 4. Stein 1996* 5. Goldman 2010 6. Frank 1988 7. Grace 1985 *Not placebo-controlled trials	Outcomes were presented descriptively only	This review included trials conducted in different types of musculoskeletal pain, namely low back pain, arm pain, whiplash, and rheumatoid arthritis.

8.9 Neuropathic pain

Review	Trials	Effect sizes	Comments
INCLUDED REVIEW Caruso Pain. 2019 Oct;160(10):2186-2198.	**SNRI** 1. Allen 2014 2. Fann 2015 3. Forssell 2004 4. Gao 2010 5. Gao 2015 6. Goldstein 2005 7. Harrison 2013 8. Hyer 2015 9. Marks 2014 10. Raskin 2015 11. Richards 2015 12. Rowbotham 2004 13. Schukro 2016 14. Simpson 2001* 15. Smith 2013 16. Tasmuth 2002 17. Vollmer 2014 18. Vranken 2011 19. Wernicke 2006 20. Yasuda 2011	**Outcome: Pain intensity (continuous)** MD: -6.8 (-8.7 to -4.8) (12 trials, n = 3010)	Some trials were not analysed as their population was not judged by us to be neuropathic pain (see supplementary file 6 under Caruso 2019 for more details) The review also included trials of other antidepressant classes (e.g. TCA)
INCLUDED REVIEW Finnerup Lancet Neurol. 2015 Feb;14(2):162-73	**TCA** 1. Leijon 1989 2. Rintala 2007 3. Max 1987 4. Max 1991 5. Vrethem 1997 6. Sindrup 2003 7. Kieburtz 1998 8. Watson 1982 9. Graff-Radford 2000	**Outcome: Pain reduction ≥30% (dichotomous)** RR: 3.4 (2.1 to 5.5) (14 trials, n = 948)	The review also included trials of other antidepressant classes (e.g. SNRI)

	10. Kishore-Kumar 11. Raja 2002 12. Robinson 2004 13. Kalso 1996 14. Khoromi 2007 15. Panarai 1990 16. Osterberg 2005 17. PhRMA 1008-040 2007		
Falk Can Fam Physician. 2021 May;67(5):e130-e140.	**SNRI** 18. Allen 2014 19. Gao 2010 20. Gao 2015 21. Goldstein 2005 22. Raskin 2005 23. Rowbotham 2005 24. Wernicke 25. Yasuda 2011 **TCA** 1. Shabbir 2011 2. Achar 2010* *Not a placebo-controlled trial	**Outcome: Proportion of patients with a clinically meaningful response to treatment (dichotomous)** **SNRI** RR: 1.45 (1.33 to 1.59) (8 trials, n = 2746) **TCA** RR: 2.35 (0.79 to 6.95) (2 trials, n = 170)	Achar 2010 was not placebo-controlled. It compared amitriptyline to pregabalin to both drugs combined. Shabbir 2011 is a 3-arm placebo-crossover controlled trial comparing amitriptyline to pregabalin to placebo. Outcomes are presented as response to therapy, but data are presented as if the trial had a parallel design. The data do not comply with the minimum data required for pooling of crossover trials according to the Cochrane Handbook (section 23.2.5).
Di Pain Res Manag.2021;2021(0)	**SNRI** 1. Majdinasab 2019* 2. Farshchian 2018 3. Richards 2015 **TCA** 4. Brown 2016* 5. Holbech 2015	The review presented data descriptively only	Farshchian 2018 did not report pain outcomes, but "neuropathic pain grade" which was not defined in the manuscript. Richards 2015 reported pain outcomes in each group stratified by type of pain (neuropathic, nociceptive and mixed). There is a unit of analysis issue with this trial that precludes statistical pooling with other trials. Authors did not report data by participant, but by pain site (a

			participant could have up to 3 pain sites). Holbech 2015 compared imipramine to placebo and found that imipramine resulted in a significant reduction in pain (measured on a 0-10 scale) compared to placebo: MD: -1.08 (-1.52 to -0.64)
Liampas Pain Ther.2021;10(1)	**SNRI** 1. Rowbothan 2004 2. Hai-Yan 2006* 3. Sindrup 2003 4. Razazian 2014* 5. Raskin 2005 6. Goldstein 2005 7. NCT00552175 2007 (Yasuda 2011) 8. Smith 2013 9. Majdinasab 2019* 10. NCT02417935 2015* **SSRI** 11. Otto 2008 **TCA** 12. Vrethem 1997 13. Morello 1999* 14. Bansal 2009* 15. Gilron 2009* 16. Kieburtz 1998 17. Dinat 2015 18. Holbech 2015	The review presented data descriptively only	**SSRI** In Otto 2008, escitalopram significantly reduced pain in patients with polyneuropathy. However, data are presented as if the trial had a parallel design. The data do not comply with the minimum data required for pooling of crossover trials according to the Cochrane Handbook (section 23.2.5). **TCA** Data from the first period in Dinat 2015 showed no significant differences between amitriptyline and placebo on pain intensity (0-10) MD: -0.60 (-1.68, 0.48)

	*Not a placebo-controlled trial		
Moisset Rev Neurol (Paris).2020;176(5)	**SNRI** 1. Schukro 2016 2. Gao 2015 3. Vollmer 2014 4. Enomoto 2018* 5. Zakerkish 2017 (vs TCA) **TCA** 6. Gilron 2015* 7. Holbech 2015 *Not a placebo-controlled trial	The review presented data descriptively only	
Roche Bueno Neurologia (Engl Ed).2020;35(8)	**SNRI** 8. Tasmuth 2002 9. Forssell 2004 10. Yucel 2005		The review pools data from trials of neuropathic pain (Tasmuth 2003 and Yucel 2005) and orofacial pain (Forssell 2004), therefore findings from the meta-analysis are not informative.
Song Pain Physician.2018;21(1)	**TCA** 11. Graff-Radford 2000 12. Raja 2002 13. Chandra 2006* *Not a placebo-controlled trial	**Outcome: Pain intensity (no scale)** SMD: -0.7 (-1.36 to -0.04)	Number of trials that contribute to the direct comparison was not reported. Presumably only Graff-Radford as it is the only placebo-controlled trial to report pain outcomes on a continuous scale.
Aiyer Pain Med.2017;18(10)	**SNRI** 1. Tasmuth 2002 2. Sindrup 2003 3. Forssell 2004 4. Rowbotham 2004 5. Yucel 2005 6. Jia 2006* 7. Kadiroglu 2008* 8. Amr 2010 9. Durand 2012	The review presented data descriptively only	This review included studies conducted in several types of distinct pain conditions, for example: • Atypical chronic orofacial pain (Forssell 2004) • Post-surgical pain (Amr 2010) • Neuropathic pain (eg Sindrup 2003)

	10. Razazian 2014* 11. Richards 2015 *Not a placebo-controlled trial		
Waldfogel Neurology.2017;88(20)	**SNRI** 12. Rowbothan 2003 13. Raskin 2005 14. Goldstein 2005 15. Wernicke 2006 16. Gao 2010 17. Yasuda 2011 18. Allen 2014 19. Gao 2015	**Outcome: Pain intensity (no scale)** **SNRI** Results are presented as the pooled comparison in another systematic review (Griebeler Ann Intern Med. 2014 Nov 4;161(9): 639-49) + two more recent trials (in 1 an SMD could not be calculated) **<u>Duloxetine</u>** SMD (review): -1.33 (-1.82 to -0.86) SMD (trial 1): -0.33 (-0.54 to -0.12) (7 trials, n = 2203) **<u>Venlafaxine</u>** SMD (review): -1.53 (-2.41 to -0.65) (2 trials, n = 304) **TCA** SMD (review): -0.78 (-1.24 to -0.33) (4 trials, n = 81)	
Guan Clin J Pain.2016;32(8)	**SNRI** 1. Smith 2013 **TCA** 2. Gewandter 2014* *Placebo-controlled trial of combination therapy (ketamine	MD: -0.55 (-0.94 to -0.14) (2 trials, n = 639)	Combined data from Smith (duloxetine) and Gewandter (amitriptyline + ketamine combination therapy) into a single forest plot, which we did not consider to be appropriate.

	+ amitriptyline cream vs placebo cream) – the effect of amitriptyline over placebo could not be determined		
Hossain Clin J Pain.2016;32(11)	**SNRI** 1. Gao 2015 2. Tesfaye 2013* 3. Kaur 2011* 4. Yasuda 2011 5. Gao 2010 6. Wernicke 2006 7. Goldstein 2005 8. Raskin 2005 *Not a placebo-controlled trial	The review presented data descriptively only	
Derry Cochrane Database Syst Rev. 2015 Jan 8;1(1):CD011209.	**TCA** 1. Chandra 2006* 2. Gilron 2009* 3. Hammack 2002 4. Khoromi 2007 5. Panerai 1990 6. Watson 1998* *Not a placebo-controlled trial	The review presented data descriptively only	
Derry Cochrane Database Syst Rev.2015;2015(7)	**SNRI** 1. NCT01225068 2014	The review presented data descriptively only	
Gallagher Cochrane Database of Systematic Reviews.2015;0(8)	**SNRI** 1. Forssell 2004 2. Jia 2006* 3. Rowbotham 2004 4. Sindrup 2003 5. Yucel 2005 *Not a placebo-controlled trial	The review presented data descriptively only	Forssell 2004 was conducted in people with atypical chronic orofacial pain, which is not classified as a form of neuropathic pain

Moore Cochrane Database of Systematic Reviews.2015;0(7)	**TCA** 2. Anon 2000 3. Biesbroeck 1995* 4. Boyle 2012 5. Cardenas 2002 6. Graff-Radford 2000 7. Jose 2007 8. Kautio 2008 9. Leijon 1989 10. Max 1992 11. Max 1988 12. Mishra 2012 13. Rintala 2007 14. Rowbotham 2005* 15. Watson 1992* 16. Watson 1998* 17. Vrethem 1997 18. Shlay 1998	The review presented data descriptively only	Max 1992 conducted two crossover trials; the amitriptyline comparison was not placebo-controlled; only the fluoxetine (SSRI) comparison.
Mulla Stroke.2015;46(10)	**TCA** 1. Leijon 1989	**Outcome: Pain intensity (0-10) (continuous)** Leijon was pooled with other three trials of anticonvulsants. The authors' estimated the effect of TCA in Leijon's trial to be: **MD:** -1.22 (-2.72 to 0.28) (1 trial, n = 29)	It is unclear why the MD and (95% CI) for the Leijon 1989 trial are -1.22 (-2.72 to 0.28). Reviewers mentioned having re-analysed the data but no further details were provided. Using data from pain scores at the end of treatment (4 weeks) in table 3, the estimated MD (95% CI) are: Amitriptyline mean, SD, N: 4.2, 1.6, 15 Placebo mean, SD, N: 5.3, 2, 15 MD: -1.1 (-2.4 to 0.2).
Snedecor Pain Pract.2014;14(2)	**SNRI** 2. Gao 2010 3. Goldstein 2005	**Outcome: ≥ 50% pain reduction (0-10) (dichotomous)**	Kvinesdal 1984 is a crossover placebo-controlled trial of imipramine. No

	4. Kadiroglu 2008* 5. Raskin 2005 6. Raskin 2006* 7. Rowbotham 2004 8. Wernicke 2006 9. Yasuda 2011 **TCA** 10. Bansal 2009* 11. Biesbroeck 1995* 12. Dallochio 2000* 13. Jose 2007* 14. Kvinesdal 1984 15. Max 1987 16. Max 1991 17. Max 1992* 18. Morello* *Not a placebo-controlled trial	Venlafaxine RR: 1.54 Duloxetine RR: 1.76* Amitriptyline RR: 0.98 *Denotes a statistically significant effect. The number of trials in each comparison are not reported.	washout period was employed between both treatment periods. Max 1992 conducted two crossover trials; the amitriptyline comparison was not placebo-controlled; only the fluoxetine (SSRI) comparison.
Thompson J Clin Pharm Ther.2015;40(5)	**TCA** 1. Lynch 2003 2. Lynch 2005 3. Ho 2008 4. Barton 2011* 5. Gewandter 2014* 6. Lynch 2005* *Barton 2011 is a placebo-controlled trial of combination therapy that includes amitriptyline *Gewandter 2014 is a placebo-controlled trial of combination	The review presented data descriptively only	We identified a series of issues with the data of the three potentially eligible placebo-controlled crossover trials included in the review which precluded their pooling. Based on guidance from the Cochrane Handbook, we judged whether the data in each trial were sufficient to allow statistical pooling (See section 23.2.5 of the Handbook). For Lynch 2003, Lynch 2005, and Ho 2008 the data do not comply with the minimum data required for pooling of

	therapy that includes amitriptyline *Lynch 2005 is not placebo-controlled		crossover trials according to the Cochrane Handbook (section 23.2.5).
Hearn Cochrane Database Syst Rev. 2014 Sep 23;2014(9):CD011003	**TCA** 1. Kishore-Kumar 1990 2. Max 1991 3. Max 1992 4. Rowbotham 2005 5. Sindrup 1990	The review presented data descriptively only	
Hearn Cochrane Database Syst Rev. 2014 May 19;2014(5):CD010769	**TCA** 1. Kvinesdal 1984 2. Sindrup 1990 3. Sindrup 1992 4. Turkington 1980* *Not a placebo-controlled trial	The review presented data descriptively only	
Snedcor J Pain Res.2013;6(0)	**SNRI** 1. Vranken 2011 **TCA** 2. Cardenas 2011 3. Rintala 2007	The review presented data descriptively only	
Moore Cochrane Database Syst Rev. 2012 12:CD008242	**TCA** 1. Anon 2000 2. Biesbroeck 1995* 3. Jose 2007* 4. Max 1992 5. Graff-Radford 2000 6. Max 1988 7. Rowbotham 2005* 8. Watson 1992* 9. Watson 1998*	The review presented data descriptively only	Max 1992 conducted two crossover trials; the amitriptyline comparison was not placebo-controlled; only the fluoxetine (SSRI) comparison.

	10. Cardenas 2002 11. Rintala 2007 12. Vrethem 1997 13. Kautio 2008 14. Shlay 1998 15. Leijon 1989 *Not placebo-controlled trials		

8.10 Non-cardiac chest pain

Review	Trials	Effect sizes	Comments
INCLUDED REVIEW Atluri Aliment Pharmacol Ther. 2015 Jan;41(2):167-76.	**SSRI** 1. Doraiswamy 2006 2. Keefe 2011 3. Spinhoven 2010 4. Varia 2000	**Outcome: Pain intensity (0-100) (continuous)** MD: -3.8 (-9.8 to 2.3) (4 trials, n = 184)	
Wang Pain Physician.2012;15(2)	**SNRI** 1. Lee 2010 **SSRI** 1. Doraiswamy 2006 2. Spinhoven 2010 3. Varia 2000 4. Zheng 2006 **TCA** 5. Cannon 1994 6. Cox 1998	Meta-analysis combined data from different antidepressant classes (e.g. TCA and SSRI)	Lee 2010's primary outcome was a 'symptom score': a composite measure including pain intensity measured as an ordinal variable (mild, moderate, severe, disabling) and daily frequency. Cannon 1994 did not report pain outcomes neither as a continuous (eg pain intensity) or dichotomous (eg responder analysis) Cox 1998 has a unit-of-analysis issue; they reported the proportion of chest pain episodes, and participants could have reported multiple episodes Zheng 2006 reported that mean (SD) baseline pain scores for all three groups (fluoxetine, placebo, and fluoxetine + olanzapine) were 10 (0). This caused concerns about the data from this trial, and we chose not to include it.
Nguyen Aliment Pharmacol Ther.2012;35(5)	**SNRI** 2. Lee 2010 **SSRI** 3. Doraiswamy 2006 4. Spinhoven 2010 5. Varia 2000	The review presented data descriptively only	Lee 2010's primary outcome was a 'symptom score': a composite measure including pain intensity measured as an ordinal variable (mild, moderate, severe, disabling) and daily frequency.

	TCA 6. Cannon 1994 **SARI** 7. Clouse 1987		Cannon 1994 did not report pain outcomes neither as a continuous (eg pain intensity) or dichotomous (eg responder analysis) Clouse 1987 included participants with oesophageal symptoms, not necessarily non-cardiac chest pain. Only 19/29 included participants had reported chest pain as a symptom.
Burgstaller PLoS One.2014;9(8)	**SSRI** 1. Doraiswamy 2006 2. Keefe 2011 3. Varia 2000 **TCA** 4. Cannon 1994 5. Cox 1998	N/A	Data from SSRI, TCAs and other non-pharmacological treatments (e.g. cognitive behavioural therapy) were pooled in the same meta-analysis; Cannon 1994 did not report pain outcomes neither as a continuous (eg pain intensity) or dichotomous (eg responder analysis) Cox 1998 has a unit-of-analysis issue; they reported the proportion of chest pain episodes, and participants could have reported multiple episodes.

8.11 Postoperative pain

Review	Trials	Effect sizes	Comments
INCLUDED REVIEW Wang Br J Anaesth. 2022 Jan;128(1):118-134.	**SNRI** 1. Amr 2010 2. Ho 2010 3. Saoud 2013 4. Nasr 2014 5. Hyer 2015 6. Castro-Alves 2016 7. Mantay 2016 8. YaDeau 2016 9. Attia 2017 10. Bedin 2017 11. Altiparmak 2018 12. Kassim 2018 13. El-Behairy 2019 14. Koh 2019 15. Bansal 2020 16. Bastanhagh 2020 17. Govil 2020 18. Hatami 2020 19. Hetta 2020 20. Sattari 2020 21. Takmaz 2020 **SSRI** 22. Gordon 1994 23. Chocron 2013 24. Lunn 2015	**Outcome: Pain intensity at 24h (0-100) (continuous)** **SNRI** MD: -7.3 (-12.9 to -1.7) (16 trials, n = 1128) **SSRI** MD: 0 (-7.1 to 7.1) (1 trial, n = 114)	
de Oliveira Filho J Clin Anesth.2020;63(0)	**SNRI** 1. Altiparmak 2018 2. Attia 2017 3. Bedin 2017 4. Castro-Alves 2016 5. El-Behairy 2019 6. Govil 2020	**Outcome: Pain intensity at 24h (0-100) (continous)** MD: -5.9 (-10.6 to -1.2) (10 trials, n = 666)	This review included less trials in the primary comparison of interest (pain at 24 hours)

	7. Ho 2010 8. Kassim 2018 9. Koh 2019 10. Mantay 2016 11. Nasr 2013 12. Takmaz 2019 13. YaDeau 2016		
Bae S Br J Anaesth. 2022 Jan;128(1):98-117	**SNRI** 1. Govil 2020	N/A	This network meta-analysis only included one trial of duloxetine in the duloxetine node and did not report direct effects of duloxetine vs placebo in the manuscript.
Schnabel J Clin Anesth.2021;75(0)	**SNRI** 1. Altiparmak 2018 2. Amr 2010 3. Attia 2017 4. Bedin 2017 5. Castro-Alves 2016 6. El-Behairy 2019 7. Govil 2020 8. Ho 2010 9. Hyer 2015 10. Kassim 2018 11. Koh 2019 12. Mantay 2016 13. Nasr 2013 14. YaDeau 2016	**Outcome: Pain intensity at 24h (0-100) (continuous)** MD: -4.5 (-7.4 to -1.5) (8 trials, n = 569)	Trials included in Schnabel meta-analysis are The following trials were included in the Wang 2022 meta-analysis of pain at 24h, but not in the Schnabel 2021 review: 1. Amr 2010 2. Saoud 2013 3. Nasr 2014 4. Mantay 2016 5. El-Behairy 2019 6. Hatami 2020 7. Hetta 2020 8. Sattari 2020
Branton Int J Clin Pharm.2021;43(2)	**SNRI** 1. Altiparmak 2018 2. Attia 2017 3. Bedin 2017 4. Ho 2010 5. Saoud 2013 6. YaDeau 2016	Outcomes of the review were opioid use.	

Bayoumi Asian Spine J.2019;13(6)	**SNRI** 1. Konno 2016 (Back pain) 2. Fann 2015 (Spinal cord injury) 3. Richards 2015 (Spinal cord injury) 4. Cardenas 2002 (Neuropathic pain)	N/A	This review included both trials and observational studies. Among the trials, there were trials investigating non-antidepressants (eg Farrokhi 2016 – Methylene blue), trials of duloxetine for different conditions (eg Konno 2016 – back pain; Cardenas 2002 – spinal cord injury). All trials of antidepressants were included in other eligible reviews.

8.12 Rheumatic diseases

Review	Trials	Effect sizes	Comments
INCLUDED REVIEW Richards Cochrane Database Syst Rev. 2011 Nov 9;(11):CD008920	**TCA** 1. Ash 1999 2. Bird 2000 3. Fowler 1977 4. Frank 1988 5. Grace 1985 6. Macfarlane 1986 7. Saarialho-Kere 1988 8. Sarzi 1988	Not estimable. No benefit of TCA in the descriptive analysis	
Richards J Rheumatol Suppl. 2012 Sep;90:21-7	**TCA** 1. Ash 1999 2. Bird 2000 3. Fowler 1977 4. Frank 1988 5. Grace 1985 6. Macfarlane 1986 7. Saarialho-Kere 1988 8. Sarzi 1988 9. Koh 1997	Not estimable. No benefit of TCA in the descriptive analysis	This is a slightly modified version of the Richards 2011 Cochrane review included in our overview. Richards 2011 specifically included trials in rheumatoid arthritis, whereas Richards 2012 expanded the previous review by including one extra trial in patients with ankylosing spondylitis. As rheumatoid arthritis and ankylosing spondylitis are two different diseases, we decided to include the 2011 Cochrane review that had a more homogenous inclusion criteria
Ramiro Cochrane Database Syst Rev. 2011 Oct 5;(10):CD008886.	**TCA** 1. Puttini 1988* 2. Saarialho-Kere 1988 *Not a placebo-controlled trial	N/A	Review investigated the effectiveness of combination therapy. Two trials of antidepressants were included, only one was placebo-controlled (Sarrialho-Kere 1988).
Perrot Rheumatology (Oxford). 2008 Aug;47(8):1117-23	**TCA** 1. McDonald 1969 2. Thorpe 1976 3. Gringras 1976 4. MacNeill 1976	NA	Most trials of rheumatic diseases could not have an effect size calculated (e.g. McDonald 1969, Thorpe 1976, Gringras 1976, MacNeill 1976, Wheatley 1986) or included mixed populations (e.g.

	5. Grace 1985 6. Macfarlane 1986 7. Wheatley 1986 8. Frank 1988 9. Usha Rani 1996 10. Koh 1997 11. Ash 1999 12. Bird 2000		Usha Rani 1996 included low back pain, osteoarthritis, rheumatoid arthritis and fibromyalgia). The others (eg Grace 1985, Macfarlane 1986, Frank 1988, Ash 1999, and Bird 2000) were included in the Richards 2011 review that was included in the overview.

Supplementary file 9. Sensitivity analysis excluding trials that appeared in more than one review. Data are presented as either mean difference (MD) or risk ratio (RR) and their respective 95% confidence intervals.

Condition (antidepressant class) [Review]	Original estimate	Sensitivity analysis
Back pain (SSRI) [Ferreira 2021][32] Trial excluded: Dickens 2000	MD: 1.5 (-5.4 to 8.5) 3 trials (n = 170)	MD: 3 (-6.7 to 12.8) 2 trials (n = 78)
Depression and comorbid pain (SSRI) [Gebhardt 2016][31] Trial excluded: Dickens 2000	MD: -5.9 (-10.1 to -1.7) 4 trials (n = 947)	MD: -7 (-12 to -1.9) 3 trials (n = 855)
Sciatica (SNRI) [Ferreira 2021][32] Trial excluded: Marks 2014	MD: -17.8 (-45.5 to 9.9) 3 trials (n = 96)	MD: -7.6 (-33.5 to 18.3) 2 trials (n = 85)
Neuropathic pain (SNRI) [Caruso 2019][36] Trial excluded: Marks 2014	MD: -6.8 (-8.7 to -4.8) 12 trials (n = 3010)	MD: -6.6 (-8.5 to -4.7) 11 trials (n = 3002)
Sciatica (TCA) [Ferreira 2021][32] Trial excluded: Khoromi 2007	MD: -16 (-31.5 to -0.4) 2 trials (n = 116)	MD: -23 (-32.1 to -13.9) 1 trial (n = 30)
Neuropathic pain (TCA) [Finnerup 2015][17] Trial excluded: Khoromi 2007	RR: 3.4 (2.1 to 5.5) 14 trials (n = 948)	RR: 3.8 (2.3 to 6.3) 13 trials (n = 884)

Supplementary file 10. Safety of antidepressants, by class and condition.

Condition	Type of AE	RR (95% CI)	Number of trials (total sample size)
SNRI			
Post-operative pain	PONV Dizziness Drowsiness Headache Pruritus	0.93 (0.70 to 1.23) 1.27 (0.78 to 2.06) 0.99 (0.40 to 2.50) 1.25 (0.63 to 2.48) 0.82 (0.38 to 1.78)	13 (850) 11 (711) 7 (425) 7 (425) 7 (425)
Aromatase inhibitor therapy-induced pain in breast cancer	Any AE	1.58 (1.3 to 1.9)	1 (279)
Back pain, sciatica, and knee osteoarthritis	Any AE	1.23 (1.16 to 1.30)	13 (3447)
Tension-type headache	Any AE	2.55 (0.78 to 8.34)	1 (60)
SSRI			
Post-operative pain	PONV Dizziness Drowsiness	2.95 (0.31 to 28.1) 4.92 (0.24 to 101.7) 4.92 (0.24 to 101.7)	1 (361) 1 (361) 1 (361)
Back pain, sciatica, and knee osteoarthritis	Any AE	1.53 (0.19 to 12.61)	2 (80)
Irritable bowel syndrome	Any AE	1.36 (0.70 to 2.66)	2 (63)
Migraine	Any AE	1.35 (0.54 to 3.41)	2 (84)
Tension-type headache	Any AE	1 (0.57 to 1.76)	1 (80)
TCA			
Back pain, sciatica, and knee osteoarthritis	Any AE	1.49 (0.95 to 2.34)	8 (711)
Functional dyspepsia	Any AE	1.65 (1.11 to 2.45)	2 (232)
Fibromyalgia	Any AE	1.92 (0.95 to 3.85)	4 (318)
Bladder pain syndrome	Any AE	2.20 (0.56, 8.75)	2 (319)
Irritable bowel syndrome	Any AE	1.59 (1.23 to 2.06)	6 (388)
Vulvodynia	Dry mouth Hot flushes Dizziness Soreness Tachycardia (+100bpm) Liver enzymes Hypertension	2.89 (1.11, 7.58) 4.08 (1.20, 13.85) 3.06 (1.04, 9.04) 0.40 (0.15, 1.03) 8.91 (1.15, 68.87) 3.33 (0.14, 80.11) 3.33 (0.14, 80.11)	1(112)
Acute oral mucositis	Stinging or burning Drowsiness	5.6 (2.9 to 8.3)* 1.7 (-1.2 to 4.6)*	1 (127)
Tension-type headache	Abdominal Pain Blurred vision Dizziness Drowsiness Dry mouth Nausea/vomiting Sleep Disturbance Diaphoresis Weight gain	1.4 (0.84 to 2.4) 1.04 (0.56 to 1.9) 1.1 (0.71 to 1.7) 1.9 (1.2 to 2.9) 2.3 (1.6 to 3.3) 0.73 (0.25 to 2.2) 0.6 (0.34 to 1.1) 1.1 (0.39 to 3.1) 1.5 (0.63 to 3.4)	5 (415) 3 (366) 6 (366) 6 (578) 3 (203) 7 (564) 2 (221) 2 (193) 3 (268)
Phantom limb pain	Dry mouth Drowsiness Blurred vision Constipation Dizziness Heartburn	1.06 (0.69 to 1.6) 1.06 (0.54 to 2.05) 0.21 (0.03 to 1.64) 1.41 (0.36 to 5.43) 0.7 (0.13 to 3.37) 0.15 (0.01 to 2.72)	1 (39)

	Poor sleep Palpitations Nausea/vomiting Better sleep Urinary retention Diarrhea Tinnitus Tremor Sweating Headache	1.06 (0.17 to 6.72) 0.21 (0.01 to 4.11) 5.26 (0.27 to 102.66) 5.26 (0.27 to 102.66) 1.06 (0.07 to 15.64) 1.06 (0.07 to 15.64) 1.06 (0.07 to 15.64) 0.35 (0.02 to 8.09) 0.35 (0.02 to 8.09) 0.35 (0.02 to 8.09)	
NDRI			
Back pain, sciatica, and knee osteoarthritis	Any AE	2.80 (1.30 to 6.02)	1 (99)
Atypical/tetracyclic			
Back pain, sciatica, and knee osteoarthritis	Any AE	0.96 (0.79 to 1.16)	1 (36)
Functional dyspepsia	Any AE	1.00 (0.16 to 6.30)	1 (34)
Fibromyalgia	Any AE	1.16 (0.97 to 1.39)	3 (606)
Tension-type headache	Abdominal Pain Blurred vision Dizziness Drowsiness Dry Mouth Nausea/vomiting Sleep Disturbance Diaphoresis Weight gain	2.4 (0.89 to 6.5) 3.9 (0.48 to 31.1) 0.86 (0.16 to 4.8) 1.8 (0.71 to 4.6) 2 (0.41 to 10.1) 0.26 (0.03 to 2.1) 0.33 (0.01 to 7.8) 1.3 (0.19 to 8.6) 2 (0.19 to 20.6)	2 (108) 1 (62) 1 (62) 1 (46) 2 (108) 1 (46) 1 (62) 1 (46) 1 (76)
MAOI			
Fibromyalgia	Depression Dizziness Gastric discomfort Headache Insomnia Nausea and vomiting Pain increase Palpitations Sleepy during the day	4.89 (0.24 to 99.08) 3.91 (0.45 to 33.63) 1.96 (0.18 to 20.80) 2.93 (0.63 to 13.76) 2.93 (0.32 to 27.14) 7.82 (1.02 to 59.97) 4.89 (0.24 to 99.08) 2.93 (0.32 to 27.14) 4.89 (0.24 to 99.08)	1 (89)

SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors, TCA, tricyclic antidepressants, NDRI, noradrenaline-dopamine reuptake inhibitor; MAOI, Monoamine oxidase inhibitors, PONV, postoperative nausea and vomiting

*Data measured on a continuous 0-10 scale

Supplementary file 11. Tolerability (withdrawals due to adverse events) of antidepressants, by class and condition. Comparison between antidepressants versus placebo expressed as risk ratios (RR) and 95% CIs.

Condition	RR (95% CI)	Number of trials (total sample size)
SNRI		
Aromatase inhibitor therapy-induced pain in breast cancer	1.10 (0.62, 1.96)	1 (279)
Back pain, sciatica, and knee osteoarthritis	2.16 (1.71 to 2.73)	12 (3638)
Functional dyspepsia	4.25 (1.50 to 12.07)	1 (160)
Atypical chronic orofacial pain	3 (0.70 to 12.9)	1 (36)
Neuropathic pain	2.66 (1.98 to 3.57)	13 (2743)
Fibromyalgia	1.94 (1.60, 2.35)	15 (7029)
Migraine	6.2 (0.37 to 104.6)	1 (60)
Tension-type headache	10 (0.59 to 170.3)	1 (60)
SSRI		
Back pain, sciatica, and knee osteoarthritis	2.36 (0.39 to 14.28)	2 (107)
Functional dyspepsia	1.94 (1.03 to 3.67)	2 (388)
Chronic prostatitis	1.60 (0.63, 4.09)	1 (42)
Fibromyalgia	1.44 (0.62, 3.33)	5 (284)
Migraine	1.2 (0.41 to 3.53)	4 (161)
Tension-type headache	0.33 (0.01 to 8.22)	2 (130)
Non-cardiac chest pain	2.08 (0.77 to 5.60)	3 (154)
TCA		
Back pain, sciatica, and knee osteoarthritis	1.48 (0.88 to 2.50)	11 (969)
Functional dyspepsia	1.31 (0.40 to 4.29)	4 (394)
Vulvodynia	1.97 (0.37, 10.39)	1 (133)
Tension-type headache	1.6 (0.78 to 3.1)	8 (894)
Phantom limb pain	4.76 (0.24, 93.19)	1 (39)
Fibromyalgia	1.03 (0.49 to 2.16)	4 (298)
Neuropathic pain	2.69 (1.57 to 4.61)	13 (931)
Rheumatoid arthritis	0.98 (0.59 to 1.64)	6 (455)
NDRI		
Back pain, sciatica, and knee osteoarthritis	6.86 (0.36 to 129.48)	1 (99)
SARI		
Back pain, sciatica, and knee osteoarthritis	2.73 (0.31 to 24.14)	1 (42)
Burning mouth syndrome	3.69 (0.88, 15.49)	1 (37)
Atypical/tetracyclic		
Back pain, sciatica, and knee osteoarthritis	3.18 (0.41 to 24.39)	1 (52)
Fibromyalgia	1.01 (0.41 to 2.46)	3 (606)
Tension-type headache	4 (1.5 to 10.9)	1 (76)
MAOI		
Fibromyalgia	1.72 (0.53 to 5.59)	2 (149)

SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors, TCA, tricyclic antidepressants, NDRI, noradrenaline-dopamine reuptake inhibitor; SARI, serotonin antagonist and reuptake inhibitors; MAOI, Monoamine oxidase inhibitors