Appendix 1

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Guideline and Systematic Reviewer Disclosed Conflicts of Interests

Name	Affiliation	Written Articles*	Presented*	Created Apps, Software, Tools, etc.*	Advisory Board	Speaker's bureau	Payment	Grant(s) or Honorariums	Patents	Investments	Clinical Trial
Guideline Committee											
Christina Korownyk	Professor, Dept of Family Medicine, University of Alberta	Tools for practice	PEIP - Practical Evidence for Informed Practice	X	X	X	X	ACFP, CFPC	X	X	CIHR, PRIHS
Simon Moore	Clinical Associate Professor, UBC Department of Family Practice	X	UBC CPD, Cannabis flowchart, VGH Family Medicine Review conference, Cannabis flowchart	X	The Review Course in Family Medicine, Co-Founder Vital FM Update, Speaker BC College of Family Physicians, Consultant College of Family Physicians of Canada, Consultant Doctors of BC, Consultant UBC Continuing Professional Developmen t, Consultant & Speaker University of British	X	X	The Review Course in Family Medicine, Co-Founder Vital FM Update, Speaker BC College of Family Physicians, Consultant College of Family Physicians of Canada, Consultant Saskatchewan College of Family Physicians, Speaker PEI College of Family Physicians, Speaker	X	X	X

					Columbia, Clinical Faculty			Doctors of BC, Consultant Seymour Clinic, Clinician Fraser Health, Clinician Vancouver Coastal Health, Clinician Govt. of Northwest Territories, Clinician UBC Continuing Professional Development, Consultant & Speaker University of British Columbia, Clinical Faculty Fraser Valley CPA Association, Speaker Alberta College of Family Physicians, Speaker			
Candice Rochford	Nurse Practitioner	X	X	X	X	X	X	X	X	X	X

Kira Ellis	Senior Consultant, Physiotherapist, Alberta Health Services Rehabilitation Advice Line	X	X	x	X	X	X	GLAD Canada – previous role as Senior Practice Lead with Bone and Joint Health Strategic Clinical Network, I collaborated with GLAD Canada to implement the program in Alberta.	X	X	X
Sean Darling	PhD, Adjunct Assistant Professor, School of Public Administration, University of Victoria	X	X	X	X	X	X	X	X	X	X
Lori Montgomery	Family physician with focused practice in chronic pain	Montgomery LS, Pain management with opioids in adults, J Neurosci Res;00:1–9m, 2020. -- AJ Clark, P Taenzer, N Drummond, CC Spanswick, LS Montgomery , T Findlay, JX Pereira, T	Multiple events	Headache Pro, a free app designed and provided through Alberta Health Services to guide patients and providers through the	X	X	X	Alberta College of Family Physicians: teaching honoraria and mentorship in the Collaborative Mentorship Network College of Family Physicians of Canada:	X	X	Hotchkiss Brain Institute (University of Calgary)

		Williamson, L Palacios-Derflingher, T Braun, Physician-to-physician telephone consultations for chronic pain patients: A pragmatic randomized trial. Pain Res Manag. 2015 Oct 16. -- J. Cote and LS Montgomery, Sublingual Buprenorphine as an Analgesic in Chronic Pain: A Systematic Review, Pain Medicine, 15(7):1171–1178, July 2014		TOP headache guidelines.				honoraria for committee work and teaching CBT Canada: teaching Alberta Health Services - medical leadership role			
Jennifer Young	Community Family Physician	X	X	X	X	X	X	X	X	X	X
Marie-Christine Taillefer	Clinical Psychologist, Pain Clinic of the Centre Hospitalier de l'Université de Montréal (CHUM), Montreal	As part of my post-doc duties (before 2007); Since then, with colleagues. Stopped being an external reviewer for Hong Kong	Migraine Québec.	X	X	X	X	X	X	X	X

	(Quebec), Canada	Medical Research Office (grant proposals; with honorarium) in July 2021									
Alexander Singer	Associate Professor, University of Manitoba	X	X	X	X	X	X	CIHR, Research Manitoba, CIMVHR, IBM, Calian - Grant funding for investigator driven research	X	X	X
Jacqueline Myers	Clinical Pharmacist - Saskatchewan Health Authority, Regina Area	Co-author of "Buprenorphine -naloxone microdosing" in Canadian Family Physician	RxFiles Conference, Saskatchewan Health Authority Chronic Pain Pathway Engagement Session	X	X	X	X	University of Toronto	X	X	X
Peter MacDougall	Professor, Department of Anesthesia Pain Management and Perioperative Medicine, Dalhousie University	A P journal club	Multiple events	X	X	X	X	X	X	X	X
Adrienne Lindblad	Clinical Evidence Expert Lead, College of Family Physicians of	Author on PEER Systematic Reviews and KT documents on	Pain Guideline at the Practical Evidence for Informed Practice	Assisted in the developme nt of Pain calculator	X	X	X	Alberta College of Family Physicians, Alberta Pharmacists	X	X	X

	Canada; Associate Clinical Professor, Department of Family Medicine, University of Alberta	osteoarthritis, chronic low back pain and chronic neuropathic pain. Author on Tools for Practice articles #266 (exercise-induced osteoarthritis), 254 (physical activity prescriptions). Author on PEER medical cannabinoid systematic review and guideline.	Conference in 2021; Pain Jeopardy at the Alberta College of Family Physicians Family Medicine Summit 2019; Exercise is Medicine at the Practical Evidence for Informed Practice Conference in 2019; Medical Cannabinoids at the Canadian Anesthesia Society Conference in 2019, and The Canadian Society for Pharmacology and Therapeutics in 2019, the Family Medicine Forum in 2018 and the Occupational and Emergency					Association, North of 44 Primary Care Symposium, Canadian Anesthesia Society, Canadian Society for Pharmacology and Therapeutics, College of Family Physicians of Canada, Occupational and Emergency Medicine Association of Canada			

			Medicine Association of Canada in 2018.								
Evidence Review team											
G. Michael Allan	Director Practice Support at The College of Family Physicians of Canada, Adjunct Professor University of Alberta	Tools for Practice, Canadian Family Physician journal	Multiple events	Pain calculator and decision support tools that accompanied the systematic reviews	X	X	X	Colleges of Family Physicians Provincial Chapters. Hospital/Regional Health (Peterborough Hospital, Pain Society, Sharp Rees-Stealy Medical Group, William Osler Health Region); Other (AMMI Canada, Diabetes Society Edmonton, SRPC, Vital FM, Best Science Medicine)	X	X	BedMed clinical trial
Samantha Moe	Clinical Evidence Expert, The College of Family Physicians of Canada	PEER	CFPC, FMF	For PEER	X	X	X	X	X	X	X

Jennifer Potter	Assistant Professor, University of Manitoba Department of Family Medicine	X	X	X	X	X	X	College of Family Physicians of Canada, Doctors Manitoba, Winnipeg Regional Health Authority and the University of Manitoba	X	X	X
Scott Garrison	Professor, University of Alberta, Dept of Family Medicine	co-author on the PEER systematic reviews	X	X	X	X	X	X	X	X	Canadian Institutes of Health Research (CIHR), Alberta Innovates Health Solutions (AHS)
Betsy Thomas	Clinical Evidence Expert, The College of Family Physicians of Canada	PEER Systematic Reviews on Osteoarthritis Pain, Chronic Low Back Pain and Neuropathic Pain	Collaborative Mentorship Network (March 2020)	X	X	X	X	X	X	X	X
Michael R Kolber	Professor University of Alberta Department of Family Medicine	X	X	X	X	X	X	X	X	EMPRSS - Co-founder of University of Alberta spin off company - that works	Co-investigator BedMed study: funded by CIHR

										on synthesizing and reporting quality metrics in endoscopy	
Allison Paige	Assistant Professor, University of Manitoba Department of Family Medicine	X	X	X	X	X	X	X	X	X	X
Jessica Kirkwood	Assistant Professor, University of Alberta	PEER systematic reviews and knowledge translation tools on chronic low back pain and chronic neuropathic pain	Presented to the ACFP's Collaborative Mentorship Network on Chronic Low Back Pain and Chronic Neuropathic Pain	X	X	X	X	Alberta College of Family Physicians	X	X	X
Anthony D. Train	Assistant Professor, Queen's University Dept. of Family Medicine	Management of chronic neuropathic pain in primary care. Canadian Family Physician,	X	X	X	X	X	College of Family Physicians of Canada (CFPC) Canadian Task Force on Preventive Health Care (CTFPHC)	X	X	X
Joey Ton	Program Manager, College of Family Physicians of Canada	Written tools for practice evidence summaries related to chronic pain for	ACFP conference about chronic pain conditions.	Project managed the pain-calculator project which is an	X	X	X	ACFP: Speaker Honoraria, and OCFP: Contract Project Work	X	X	X

		the CFPC, part of three systematic reviews about various chronic pain conditions as part of the work of the CFPC.		online based calculator that helps clinicians select interventions for chronic pain.							
Ricky Turgeon	Assistant Professor / Clinical Pharmacy Specialist	X	X	X	X	X	X	X	X	X	X
Karenn Chan	Associate Professor University of Alberta	PEER systematic reviews on chronic pain for OA, low back pain, and neuropathic pain.	X	X	Roche - Alzheimer's Disease Pathway Co-creation workshop (no financial incentive was accepted)	X	X	Office of the Public Guardian and Trustee of Alberta. Medical Council of Canada. University of Calgary. Alberta College of Family Physicians. Health Canada. Northern Alberta Academic Family Physician Fund.	X	X	X
Tony Nickonchuk	Alberta Health Services, Drug Utilization and	X	X	X	X	X	X	Alberta Expert Committee	X	X	X

	Stewardship Pharmacist							for Drug Evaluation and Therapeutics Practical Evidence for Informed Practice Conference			
Danielle Perry	Clinical Evidence Expert, College of Family Physicians of Canada	Three systematic reviews published in Canada Family Physician related to this guideline (Osteoarthritis, Low Back Pain, Neuropathic Pain).	X	Involved in clinical decision aids for osteoarthritis, low back pain and neuropathic pain.	X	X	X	College of Family Physicians of Canada, Correctional Services of Canada, Alberta College of Family Physicians, Centre for Effective Practice, Dalhousie Continuing Professional Development Program, Prince Edward Island College of Family Physicians	X	X	X
Justin Weresch	Assistant Professor, Department of Family Medicine,	X	X	X	X	X	X	Family Medicine Associates	X	X	X

	McMaster University										
Jamie Falk	Associate Professor and Pharmacist, College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba	PEER Neuropathic Pain SR PEER Simplified decision aid for neuropathic pain	BC Naturopathic Association education series: chronic low back pain and neuropathic pain (2021) and topical analgesics (2020) Therapeutics Initiative annual conference: topical analgesics (2019)	X	X	X	X	College of Pharmacists of Manitoba	X	X	X
James McCormack	Professor, UBC	X	X	X	X	X	X	X	X	X	X
Nicolas Dugré	Pharmacist, CIUSSS du Nord-de-l'Ile-de-Montréal, Assistant clinical professor, Faculty of pharmacy, University of Montréal	Multiple PEER articles	X	X	X	X	X	X	X	X	X

* On Topics related to guidelines.

Evidence Summary: Drugs and Doses

Evidence Summary: Drugs and Doses			
Low Back Pain			
Class	**Author, Year**	**Intervention(s)**	**Dose and Frequency**
Anticonvulsants	Atkinson, 2016	Gabapentin	3265 mg (mean)
Cannabinoids	Pinsger, 2006	Nabilone	0.25 mg to 1 mg per day
Corticosteroid Injections	Arden, 2005	Corticosteroids	Injections at week 0, 3, 6 Lumbar epidural steroid injections
Corticosteroid Injections	Carette, 1997	Methylprednisolone	Injections at weeks 0, 3, 6 Epidural injections
Corticosteroid Injections	Ghahreman, 2010	Bupivacaine 0.5% followed by Triamcinolone	Up to 3 transforaminal injections
Corticosteroid Injections	Ghai, 2015	Lidocaine 0.5% mixed with Methylprednisolone	Multiple fluoroscopic guided epidural injections, offered if deterioration of pain relief was <50% (spaced 15 days apart at minimum)
Corticosteroid Injections	Manchikanti, 2012	Lidocaine 0.5% mixed with Betamethasone	Multiple caudal epidural injections offered
Corticosteroid Injections	Manchikanti, 2012a	Lidocaine 0.5% mixed Methylprednisolone or Betamethasone	Multiple fluoroscopic caudal epidural injections offered if deterioration of pain relief was <50%
Corticosteroid Injections	Manchikanti, 2014	Local anesthetic and Betamethasone	Transforaminal epidural injections; 6 procedures in 104 weeks
Corticosteroid Injections	Ng, 2005	Methylprednisolone and Bupivacaine	Periradicular infiltration under fluoroscopic guidance (single injection)

Corticosteroid Injections	Nguyen, 2017	Contrast and Prednisolone	One intradiscal injection
Corticosteroid Injections	Saqib, 2016	Methylprednisolone and Bupivacaine Single Injection Bupivacaine	One fluoroscopic guided intralaminar injection
Oral NSAIDs	Coats, 2004	Valdecoxib	40 mg; daily
Oral NSAIDs	Katz, 2011	Naproxen	1000 mg; daily
Oral NSAIDs	Katz, 2003	Rofecoxib	25 or 50 mg; once daily
Oral NSAIDs	Kivitz, 2013	Naproxen	500 mg; twice daily
Rubefacients	Chrubasik, 2010	Capsaicin	0.05%
Rubefacients	Frerick, 2003	Capsaicin Plaster	Applied once daily for 4-8 hours
Rubefacients	Keitel, 2001	Capsaicin Plaster	11 mg; applied once daily for 4-12 hours
SNRIs	Konno, 2016	Duloxetine	60 mg; daily
SNRIs	Skljarevski, 2009	Duloxetine	20, 60 or 120 mg; daily
SNRIs	Skljarevski, 2010	Duloxetine	60 mg; daily
SNRIs	Skljarevski, 2010a	Duloxetine	60 or 120 mg; daily
Spinal Manipulation	Bialosky, 2014	Lumbar manipulation	6 Sessions; performed a licensed physical therapist
Spinal Manipulation	Bond, 2020	Lumbopelvic manipulation	7 Sessions (three sessions per week for two weeks followed by one follow-up session)
Spinal Manipulation	Ford, 2019	Lumbar manipulation	10, 30-minute sessions; performed by a physiotherapist
Spinal Manipulation	Goertz, 2017	Spinal manipulation: focused on the low back, however, could be delivered to the full spine or extremities	17.5 visits (mean)
Spinal Manipulation	Licciardone, 2013	Lumbar manipulation; soft tissue stretching, kneading and pressure;	6, 15-minute sessions

		myofascial stretching and release	
Topical NSAIDs	Song, 2008	Flurbiprofen Tape	63 mg; worn 12 or 24 hours
Neuropathic Pain			
Drug Class	**Author, Year**	**Intervention(s)**	**Dose and Frequency**
Anticonvulsants	Achar, 2010	Pregabalin	75 mg; twice daily
Anticonvulsants	Arezzo, 2008	Pregabalin	300 mg; twice daily
Anticonvulsants	Baba, 2020	Pregabalin	150 mg; twice daily
Anticonvulsants	Backonja, 1998	Gabapentin	3600 mg (max daily dose)
Anticonvulsants	Backonja, 2011	Gabapentin	624 mg; daily
Anticonvulsants	Beydoun, 2006	Oxcarbazepine	300, 600, or 900 mg; twice daily
Anticonvulsants	CTRI476G2301	Oxcarbazepine	1200 mg; daily
Anticonvulsants	Dogra, 2005	Oxcarbazepine	900 mg; twice daily
Anticonvulsants	Dworkin, 2003	Pregabalin	100-200 mg; three times daily
Anticonvulsants	Guan, 2011	Pregabalin	150-600 mg; daily
Anticonvulsants	Freynhagen, 2005	Pregabalin	Flexible Dose: 75-300 mg; twice daily Fixed Dose: 300 mg; twice daily
Anticonvulsants	Huffman, 2015	Pregabalin	150-300 mg; three times daily
Anticonvulsants	Lesser, 2004	Pregabalin	25, 100, or 300 mg; three times daily
Anticonvulsants	Liu, 2017	Pregabalin	300 mg; daily
Anticonvulsants	McDonnell, 2018	Pregabalin	150 mg; twice daily
Anticonvulsants	Moon, 2010	Pregabalin	600 mg; daily
Anticonvulsants	Mu, 2018	Pregabalin	300 mg; daily
Anticonvulsants	NCT02215252 2014	Pregabalin	300 mg; daily
Anticonvulsants	NCT00394901 2006	Pregabalin	150, 300 or 600 mg; daily
Anticonvulsants	Perez 2000	Gabapentin	1200 mg; daily
Anticonvulsants	Raskin 2004	Topiramate	400 mg; daily
Anticonvulsants	Rauck, 2012	Gabapentin Pregabalin	1200, 2400, or 3600 mg; daily 300 mg; daily
Anticonvulsants	Rice, 2001	Gabapentin	1800 or 2400 mg; daily
Anticonvulsants	Richter, 2005	Pregabalin	150 or 600 mg; daily
Anticonvulsants	Rosenstock, 2004	Pregabalin	300 mg; daily
Anticonvulsants	Rowbotham, 1998	Gabapentin	3600 mg (max daily dose)
Anticonvulsants	Sabatowski, 2004	Pregabalin	150 or 300 mg; daily

Anticonvulsants	Sandercock, 2012	Gabapentin	3000 mg; single daily dose or divided twice daily
Anticonvulsants	Sang, 2013	Gabapentin	1800 mg daily
Anticonvulsants	Satoh, 2011	Pregabalin	150 or 300 mg; twice daily
Anticonvulsants	Shabbir, 2011	Pregabalin	600 mg; daily
Anticonvulsants	Sharma, 2006	Pregabalin	300 mg; twice daily
Anticonvulsants	Smith, 2014	Pregabalin	300 mg; daily
Anticonvulsants	Stacey, 2008	Pregabalin	Flexible (mean 396 mg daily) Fixed (mean 295 mg daily)
Anticonvulsants	Tolle, 2008	Pregabalin	150, 300, or 600 mg; daily
Anticonvulsants	Van-Seventer, 2006	Pregabalin	150, 300, or 600 mg; daily
Anticonvulsants	Vinik, 2014	Pregabalin	300 mg; daily
Anticonvulsants	Wallace, 2010	Gabapentin	1800 mg; single daily dose or divided twice daily
Anticonvulsants	Zhang, 2013	Gabapentin	1200, 2400 or 3600 mg; daily
Anticonvulsants	Ziegler, 2015	Pregabalin	150 mg; twice daily
Cannabinoids	Abrams, 2007	Prerolled, whole-herb Cannabis cigarettes	3.56% THC; one cigarette daily Dose estimate: 32 mg THC per session; 96 mg THC per day
Cannabinoids	Berman, 2004	Nabiximols (Sativex)	Maximum 48 sprays in 24 hours
Cannabinoids	Ellis, 2009	Prerolled, whole-herb Cannabis cigarettes	Titrating dose up or down, starting at 4% and ranging between 1% and 8% THC concentration. Four daily smoking sessions
Cannabinoids	GW Pharmaceuticals, 2005	Nabiximols (Sativex)	Maximum 24 sprays in 24 hours
Cannabinoids	Johnson, 2010	Nabiximols (Sativex)	Maximum 8 sprays in 24 hours
Cannabinoids	Langford, 2013	Nabiximols (Sativex)	Maximum 12 sprays in 24 hours
Cannabinoids	Lynch, 2014	Nabiximols (Sativex)	Maximum 12 sprays in 24 hours
Cannabinoids	Nurmikko, 2007	Nabiximols (Sativex)	Maximum 48 sprays in 24 hours
Cannabinoids	Portenoy, 2012	Nabiximols (Sativex)	Maximum 4, 6-10, or 11-16 sprays per day
Cannabinoids	Rog, 2005	Nabiximols (Sativex)	Maximum 48 sprays in 24 hours
Cannabinoids	Selvarajah, 2010	Nabiximols (Sativex)	Unclear
Cannabinoids	Serpell, 2014	Nabiximols (Sativex)	Maximum 24 sprays in 24 hours
Cannabinoids	Ware, 2010	Gelatin capsules, inhaled through a pipe	3 different potencies of THC: 2.5%, 6%, 9.4%

			1.625 mg, 3.9 mg 5.85 mg/d (average) THC per period
Cannabinoids	Wilsey, 2008	Cannabis cigarettes	3.5% to 7% Dose estimate: 19.25 mg (low dose 7-30.45 mg), 34.3 mg (high dose 18.9-60.9 mg) THC/day
Cannabinoids	Wilsey, 2013	Volcano Vaporizer	8 (minimum) to 12 (maximum) puffs Dose estimate: 10.32 mg, 28 mg TC/d (session) presuming they were administered the entire 800 mg dose
Opioids	Freeman, 2007	Tramadol/ Acetaminophen	37.5 mg/325 mg; 1-2 tablets, four times daily
Opioids	Hanna, 2008	Oxycodone	10-80 mg; daily
Opioids	Jensen, 2006	Oxycodone	60 mg; twice daily
Opioids	NCT01124617 2010	Tapentadol	25-250 mg; twice daily
Opioids	Simpson, 2016	Buprenorphine Patch	5-40 mg/hour
Opioids	Zin, 2010	Oxycodone	2 mg/ml (5mg); twice daily
Rubefacients	Backonja, 2008	Capsaicin Patch	8%; applied once for 60 minutes
Rubefacients	Bernstein, 1989	Capsaicin Cream	0.075%; applied 3-4 times daily
Rubefacients	Capsaicin Study Group, 1992	Capsaicin Cream	0.075%; applied 4 times daily
Rubefacients	Irving, 2011	Capsaicin Patch	8%; applied for one, 60-minute session
Rubefacients	Moon, 2017	Capsaicin Cream	0.075%; applied 3-4 times daily 0.625%; applied in 4-days cycles (3 days on, 1 day off) 1.25%; applied in 4-day cycles (3 das on, 1 day off)
Rubefacients	Simpson, 2017	Capsaicin Patch	8%; applied once for 30 minutes
Rubefacients	Tandan, 1992	Capsaicin Cream	0.075%; applied 4 times daily
Rubefacients	Vinik, 2015	Capsaicin Patch	8%; 60-minute sessions, spaced 8 weeks apart (1-7 treatments) 8%; 30-minutes sessions, spaced 8 weeks apart (1-7 treatments)
Rubefacients	Watson, 1993	Capsaicin Cream	0.075%; applied 4 times daily
Rubefacients	Webster, 2010	Capsaicin Patch	8%; applied for one, 60-minute session

SNRIs	Allen, 2014	Desvenlafaxine	50, 100, 200, or 400 mg; daily
SNRIs	Gao, 2010	Duloxetine	60-120 mg; daily
SNRIs	Gao, 2014	Duloxetine	60 mg; daily
SNRIs	Goldstein, 2005	Duloxetine	20 or 60 mg; daily 120 mg; twice daily
SNRIs	Raskin, 2005	Duloxetine	60 mg; one to two times daily
SNRIs	Rowbotham, 2005	Venlafaxine	75 mg or 150-225 mg; daily
SNRIs	Wernicke, 2006	Duloxetine	60 mg; one to two times daily
SNRIs	Yasuda, 2011	Duloxetine	40 or 60 mg; daily
TCAs	Achar, 2010	Amitriptyline	25 mg; daily
TCAs	Shabbir, 2011	Amitriptyline	10 mg; daily (max dose 75 mg)
Osteoarthritis			
Drug Class	**Author, Year**	**Intervention(s)**	**Dose and Frequency**
Acetaminophen	Herrero-Beaumont, 2007	Acetaminophen	1000 mg; three times daily
Acetaminophen	Miceli-Richard, 2004	Acetaminophen	1000 mg; three times daily
Cannabinoids	Huggins, 2012	PF-04457845 "a potent and selective FAAH1 inhibitor with endocannabinoid properties"	4 mg per day
Chondroitin	Bourgeois, 1998	Chondroitin	1200 mg; daily
Chondroitin	Bucsi, 1998	Chondroitin	800 mg; daily
Chondroitin	Clegg, 2006	Chondroitin	1200 mg; daily
Chondroitin	Kahan, 2009	Chondroitin	800 mg; daily
Chondroitin	Mazieres, 2001	Chondroitin	1000 mg; daily
Chondroitin	Mazieres, 2007	Chondroitin	1000 mg; daily
Chondroitin	Moller, 2010	Chondroitin	800 mg; daily
Chondroitin	Railhac, 2012	Chondroitin	1000 mg; daily
Chondroitin	Reginster, 2017	Chondroitin	800 mg; daily

Corticosteroids	Atchia, 2011	Methylprednisolone	120 mg
Corticosteroids	Conaghan, 2018	Triamcinolone	16 or 32 mg
Corticosteroids	Jones, 1996	Methylprednisolone	40 mg
Corticosteroids	Lambert, 2007	Triamcinolone	40 mg
Corticosteroids	Qvistgaard, 2006	Methylprednisolone	40 mg
Corticosteroids	Ravaud, 1999	Cortivazol	3.75 mg
Corticosteroids	Smith, 2003	Methylprednisolone	120 mg
Glucosamine	Chopra, 2011	Glucosamine	100 mg; daily
Glucosamine	Clegg, 2006	Glucosamine	1500 mg; daily
Glucosamine	Drovanti, 1980	Glucosamine	1500 mg; daily
Glucosamine	Herrero-Beaumont, 2007	Glucosamine	1500 mg; daily
Glucosamine	Hughes and Carr, 2002	Glucosamine	1500 mg; daily
Glucosamine	Noack, 1994	Glucosamine	1500 mg; daily
Glucosamine	Pavelka, 2002	Glucosamine	1500 mg; daily
Glucosamine	Pujalte, 1980	Glucosamine	1500 mg; daily
Glucosamine	Rindone, 2000	Glucosamine	1500 mg; daily
Opioids	Afifalo, 2010	Tapentadol Oxycodone	100-250 mg; twice daily 20-50 mg; twice daily
Opioids	Breivik, 2010	Buprenorphine Transdermal Patch	10-20 mcg; worn for seven days
Opioids	Burch, 2007	Tramadol Contramid	200-300 mg; daily
Opioids	Chindalore, 2005	Naltrexone + Oxycodone Oxycodone	0.002-0.004 mg + 10-40 mg; daily 10-40 mg; daily
Opioids	Fleischmann, 2001	Tramadol	400 mg; daily (maximum)
Opioids	Friedmann, 2011	Oxycodone	10-80 mg; daily
Opioids	Hartrick, 2009	Tapentadol Oxycodone	50-75 mg; every 4-6 hours 10 mg; every 4-6 hours
Opioids	Katz, 2010	Morphine + Naltrexone	20-160 mg; daily
Opioids	Kean, 2009	Tramadol	100-300 mg; daily
Opioids	Malonne, 2004	Tramadol	200 mg; daily
Opioids	Munera, 2010	Buprenorphine Transdermal	5-20 mcg per hour
Opioids	NCT00486811	Tapentadol Oxycodone	100-250 mg; twice daily 20-50 mg; twice daily
Opioids	Spierings, 2013	Oxycodone	10-40 mg every 12 hours

Opioids	Thorne, 2008	Tramadol	400 mg; daily (maximum)
Opioids	Zautra, 2005	Oxycodone	10 mg every 12 hours
Oral NSAIDs	Baerwald, 2010	Naproxcinod Naproxen	750 mg; twice daily 500 mg; twice daily
Oral NSAIDs	Bensen, 1999	Celecoxib Naproxen	50-200 mg; twice daily 500 mg; daily
Oral NSAIDs	Caruso, 1987	Naproxen	250 mg; three times daily
Oral NSAIDs	Clegg, 2006	Celecoxib	200 mg; daily
Oral NSAIDs	Conaghan, 2013	Celecoxib	100 mg; twice daily
Oral NSAIDs	Dieppe, 1993	Diclofenac	100 mg; daily
Oral NSAIDs	Dore, 1995	Etodolac Naproxen	400 mg; twice daily 500 mg; twice daily
Oral NSAIDs	Ekman 1015, 2014	Naproxen	500 mg; twice daily
Oral NSAIDs	Ekman 1018; 2014	Naproxen	500 mg; twice daily
Oral NSAIDs	Essex, 2014	Celecoxib Naproxen	200 mg; daily 500 mg; twice daily
Oral NSAIDs	Essex, 2012	Celecoxib Naproxen	200 mg; daily 500 mg; twice daily
Oral NSAIDs	Fleischmann, 2006	Celecoxib Lumiracoxib	200 mg; daily 200-400 mg; daily
Oral NSAIDs	Fleischmann, 1997	Naproxen CR Nabutmetone	1000 mg; daily 1500 mg; daily
Oral NSAIDs	Giansiracusa, 1977	Ibuprofen ASA	450 mg; four times daily 3600 mg; daily
Oral NSAIDs	Gibofsky, 2003	Celecoxib Rofecoxib	200 mg; daily 25 mg; daily
Oral NSAIDs	Hochberg 307, 2011	Naproxen/Esomeprazole Celecoxib	500/20 mg; twice daily 200 mg; daily
Oral NSAIDs	Hochberg 309, 2011	Naproxen/Esomeprazole Celecoxib	500/20 mg; twice daily 200 mg; daily
Oral NSAIDs	Kivitz, 2001	Celecoxib Naproxen	100-400 mg; daily 500 mg; twice daily
Oral NSAIDs	Kivitz, 2004	Rofecoxib Nabumetone	12.5 mg; daily 100 mg; daily
Oral NSAIDs	Lee, 1985	Diflusinal	375-500 mg; twice daily
Oral NSAIDs	Lehmann, 2005	Lumiracoxib	100 mg; daily

		Celecoxib	200 mg; daily
Oral NSAIDs	Lohmander, 2005	Naproxcinod Naproxen	750 mg; twice daily 500 mg; twice daily
Oral NSAIDs	McKenna, 2001	Celecoxib Diclofenac	100 mg; twice daily 50 mg; three times daily
Oral NSAIDs	McKenna, 2001a	Celecoxib Diclofenac	100 mg; twice daily 50 mg; three times daily
Oral NSAIDs	McKenna, 2001b	Celecoxib Rofecoxib	200 mg; daily 25 mg; daily
Oral NSAIDs	Moore 07, 2010	Etoricoxib	30-60 mg; daily
Oral NSAIDs	Moore 18, 2010	Etoricoxib Naproxen	60 mg; daily 1000 mg; daily
Oral NSAIDs	Moore 19, 2010	Etoricoxib Naproxen	60 mg; daily 1000 mg; daily
Oral NSAIDs	Moore 71, 2010	Etoricoxib Ibuprofen	60 mg; daily 2400 mg; daily
Oral NSAIDs	Moore 73, 2010	Etoricoxib Ibuprofen	30 mg; daily 2400 mg; daily
Oral NSAIDs	Moore 76, 2010	Etoricoxib Celecoxib	30 mg; daily 200 mg; daily
Oral NSAIDs	Moore 77, 2010	Etoricoxib Celecoxib	30 mg; daily 200 mg; daily
Oral NSAIDs	Rother, 2007	Celecoxib	100 mg; twice daily
Oral NSAIDs	Saag, 2000	Rofecoxib Ibuprofen	12.5-25 mg; daily 800 mg; three times daily
Oral NSAIDs	Schnitzer, 2011	Lumiracoxib Celecoxib	100 mg; daily 200 mg; daily
Oral NSAIDs	Schnitzer, 2005b	Naproxcinod Rofecoxib	125, 375, or 750 mg; twice daily 25 mg; daily
Oral NSAIDs	Sheldon, 2005	Lumiracoxib Celecoxib	100 mg; daily 200 mg; daily
Oral NSAIDs	Smugar 112, 2006	Rofecoxib Celecoxib	12.5-25 mg; daily 200 mg; daily
Oral NSAIDs	Smugar 116, 2006	Rofecoxib Celecoxib	25 mg; daily 200 mg; daily
Oral NSAIDs	Svensson, 2006	Naproxen	500 mg; twice daily
Oral NSAIDs	Williams, 1989	Etodolac	300 mg; twice daily

Oral NSAIDs	Williams, 2000	Celecoxib	100 mg; twice daily 200 mg; daily
Oral NSAIDs	Williams, 2001	Celecoxib	100 mg; twice daily 200 mg; daily
Oral NSAIDs	Yocum, 2000	Meloxicam Diclofenac	3.75, 7.5, or 15 mg; once daily 50 mg; twice daily
Rubefacients	Altman, 2004	Capsaicin Cream	0.025%; four times daily
SNRIs	Abou-Raya, 2012	Duloxetine	60 mg; daily
SNRIs	Chappell, 2009	Duloxetine	60-120 mg; daily
SNRIs	Chappell, 2011	Duloxetine	60-120 mg; daily
SNRIs	Frakes, 2011	Duloxetine	60-120 mg; daily
SNRIs	Uchio, 2018	Duloxetine	60 mg; daily
SNRIs	Wang, 2017	Duloxetine	60 mg; daily
Topical NSAIDs	Altman, 2009	Diclofenac Gel	1%; four times daily
Topical NSAIDs	Baer, 2005	Diclofenac Gel	1.5%; four times daily
Topical NSAIDs	Baraf, 2011	Diclofenac Gel	1.5%; four times daily
Topical NSAIDs	Barthel, 2009	Diclofenac Gel	1%; four times daily
Topical NSAIDs	Bookman, 2004	Diclofenac Gel	Four times daily
Topical NSAIDs	Brühlmann, 2003	Diclofenac Patch	1.3%; twice daily
Topical NSAIDs	Conaghan, 2013	Ketoprofen Gel	50-100 mg; twice daily
Topical NSAIDs	Dreiser, 1993	Diclofenac Patch	180 mg; twice daily
Topical NSAIDs	Ergun, 2007	Nimesultide Gel	1%; three times daily
Topical NSAIDs	Grace, 1998	Diclofenac Gel	2%; three times daily
Topical NSAIDs	Kageyama, 1987	Piroxicam Gel	0.5%; three to four times daily
Topical NSAIDs	Kneer, 2013	Ketoprofen Gel	25-100 mg; two times daily
Topical NSAIDs	NCT01980940	Etoricoxib Gel	50 mg; twice daily
Topical NSAIDs	Niethard, 2005	Diclofenac Gel	1.16%; four times daily
Topical NSAIDs	Rose, 1991	Piroxicam Gel	5%; four times daily
Topical NSAIDs	Roth, 2004	Diclofenac Gel	1.5%; four times daily
Topical NSAIDs	Rother, 2007	Ketoprofen Gel	110 mg; twice daily
Topical NSAIDs	Rovensky, 2001	Ibuprofen Cream	5%; three times daily
Topical NSAIDs	Simon, 2009	Diclofenac Gel	1.5%; four times daily
Topical NSAIDs	Trnasky, 2004	Ibuprofen Cream	5%; three times daily

Topical NSAIDs	Wadsworth, 2016	Diclofenac	2%; twice daily
Viscosupplementation	Altman, 1998	Hyalgan®	20 mg; five weekly injections
Viscosupplementation	Altman, 2004	Non-animal stabilized hyaluronic acid (NASHA)	60 mg (3 ml); single injection
Viscosupplementation	Altman, 2009	Sodium hyaluronate	20 mg (2 ml); three weekly injections
Viscosupplementation	Arden, 2014	Non-animal stabilized hyaluronic acid (NASHA)	60 mg (3 ml); single injection
Viscosupplementation	Atchia, 2011	Durolane®	3 ml; single injection
Viscosupplementation	Baltzer, 2009	Hya-ject®	2 ml; three weekly injections
Viscosupplementation	Brgantini, 1987	Hyalgan®	20 or 40 mg; 3 weekly injections
Viscosupplementation	Brander, 2018	Hylan G-F 20	48 mg; single injection
Viscosupplementation	Chevalier, 2010	Hylan G-F 20 (Synvisc One®)	6 ml; single injection
Viscosupplementation	Corrado, 1995	Hyalgan®	20 mg; five weekly injections
Viscosupplementation	Creamer, 1994	Hyalgan® (Sodium Hyaluronate)	20 mg; five weekly injections
Viscosupplementation	Dahlberg, 1994	Sodium hyaluronate	2.5 ml; five weekly injections
Viscosupplementation	Formiguera Sala, 1995	Hyalgan®	20 mg; five weekly injections
Viscosupplementation	Grecomoro, 1987	Hyalgan®	20 mg; three weekly injections
Viscosupplementation	Henderson, 1994	Hyalgan®	20 mg; five weekly injections
Viscosupplementation	Huang, 2011	Hyalgan®	20 mg; five weekly injections
Viscosupplementation	Huskisson, 1999	Hyalgan®	20 mg; five weekly injections
Viscosupplementation	Jubb, 2003	Hyaluronic Acid	20 mg; three weekly injections
Viscosupplementation	Kahan, 2003	Synvisc®	Three weekly injections
Viscosupplementation	Karlsson, 2002	Synvisc® (0.8% hyaluronan) Artzal® (1% hyaluronan)	2.5 ml; three weekly injections
Viscosupplementation	Kul-Panza, 2010	Orthovisc®	2 ml; three weekly injections
Viscosupplementation	Lundsgaard, 2008	Hyalgan®	2 ml; four weekly injections
Viscosupplementation	Navarro-Sarabia, 2011	Adant®	Five weekly injections over four cycles
Viscosupplementation	Neustadt, 2005	Orthovisc®	Four weekly injections
Viscosupplementation	Pham, 2004	NRD101 (HA compound)	25 mg; three weekly injections over three months
Viscosupplementation	Qvistgaard, 2006	Hyalgan®	Three injections every 14 days
Viscosupplementation	Raynauld, 2002	Hylan G-F 20	Three weekly injections
Viscosupplementation	Richette, 2009	Adant®	2 ml; single injection

Viscosupplementation	Strand, 2012	Gel-One®	30 mg; single injection
Viscosupplementation	Van der Weegen, 2015	Fermathon Plus®	15 mg; three weekly injections
Viscosupplementation	Wobig, 1998	Hylan G-F 20	2 ml; three weekly injections

GRADE Quality of Evidence Table for All Recommendations

Topic	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Final GRADE
Exercise for OA[1]	-1	0	0	0	0	Low
Exercise for chronic low back pain[2]	0	0	-1	0	-1	Moderate
TCAs for low back pain	0	0	0	-1	0	Moderate
Topicals (non-nitrate)	-1	0	0	0	0	Moderate
Topicals (nitrates)	-1	0	0	-1	0	Low
Psychological Treatments	-1	-1	0	0	0	Low
Best exercise type	0	-1	0	-1	0	Low
Tapering Opioids	-1	-1	-1	-1	0	Very Low
Cannabinoids	-2	0	-1	-1	0	Very Low
Assisting to Exercise	-1	-1	0	-1	0	Very Low
Drug Combinations	0	-1	-1	-1	0	Very Low
Weight loss for OA	-1	0	-1	0	0	Low
IAI for OA[1]	0	-1	-1	0	-1	Very Low
SNRIs for OA[1]	-1	0	0	0	0	Moderate
PO NSAIDs for OA[1]	-1	0	0	0	0	Moderate
Topical NSAIDs for OA[1]	-1	-1	0	0	0	Low
Glucosamine for OA[1]	-1	-1	0	0	-1	Very Low
Chondroitin for OA[1]	-1	0	0	0	0	Moderate
Viscosupplemen-tation for OA[1]	-1	-1	0	0	-1	Very Low
Opioids for OA[1]	-1	-1	-1	0	0	Very Low
Acetaminophen for OA[1]	0	0	-1	0	-1	Low
Oral NSAIDs for back pain[2]	-1	0	0	0	0	Moderate
SNRIs for back pain[2]	-1	0	0	0	0	Moderate
Spinal manipulation for back pain[2]	-1	-1	0	0	0	Low
Acupuncture for back pain[2]	-1	-1	0	0	-1	Very Low
Rubefacients for back pain[2]	-1	0	-1	0	0	Low
Corticosteroid injections for back pain[2]	-1	0	-1	-1	0	Very Low

Opioids for low back pain[2]	-1	0	-1	-1	0	Very Low
Anticonvulsants for neuropathic pain[3]	0	0	0	0	-1	Moderate
SNRIs for neuropathic pain[3]	0	0	0	0	-1	Moderate
Rubefacients for neuropathic pain[3]	-1	0	0	0	-1	Low
TCAs for neuropathic pain[3]	-1	-1	-1	-1	-1	Very Low
Opioids for neuropathic pain[3]	0	0	-1	0	-1	Low

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Pain Guidelines Supplemental Questions

Introduction

This document comprises answers to various clinical questions surrounding the management of chronic pain in a primary care setting. The answers explore a variety of treatment modalities and how they apply to different types of chronic pain.

Methods

Each clinical question was assigned to a 2-person team to answer. The team drafted PICO questions, and conducted searches for systematic reviews using MEDLINE and Cochrane. This was limited to systematic reviews published within the last 5 years, however if the search resulted in fewer than 100 articles for title review, the search was expanded to the last 10 years. If this then yielded no systematic reviews (SR), the team responsible for the research question would then search for RCTs or observational studies pertinent to their question. This search strategy would be recorded. Results were then entered into Covidence so the teams could review the results. A PubMed and grey literature search was also performed by each team.

Based on these results the team will determine whether a search for newer RCTs is warranted considering when the last SR was done.

The answers are formatted to contain the bottom-line answer, the evidence and limitations regarding the studies involved, the context, and the suggested recommendation from this evidence. PRISMA diagrams, risk of bias assessments, and quality assessments were also created for each question.[1] The suggested recommendations were created using GRADE wording.[2] A modified AMSTAR Quality Assessment of included systematic reviews is shown in Figure 1.[3]

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Preventing Chronic Pain in Primary Care

Clinical Question

What interventions during the acute pain period help prevent progression to chronic pain?

Bottom Line

Poorly managed acute pain is often cited as a risk factor for the development of chronic pain. However, there is currently no high-quality evidence supporting interventions in the acute period that successfully modify this outcome. Moderate quality evidence suggests that over 6-24 months, compared with no intervention, exercise following the initial episode of back pain may reduce the risk of low back pain recurrence for one in every 3 patients and decrease sick leave by 4 days.

Evidence, Limitations, and Context

Both the Institute of Medicine (Institute of Medicine 2011) and the Canadian Pain Taskforce (Canadian Pain Taskforce Report 2021) highlight the importance of primary (e.g. risk management, obesity prevention) and secondary prevention (preventing progression from acute to chronic state) of chronic pain. This question primarily addresses secondary prevention, for which we identified four key areas of evidence: prevention of chronic neuropathic pain following herpes zoster, prevention of recurrence of low back pain following an acute flare, prevention of chronic pain following surgery and psychological therapies for the prevention of chronic pain. The PRISMA diagram can be seen in Figure 2. See Figures 3 and 4 for Risk of Bias assessment.

A. Prevention of Postherpetic Neuralgia

Question

What strategies reduce the risk of progression from herpes zoster to postherpetic neuralgia?

Bottom Line

Interventions such as gabapentin, corticosteroids, tricyclic antidepressants (TCAs), and antivirals for management of herpes zoster do not reduce the risk of developing postherpetic neuralgia (PHN). While outside of the scope of this question, evidence for primary prevention strategies (e.g. zoster vaccination) does exist, demonstrating that vaccination may prevent one additional case of PHN for every 334 to 520 patients over 3-4 years.

Evidence and Limitations

Supplemental Therapy

Two systematic reviews (SRs) (Watson 2010, Xing 2017) were identified which evaluated the effect of analgesics used in the acute phase of herpes zoster on the incidence of PHN. The most recent and best quality SR [3 randomized controlled trials (RCTs), 2020 patients] evaluated gabapentin, pregabalin and amitriptyline (Xing 2017). These drugs did not reduce the occurrence of PHN at three months (RR 0.76, 95% CI 0.46, 1.26). One trial (Bowsher 1997) reported amitriptyline was beneficial at 6 months using per protocol analysis but the presence of PHN was not significantly different between groups (15.8% vs 35% placebo, p=0.07) (Xing 2017). One RCT published after this SR, also showed no effect of gabapentin on incidence of PHN in 75 patients (Bulilete 2019).

Antivirals

Eight SRs were identified that examined the effect of antivirals on the incidence of PHN (Alper 2000, Chen 2014, Crooks 1991, Jackson 1997, Lancaster 1995, Schmader 1989, Watson 2010, Wood 1996). The highest quality systematic review (6 placebo- controlled RCTs, 1211 patients) included immunocompetent patients presenting within 72 hours of onset of rash (Chen 2014). Five of the RCTs included oral acyclovir (800mg 5x per day for 7-21 days) while one RCT used famciclovir at varying doses.

The risk of PHN was not different between acyclovir and placebo at 4 and 6 months. PHN at 4 months occurred in 12.4% on acyclovir vs 16.6% on placebo (RR 0.75, 95% CI 0.51, 1.11). Famciclovir similarly showed no difference from placebo. Results of other high-quality systematic reviews were generally consistent (Lancaster 1995, Alper 2000, Watson 2010). Other systematic reviews reporting beneficial effects of antivirals on incidence of PHN have significant methodological limitations (Crooks 1991, Jackson 1997, Wood 1996).

Corticosteroids

Four SRs (Lancaster 1995, Han 2013, Schmader 1989, Watson 2010) were identified. The highest quality SR (5 RCTs, 787 patients) included patients presenting with herpes zoster within 7 days of onset of rash (Han 2013). Meta-analysis of two RCTs was possible (114 participants) and found that corticosteroids do not reduce the risk of PHN six months after the onset of rash (19% in both arms, RR 0.95, 95% CI 0.45, 1.99). Two additional trials that could not be pooled were consistent with the meta-analysis results. No difference in time to cessation of pain was seen in two larger trials. Results are consistent with other SRs (Lancaster 1995, Schmader 1989, Watson 2010).

Vaccines

Two RCTs examined the effect of zoster vaccine on the incidence of PHN (Oxman 2005, Cunningham 2016). Oxman et al. compared live zoster vaccine (Zostavax®) to placebo in 38,546 patients over the age of 60. They found the risk of PHN was 0.1% in the vaccine group and 0.3% in placebo respectively, with a number needed to treat (NNT) of 520 over 3.1 years (Oxman 2005). Cunningham et al. compared recombinant zoster vaccine (Shingrix®) to placebo in 16,596 patients and found the risk of PHN was 0.03% vs 0.33%, with NNT 334 over 3.7 years.

The major limitation found with these studies looking at PHN was the presence of industry funding.

Context

Definition of PHN varies across trials; generally defined as pain lasting 90-120 days from rash onset. Interventions that would not typically be performed by family physician were excluded (e.g. interventional procedures such as epidurals; repetitive intracutaneous injections into dermatomes).

The live zoster vaccine prevents one case of herpes zoster for every 60-70 vaccinated patients while the recombinant zoster vaccine prevents one case in every 40 patients (Kolber 2019). When given during an episode of acute herpes zoster, antivirals can accelerate rash healing (~8 days versus ~11 days placebo, p=0.02) (McKendrick 1986). For patients with severe pain at presentation, antivirals can provide faster resolution of acute pain (e.g. 27 days for famciclovir 750mg versus 30 days for placebo) (Tyring 1995).

B. Exercise to Prevent Low Back Pain Recurrence

Question

What is the effect of exercise on reducing the risk of low back pain recurrence?

Bottom Line

Moderate quality evidence suggests that over 6-24 months, compared with no intervention, exercise may reduce the risk of low back pain recurrence for one in every 3 patients, and decrease sick leave by 4 days.

Evidence and Limitations

Four SRs of RCTs (from 2010-2021) were identified that evaluated whether exercise reduced the risk of recurrent low back pain (LBP) (Choi 2010, Steffens 2016, Shiri 2018, Huang 2020). The 2010 Cochrane SR evaluated the effect of exercise for secondary prevention of back pain (Choi 2010). The analysis was divided into two sections depending on when exercise was prescribed.

The first section analyzed exercise prescribed after treatment for an episode of non-specific back pain was completed, with the primary aim to reduce the risk of recurrence ("post-treatment exercises"). Based on 4 RCTs with 407 patients, exercise improved LBP outcomes over control over 0.5-2 years including: the number of patients with recurrences (33% exercise group vs 65% no intervention, NNT 3); number of recurrences (mean difference: 0.4); time to LBP recurrence [hazard ratio (HR) 0.43, 95% CI 0.21, 0.87] and number of sick days [mean difference (MD): 4 fewer days]. Choi reported that evidence was based on moderate quality evidence.

The second section analyzed was exercise as prescribed for an acute episode of LBP to treat the acute episode and reduce the risk of new episodes ("exercise treatment"). Based on 3 RCTs (949 patients), no difference in recurrence of LBP was seen between exercise and control groups, based on low quality evidence.

The remaining three SRs were published after the Cochrane Review (Steffens 2016, Shiri 2018, Huang 2020). However, they evaluated patients with mixed baseline characteristics (i.e. with or without back pain, a history of LBP) without stratifying their analysis by primary or secondary prevention. Like

the Cochrane Review, their results suggest that exercise reduced the risk of back pain recurrence. In a SR of four RCTs (898 patients), exercise reduced LBP episodes (23% in exercise group vs 15% in control group), with NNT of 12 over 6-12 months (Steffens 2016). This benefit did not persist beyond one year. Episodes of sick leave were also reduced (30% vs 5%, NNT 4 over 12 months) based on 2 RCTs (128 patients).

Context

The recurrence rate for LBP is 58% over 0.5-2 years and 72% over 3-5 years (Choi 2011). This clinical question does not address chronic pain but focuses on reducing the risk of recurrent episodes of low back pain.

Also note the exercises prescribed in the Cochrane Review included a mixture of back and leg stretching, and muscle contraction and relaxation exercises. For an acute back pain episode, advising patients to stay active (versus bed rest) after the acute event will improve function slightly and reduce sick days (by ~3 days). Adding exercise to advice to stay active gives no additional benefit (Mildenberger 2016).

C. Psychological Therapies for Prevention of Chronic Pain

Question

Can psychological therapy reduce the risk of developing chronic pain?

Bottom Line

In patients with various acute and subacute pain conditions, psychological interventions do not appear to reduce pain intensity at 3, 6, or 12 months compared with control.

Evidence and Limitations

One SR was identified that evaluated the effect of psychological therapies on reducing the risk of chronic pain in patients with pain duration less than 3 months (Berube 2021). Eleven of the 18 identified RCTs were eligible for meta-analysis (2356 patients). Nine trials included patients with back pain or pain at multiple sites (neck, shoulders, back, hip, knee) while two trials were in patients with limb pain due to trauma. Pain intensity in the psychological intervention group was no different than control at 3, 6 or 12 months. A small improvement in disability with psychological interventions was seen at 12 months when compared with standard treatment [standard mean difference (SMD): -0.3] but the clinical interpretation of results reported as SMD is limited.

Context

In patients with chronic low back pain or neuropathic pain, psychological interventions can lead to clinically meaningful improvement in pain (Kirkwood 2021). In patients with osteoarthritis, web-based pain coping skills training can improve pain over 8 weeks, but the benefits do not appear to persist at 52 weeks (Kirkwood 2021).

D. Perioperative Interventions to Prevent Chronic Pain

Question

Is there an optimal way to manage acute pain in the perioperative setting that minimizes progression to chronic pain?

Bottom Line

Poorly managed acute pain is often cited as a risk factor for the development of chronic pain, however, there is currently no high-quality evidence suggesting how early interventions could modify this outcome in the perioperative period.

Evidence and Limitations

A 2013 Cochrane SR of pharmacotherapy for the prevention of chronic pain after surgery (Chaparro 2013) reported no significant benefit with perioperative administration of gabapentin, pregabalin, antidepressants, or non-steroidal anti-inflammatory drugs (NSAIDs).

Focusing on SRs with meta-analyses from the last 5 years (prioritizing interventions that could potentially be employed in primary care), we identified 4 SRs of gabapentinoids (gabapentin or pregabalin) including 4-27 RCTs (Verret 2020, Chang 2020, Martinez 2017, Rai 2017). All 4 reported no significant effect for perioperative gabapentinoids in reducing the risk of chronic pain. The largest SR (Verret 2020) analyzed 27 RCTs with 3198 patients and reported no difference in chronic pain at 3 months following any surgery with the use of gabapentin or pregabalin (overall RR 0.89, 95% CI 0.74, 1.07). One SR (Martinez 2017) reported a high incidence of publication bias, noting that the unpublished data they acquired consistently demonstrated no benefit.

The most recent SR of antidepressants included 3 RCTs (Wong 2014). Studies were heterogeneous and meta-analysis was not completed. The authors concluded that there is currently no evidence to support antidepressant use to reduce the risk of chronic postoperative pain.

Two SRs (Dennis 2020, Wang 2016) of 5-10 RCTs assessed the impact of pre-operative exercise or rehabilitation programs on chronic post-surgical pain development for patients undergoing joint replacement. No benefit in pain outcomes were identified at 3- or 6-months post-surgery. The highest quality SR (Wang 2016) included 10 RCTs (806 patients) at 12 weeks post-op with no significant improvement in pain outcomes [weighted mean difference (WMD) -2.9, 95% CI -6.2, 0.3]. One SR assessed post-discharge interventions following total knee replacement surgery (primarily physiotherapy)

(Wylde 2018). Interventions and outcomes were heterogeneous, meta-analysis was not completed. Sixteen out of 17 RCTs reported no difference in pain at 12 months or longer. A significant limitation was that many RCTs compared different physiotherapy interventions, thus the benefit over placebo could not be assessed.

One SR meta-analyzed cognitive behavioural therapy (CBT) interventions prior to lumbar spine surgery (Janssen 2020). There was no difference in back pain between 6 weeks and 6 months (5 RCTs, 397 pts) (MD -0.3, 95% CI -5.0, 4.5), or 6 or more months following surgery (3 RCTs, 349 patients) (MD 2.6, 95% CI -2.2, 7.3). Due to high heterogeneity amongst interventions and reported outcomes, other SRs have been unable to perform meta-analyses. Two SRs (7-12 RCTs, 573-1299 patients) (Whale 2019, Bay 2018) reported on perioperative psychological interventions for joint replacement, however not all reported on long term outcomes and both groups concluded that current evidence is insufficient to support the use of routine psychological interventions.

Context

Randomized controlled trials of perioperative surgical interventions provide the most robust existing literature regarding the prevention of chronic pain following an acute injury. Twenty-56% of patients undergoing common planned surgical procedures will go on to develop chronic pain (Richebe 2018). Poorly managed acute pain is cited as a risk factor for the development of chronic pain (Richebe 2018). However, attempts to target or modify preoperative care have yet to show benefit regarding chronic pain or other long-term patient outcomes.

Investigated perioperative interventions are heterogenous in type, complexity, duration, and outcomes assessed (e.g. Beswick et al. 2019 identified 44 specific perioperative interventions for total knee replacement surgery alone). This review focused primarily on those interventions with summarized data and excluded interventions that could not be accessed in primary care (e.g. epidurals, nerve blocks). While not commonly employed in primary care, this evidence provides background on current research in an acute pain setting with the goal of reducing the risk of long-term pain.

E. Future Directions

We identified two published protocols for RCTs, one assessing the use of duloxetine in altering the transition from acute to chronic pain in patients presenting to the emergency department with acute musculoskeletal pain (Strauss 2019). The second trial was a feasibility trial to assess the use of pregabalin in acute whiplash and subsequent prevention of chronic pain (Nickles 2018). We contacted authors of both trials who indicated data was in the process of being analyzed or had been submitted for publication, so authors were not ready to share the data at the time of our review.

Suggested Recommendation

There is inadequate evidence to make a recommendation.

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Encouraging Exercise with Chronic Pain

Clinical Question

How can we encourage people with chronic pain, including low back pain or osteoarthritis, to increase their level of physical activity?

Bottom Line

In patients with chronic pain, such as osteoarthritis or chronic low back pain, wearable activity trackers improve physical activity levels on top of counselling and education for increasing daily step count by about 1500 steps and time spent in moderate-to-vigorous exercise by around 16 min/day. Motivational interviewing may increase attendance at physiotherapy training sessions (e.g. by 1 more/week compared to control).

Evidence and Limitations

Three SRs and 2 additional RCTs assessed interventions to assist people with chronic pain, including patients with osteoarthritis and chronic low back pain, to increase their physical activity (measured in steps, minutes of moderate-to-vigorous activity, attendance of training sessions). One SR with meta-analysis and one RCT looked at the use of wearable activity trackers, and the other 2 systematic reviews and remaining RCT examined various other interventions such as education, motivational interviewing, and group exercise classes. Results were statistically significant unless noted otherwise. The included systematic reviews are shown in Table 1. See Figure 5 and Figure 6 for the PRISMA diagram associated with this question for the SR and RCTs respectively.

Table 1: Summary of included systematic reviews: Encouraging Exercise with Chronic Pain

Author/Year	**Number of included trials**	**Duration**	**Age**	**Population**	**Interventions of interest**	**Comparator**
Davergne 2019	17 (15 RCTs and 2 cohorts); 7 studies contribute to the meta-analysis	Median 12 weeks (in RCTs of osteoarthritis)	Median 65 years (in RCTs of osteoarthritis)	Patients (all ages) with Rheumatic and Musculoskeletal Diseases	Wearable activity trackers +/- adjunctive intervention (e.g. education)	No wearable activity tracker

Nicolson 2017	9 RCTs	Not reported	Not reported	Patients ≥45 years with chronic low back pain and/or hip/knee osteoarthritis	Exercise adherence interventions	No adherence intervention
Oliverira 2016	8 RCTs	Not reported	Not reported	Patients with chronic musculoskeletal pain	Exercise adherence interventions	No adherence intervention

Wearable Activity Tracker

With respect to wearable activity trackers (e.g. pedometers, Fitbit), one SR included a meta-analysis of 7 RCTs (6 osteoarthritis, 1 chronic inflammatory rheumatic disease) with a total of 463 patients (Davergne 2019). For the 6 RCTs of osteoarthritis patients, the median age was 65 years and 40% were male, and the median intervention duration was approximately 12 weeks. Studies compared a wearable activity tracker (simple pedometer or with advanced features) with goal setting, plus or minus additional counselling versus usual care without a wearable activity tracker. Wearable activity trackers increased step count by an average 1500 steps/day and total moderate-to-vigorous physical activity time by 16 minutes/day (based on 3 studies, 117 patients). In studies that continued follow-up after the additional counselling ended, there was no difference found for mean daily steps or time spent in moderate to vigorous activity, suggesting that long-term adherence may be low without continued counselling and encouragement (Li 2018, Talbot 2003). In an RCT of 51 patients with knee osteoarthritis (mean age 65 years, 82% female), use of a wearable activity tracker combined with physiotherapist-led education increased moderate-to-vigorous physical activity by an average 13 minutes/day (95%, CI 1.6, 24.5) and step count by an average1100 steps/day (95% CI −20, 2233) compared to a waitlist after 13 weeks (Li 2020).

Motivational Interviewing

Looking at motivational interviewing, Nicolson et al. performed a SR of interventions to improve exercise adherence among adults with chronic low back pain or osteoarthritis (Nicolson 2017). Examples of interventions included complex behavioral interventions, behavioral graded exercise with or without booster sessions with a clinician, and action coping plans which were compared against exercise alone with or without education/advice. Three RCTs in chronic low back pain evaluated motivational interviewing provided during 10 physiotherapy sessions over 4 to 8 weeks (Basler 2007, Friedrich 1998, Vong 2011). In the RCT by Basler et al. (170 patients), patients who received motivational interviewing exercised for an average 30 mins/day compared to 25 minutes/day with control (p=0.21) during the 6-month follow-up (Basler 2007). Friedrich (93 patients) found that patients in the motivational interviewing group attended 82% of the 10 prescribed physiotherapy sessions compared to 51% in the control group (Friedrich 1998). Motivational interviewing also increased average weekly training

frequency from around 3 to 4 sessions per week at 12 months. In the RCT by Vong et al. (76 patients), patients who received 10 sessions of physiotherapy plus motivational interviewing performed an average of 14 sessions of prescribed physiotherapy home exercises per week compared with 6 sessions per week in the group who received physiotherapy alone over 8 weeks (Vong 2011). Studies of osteoarthritis were either underpowered or did not measure any important clinical outcomes (Nicolson 2017). An additional RCT by Gilbert et al. of 340 adults with arthritis (including 155 patients with knee osteoarthritis and 185 patients with rheumatoid arthritis) followed for 24 months found no improvement in average daily activity or moderate-to-vigorous activity with the addition of motivational interviewing by a physical activity advocate versus physician activity counselling alone (Gilbert 2018).

Various Exercise Interventions

Various interventions to promote increased physical activity in patients with chronic musculoskeletal pain were examined in a SR of 8 RCTs (Oliveira 2016). Of the 8 RCTs, 4 were in osteoarthritis, 3 in chronic low back pain, and 1 in fibromyalgia. Examples of interventions included cognitive behavioural physical activity intervention, web-based exercise program, pedometer-based walking program, and exercise classes. These were compared against education, self-management, waitlist, and sham control. In meta-analysis, these interventions did not increase daily step-count or moderate-to-vigorous activity at any timepoint. Individually, only one study limited to patients with fibromyalgia demonstrated statistically significant benefit. The primary limitation of this review was heterogeneity of the interventions in both groups. Additionally, included RCTs were small, many failed to blind the assessors, did not follow intention-to-treat principles, had issues with allocation concealment, and had high dropout rates.

Overall, the evidence for wearable activity trackers and motivational interviewing in patients with chronic pain is very low due to serious risk of bias (lack of blinding of participants), imprecision (wide confidence intervals), and inconsistency [evidence of high statistical heterogeneity (e.g. I2=77% for step count in Davergne 2019) along with clinical and methodological heterogeneity]. Additionally, given the short duration of these trials, it remains unclear whether benefits are sustained beyond 3-6 months. The evidence for other adherence interventions is inconclusive. The Risk of Bias Summary and Graph are show in Figures 7 and 8 respectively.

Context

Evidence for wearable activity trackers is consistent with benefit seen in patients without chronic pain (Korownyk 2010). Wearable activity trackers vary in cost and complexity: a pedometer with simple step logging may cost ~$20-50, whereas smartphones and smartwatches may offer a step-counter with additional advanced features. Giving patients a written, stepwise, and goal-oriented exercise program may be more important than any advanced technological features (Korownyk 2010). Physical activity prescriptions, combined with patient specific goals and monitoring, have been shown to increase physical activity levels in all patients by up to ~1200 steps/day at ~1 year, with an additional 1 person becoming active for every 10 prescribed activity compared to general advice alone (Lindblad 2020). An example of an exercise prescription with a wearable activity tracker might look like:

1. Wear your pedometer every day for one week.
2. Calculate your daily steps (average to the closest 1000-step increment).

3. Add 500 steps per day to your daily average. Walk that each day for the next week.
4. Repeat step three, adding 500 steps to last week's daily goal and walk that each day for the next week.
5. Continue to your personalized target (e.g. 10,000 steps per day).

Other interventions studied in broader populations, not limited to patients with chronic pain, including motivational interviewing, frequent telephone counselling, and financial incentives, have modest effect sizes (SMD around 0.2-0.3) (Chase 2015, Nguyen Luong 2021, O'Halloran 2014, Orrow 2012). These interventions tend to be most effective in individuals without chronic illness or disability (Chase 2015), suggesting they may have limited efficacy in patients with functionally limiting chronic pain.

Suggested Recommendation

In patients who request assistance to increase their physical activity, we recommend the use of wearable activity trackers with an exercise prescription (weak recommendation, very low quality evidence).

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Effective Exercises for Chronic Pain

Clinical Question

In patients with chronic pain, what is the most effective type of exercise?

Bottom Line

There is low-moderate quality evidence that little difference exists between different types of exercises for improvement of pain and function in the management of osteoarthritis and chronic low back pain. Motor control and core stabilization exercises for chronic low back pain compared to other exercises have the largest body of evidence for a potentially small (e.g. <8 point difference on a 0-100 point scale), but likely clinically insignificant, effect on pain and function. Strengthening exercises, yoga, and aerobic exercises are all likely similarly effective for osteoarthritis.

Evidence and Limitations

Systematic reviews were focused on comparisons of exercise interventions for chronic low back pain and osteoarthritis (Figure 9 PRISMA diagram). The studies reviewed included yoga, Pilates, Tai chi, aerobic exercises, aquatic exercises, motor control and stabilization exercises, strengthening and resistance, mind-body exercises, and flexibility.

Osteoarthritis

This review covered 8 studies [1 SR (Lee 2008), 4 meta-analyses (Lauche 2019, Kong 2016, Coudeyre 2016, Dong 2018), 3 network meta-analyses (Goh 2019, Zhang 2019, Uthman 2013)] showing no clear clinically important differences in pain or function between exercise types in patients with osteoarthritis.

A meta-analysis by Lauche et al. comparing yoga to other exercise interventions (primarily strengthening) reported large effect sizes in favor of yoga for pain improvement (SMD -1.07, 95% CI -1.92, -0.21, 3 RCTs, 315 patients) and for function (SMD 0.80, 95% CI 0.36, 1.24, 2 RCTs, 90 patients) at 8-12 weeks. However, the authors rated the certainty of evidence as very low for both outcomes and reported a high degree of heterogeneity for the pain outcome estimate (I2 87%). No differences were seen in quality of life or depression outcomes. A network meta-analysis by Goh et al. ranked mind-body exercises (e.g. yoga and Tai chi) as most likely to be effective for both pain improvement (along with aerobic exercise and ahead of strengthening) and function (similar to strengthening). Zhang et al. were consistent with this in their network meta-analysis subgroup ranking of yoga as first for effect on pain and for adherence among older adult women with osteoarthritis. These studies were graded as moderate methodological quality. In contrast, for tai chi compared to other exercises, a meta-analysis by Kong et al. found no statistically significant difference in pain in 2 RCTs (144 patients) which supported an earlier SR by Lee et al. reporting no consistent differences in pain reduction or function.

Although many RCTs have evaluated the efficacy of strengthening and resistance exercises in osteoarthritis, relatively few head-to-head RCTs exist comparing these interventions to other forms of

exercise. Three network meta-analyses were identified (Goh 2019, Zhang 2019, Uthman 2013), two of which ranked strengthening or resistance exercise highest for pain improvement (Zhang 2019, Uthman 2013), while Goh et al., as mentioned above, ranked strengthening exercises below mind-body exercises for pain improvement. The two that reported on function ranked strengthening exercises first or second (Goh 2019, Uthman 2013). One meta-analysis compared specific isokinetic strengthening exercises to other exercises, reporting moderate to large effect sizes in favor of isokinetic exercises for pain improvement (SMD 1.24, 95% CI 0.82, 1.67) and function (SMD 0.58, 95% CI 0.04, 1.11) at 6 to 8 weeks (Coudyre 2016). However, there was significant heterogeneity identified, in addition to low methodological quality, for an intervention requiring specialty skills and equipment to perform.

Evidence for aerobic exercise in osteoarthritis is conflicting and relies largely on indirect comparisons. While Goh et al. ranked it first (along with mind-body exercises) for pain improvement, it ranked last for function. An earlier network meta-analysis by Uthman et al. ranked land-based aerobic exercise lowest and second lowest for pain improvement and function, respectively, unless combined with aquatic strengthening which resulted in a high ranking.

A meta-analysis comparing aquatic to land-based exercise for osteoarthritis by Dong et al. showed no significant differences in pain, function, or quality of life (Dong 2018). In the network meta-analysis by Zhang et al., aquatic exercise ranked third out of six interventions behind resistance and strengthening, while aquatic combinations (often with aquatic strengthening) consistently ranked highly in the Uthman study.

Flexibility and stretching exercise in comparison to other forms of exercise was assessed in two network meta-analyses and generally ranked low for effect unless combined with other modalities (Goh 2019, Uthman 2013).

Chronic Low Back Pain

Our review of 14 studies including 5 SRs (Lin 2016, Chou 2016, Kamioka 2016, Chang 2016, Lawford 2016), 8 meta-analyses (Bystrom 2013, Smith 2014, Saragiotto 2016, Macedo 2009, Niederer 2020, Yamato 2016, Zhu 2020, Wieland 2017), and 1 network meta-analysis (Owen 2020) showed no clear clinically important differences in pain or function between exercise types in patients with chronic low back pain.

Five of the eight meta-analyses reviewed focused on motor control and core-stabilizing exercises, comprising the largest number of patients studied for direct comparisons to other exercises (Bystrom 2013, Smith 2014, Saragiotto 2016, Macedo 2009, Niederer 2020). Three of these studies (Bystrom 2013, Smith 2014, Saragiotto 2016) found similarly small statistically significant benefits on pain in the short (<3-4 months) and intermediate (>3-4 months and <8-12 months) follow-up points, but no effect at long-term follow-up. Similar patterns were reported for function and disability outcomes. All outcomes were standardized to a Visual Analogue Scale (VAS) of 0-100 with differences of <8 reported for all outcomes and were therefore considered clinically insignificant. Of these, the highest quality meta-analysis by Saragiotto et al. also reported no differences in overall or mental quality of life scores compared to other exercises. An earlier meta-analysis by Macedo et al. reported no differences in pain reduction at any time points. Another meta-analysis by Niederer et al. reported no pain or function advantage for motor control stabilizing over other exercises at short and intermediate time points, but did find a small benefit (SMD -0.29 95% CI -0.56, -0.01) in the long term (>12 months). Keeping in mind the challenge of network meta-analysis, especially when differences are consistently so small based on a relatively large body of direct evidence, the one network meta-analysis for chronic low back pain by Owen et al. ranked motor control

and core stabilization exercises third out of ten exercise interventions for pain reduction (behind aerobic exercise and Pilates) and second out of ten for function (behind resistance exercises).

Evidence for the comparison of Pilates to other exercise types in chronic low back pain is conflicting. While the Owen et al. network meta-analysis ranked it first out of ten different exercise interventions for pain reduction, it ranked fifth out of ten for function and third out of five for mental health outcomes. One meta-analysis of 4 RCTs (245 patients) by Yamato et al. did not combine data for the pain outcome due to high heterogeneity. Although they found a statistically significant effect on function at greater than 12 weeks of follow-up, this was determined to be clinically insignificant. Both studies rated the certainty of evidence as low. Among three SRs without meta-analysis (Lin 2016, Chou 2016, Kamioka 2016), two reported no clear differences in pain or function compared to other exercises (Lin 2016, Chou 2016).

The effects of yoga relative to other exercises have been quantified in several meta-analyses. The most recent by Zhu et al. included 9 RCTs (738 patients) and reported no differences in pain, function, or physical or mental components of quality of life at any time point. A smaller high-quality meta-analysis (4 RCTs, 394 patients) by Wieland et al. reported a -20.4-point difference in pain (on a 0-100 scale) (95% CI -25.5, -15.3) compared to other exercises. Importantly, however, the certainty of evidence was graded as very low and no significant differences were seen in function outcomes. Two separate SRs without meta-analyses in 2016 report small to no differences in pain and inconsistent findings related to function when comparing yoga to other exercise types (Chou 2016, Chang 2016).

Regarding aerobic exercise, Owen et al. ranked it second out of ten different exercises for pain reduction, fifth out of ten for function, and second out of five for mental health, all supported by low certainty evidence. Specific to walking, Lawford et al. reported that in seven RCTs there was no evidence that walking was more effective than other forms of exercise.

Flexibility and stretching exercises in comparison to other forms of exercise was assessed in one network meta-analysis and ranked ninth out of ten different exercises for both pain and function (Owen 2020).

Several limitations of the evidence are important to note. Although many RCTs have been performed comparing various forms of exercise to non-active controls, relatively few head-to-head RCTs exist for specific exercise comparisons. When comparisons are made, significant overlap and inconsistencies between studies exist in definitions of exercise type. For example, strengthening was separate from resistance training in some studies, but were considered under one definition in others, or yoga or tai chi were considered mind-body exercises in some studies and as strengthening or flexibility in others. Methodological quality of the included SRs ranged from low to high, with most being of low or moderate quality. Of the studies that provided grades of evidence, most findings were supported by low certainty/quality of evidence. Overall, adverse event reporting was absent in many studies and when reported, was not adequately robust to allow for quantification. Considering these limitations, direct comparison and especially network meta-analytic efforts to rank effectiveness of interventions becomes highly challenging.

Context

Chronic low back pain and osteoarthritis are common chronic pain conditions presenting to primary care clinicians. There is a large volume of higher certainty evidence that exercise is a highly important intervention for osteoarthritis and chronic low back pain (Ton 2020, Kolber 2021) and there are a myriad of health benefits associated with exercise for many other chronic conditions (Hoffman 2016). In general, the variety of exercise options reviewed are of low cost, are widely accessible, and have

similar likelihoods for pain and functional outcome improvements in the management of osteoarthritis and chronic low back pain. This allows for a great degree of flexibility in finding and prescribing exercise(s) that are effective and preferred by the individual patient.

Suggested Recommendation

We recommend any type of exercise, based on patient preference, as they are all likely similarly effective (strong recommendation, low quality evidence)

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Exercise and Chronic Neuropathic Pain

Clinical Question

Is exercise effective for chronic neuropathic pain (painful diabetic neuropathy, postherpetic neuralgia, or trigeminal neuralgia)?

Bottom Line

The available data suggest exercise results in a small potential reduction in pain scores and inconsistent improvements in quality of life measures, but the differences were generally not statistically different and of borderline clinical significance. At best, quality of life may improve by ~25%, but this is based on very low-quality data. However, exercise does provide benefits beyond pain control, such as lowering of cardiovascular disease risk.

Evidence and Limitations

No SRs report on the efficacy of exercise for chronic neuropathic pain. However, 3 RCTs are available. The PRISMA and Risk of Bias Summary and Graph are available (Figures 10, 11, and 12 respectively).

Home Based Exercise

The most recent trial was an open-label RCT in 104 patients with diabetic peripheral neuropathy in Myanmar (Win 2019). The mean age of participants was 55 and 76% were female. The mean duration of diabetes was about 6 years, and the baseline pain score on a 100-point VAS was ~23. Participants were randomized to home-based hand and foot exercises for 10 minutes 3 times/day or a waitlist. After 8 weeks, the pain scores in both groups decreased, but there was no statistical difference between groups (19.16 in the exercise group and 20.33 control; $p>0.05$).

The number of patients with "numbness and tingling" at baseline was 44% in the exercise group, and 33% in control. This changed to 40.6% and 53.5%, respectively, at 8 weeks. While the difference between endpoints appears promising, it is mainly driven by the increase in the control group from baseline, rather than the efficacy of exercise. In fact, 8-weeks after the study's conclusion, 56.3% of the exercise group, and 41.9% of the control group, reported "numbness and tingling", highlighting the spurious nature of the results.

This RCT also investigated the effects of exercise on 16 different activities of daily living (ADLs). Participants in the exercise group had difficulties with 1.6 ADLs at baseline, and 1.3 at the end of the study. The control group went from 1.8 to 1.6. Additionally, the authors compared the number of patients who had difficulty with each ADL at baseline. At follow-up, this changed for 3 ADLs: the ability to use a spoon, climbing stairs, and performing work or chores (Table 2), however, effects were not consistent. For example, the number of participants who had difficulty using a spoon increased with exercise, but there was no change in ability to use a knife, fork, or other eating utensil. Additionally,

some results appear spurious, for example, while 16% of control had difficulties performing work or chores at baseline, this number increased to 40% at the 16 week follow-up. Finally, there was no significant change in 13 other ADLs.

Table 2. Effects of Exercise versus Control on Activities of Daily Living (ADLs)

ADL	Number (%) of participants with this difficulty at baseline (exercise) n=32	Number (%) of participants with this difficulty at baseline (control) n=43	Number (%) of participants with this difficulty at follow-up (exercise) n=32	Number (%) of participants with this difficulty at follow-up (control) n=43
Using a spoon	0	3 (7%)	4 (13%)	4 (9%)
Climbing stairs	12 (38%)	21 (49%)	6 (19%)	19 (44%)
Performing work or chores	7 (22%)	7 (16%)	4 (13%)	17 (40%)

Other limitations with this RCT include: high and unbalanced withdrawal rates (22 participants withdrew from study), possible selective reporting of patients [number of patients with data available at 8 weeks (82) does not match numbers reported (75)], intention to treat (ITT) was not used, and baseline characteristics were not balanced (i.e. more patients in the exercise group reported numbness and tingling, more patients in the control group using analgesic or alternative treatments) which suggests problems with allocation concealment and/or randomization processes.

Aerobic Exercise

The second RCT was assessor-blinded in 54 patients with various peripheral neuropathies in Calgary, Alberta (Toth 2014). Approximately 59% of patients were female, the mean age was 55, and the baseline pain score was ~51 on a 100-point VAS. Patients were randomized to an individualized "balanced exercise program" created by a kinesiologist which included moderate intensity aerobic exercise and stretching from 15-60 minutes 3-5 days/week and monthly meetings with the kinesiologist, or an educational program (kinesiologist provided monthly 2-hour lectures). After 6 months, pain severity decreased by 7.9 (exercise) and 3.9 (control) on the 100-point VAS, but this was not statistically different (p=0.08). No patient in either group experienced at least a 30% reduction in their pain. There was also no difference in the Patient Global Impression of Change scale or quality of life.

While no adverse events were reported in the control group, there were 5 cases of transient worsening of chronic pain, 3 of dizziness, and 2 of muscle strain in the exercise group. Overall, 7 patients withdrew from the exercise group due to increased "discomfort", while 6 withdrew from control due to "lack of interest".

This study had some important limitations: 28% of patients withdrew, making the robustness of the data questionable. Additionally, multiple types of peripheral neuropathy were included, including diabetic polyneuropathy (30%), post-surgical/post-traumatic (28%), trigeminal neuralgia (4%),

postherpetic neuralgia (7%), complex regional pain syndrome (4%), inflammatory polyneuropathy (2%), cervical/lumbar radiculopathy (13%), and "other" (13%). The effectiveness of exercise in different polyneuropathies is unknown.

Treadmill Exercise

The third RCT was assessor-blinded in 87 patients with diabetic peripheral neuropathy (Dixit 2014a). Completed in India, 39% of participants were women and the mean age was 57. Patients were randomized to supervised, moderate intensity treadmill exercise (3-6 days/week, 150-360 minutes/week) or usual care. After 8 weeks, pain on a 5-point neuropathy quality of life sub-scale (where lower numbers indicate a better score) changed from 1.65 at baseline to 1.73 in the control group, and from 1.60 to 1.61 in the exercise group ($p=0.03$) (Table 3). While the difference between groups appears statistically different, it should be noted the score did not change in the exercise group between baseline and 8-weeks. The effects on other aspects of quality of life were also investigated. While some quality of life measures appear better at 8 weeks between exercise and control, the effects are not consistent and are of borderline clinical significance. The overall quality of life score changed from 33.55 at baseline to 34.16 in the control arm, and from 32.85 to 24.41 in the exercise arm. This change was statistically different ($p<0.001$).

The RCT also reported "absolute differences (in percentages) in neuropathy quality of life scores after 8 weeks". The overall pain score absolute percent change was 30.18% for the intervention group, and -13.75% in control, which was statistically different ($p=0.01$). The total quality of life score absolute percent change was 24.28% and -4.12% for the intervention and control groups, respectively ($p<0.001$). Unfortunately, these numbers do not correspond to the numerical changes described above, and the reason for the discrepancies are unknown. It should be noted that other discrepancies also exist in the paper. For example, another publication of this RCT (Dixit 2014b) stated the duration of diabetes in the control and intervention groups was 83.71 and 49.77 months, while this paper reported the rates as 82.10 and 65.49 months, respectively.

Table 3. Neuropathy Quality of Life Scores on 5-point Scale*

Quality of Life Measure	Mean score at baseline, Exercise (n=40)	Mean score at baseline, Control (n=47)	Mean score at 8 weeks, Exercise (n=29)	Mean score at 8 weeks, Control (n=37)
Pain	1.60	1.65	1.61	1.73
Reduced feeling/sensation	1.20	1.35	1.02	1.61
Sensory-motor symptoms	1.56	1.57	1.09	1.56
Restriction in ADL	1.63	1.72	1.07	1.60

Disruptions in social relationships	1.35	1.42	1.09	1.51
Emotional Distress	1.46	1.66	1.14	1.64
Specific impact on quality of life	2.04	2.01	1.28	1.84
Overall quality of life	2.80	2.59	2.09	2.77
Total score	32.85	33.55	24.41	34.16

*All p-values at 8 weeks were statistically different ($p<0.05$) except for emotional distress.

Context

In addition to the RCTs above, other research has utilized exercise as a component of intensive lifestyle modification to assist with weight loss in patients with type 2 diabetes. One RCT of intensive lifestyle intervention versus control (diabetes support and education) for weight loss investigated the effects on neuropathy (Horton 2017). This RCT followed 5145 obese or overweight people with type 2 diabetes for ~10 years. At various timepoints, the mean score difference on a diabetic neuropathy questionnaire was rarely clinically relevant between groups (i.e. 0.3 points different on a 15-point scale). However, the proportion of patients with "abnormal" neuropathy scores was lower in the intervention arm [e.g. 25% versus 27% (control), statistical significance not reported]. Note that the scale used was not limited to painful neuropathies, but other neuropathic symptoms as well (e.g. differentiating hot from cold).

Many authors suggest non-pharmacological therapies (e.g. exercise, physiotherapy, psychology, massage) be initiated early in the management of chronic neuropathic pain to address issues such as mood disorders, sleep problems, and pain catastrophizing (Bates 2019). Exercise is recommended as "essential to enhance outcome" in guidelines on the pharmacological management of chronic neuropathic pain (Moulin 2014). Gilron et al. recommend exercise and other non-pharmacologic treatments be considered due to their "presumed safety", despite a lack of evidence supporting their efficacy (Gilron 2006).

It should be noted that exercise has benefits beyond those theorized for pain management. For example, one SR of 47 RCTs (10,794 patients) found that exercise-based cardiac rehabilitation decreased total mortality by ~13% (relative reduction) and cardiovascular mortality by 26% in patients with coronary heart disease (Anderson 2014, Heran 2011), with some indirect comparisons suggesting the cardiovascular benefits of exercise are similar to individual medications (Naci 2013).

Suggested Recommendation

There is inadequate data to recommend for or against exercise as a treatment for chronic neuropathic pain.

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Chronic Pain and Drug Combinations

Clinical Question

Does combination pharmacological therapy improve pain outcomes more than monotherapy for patients with low back pain, neuropathic pain, or osteoarthritis?

Bottom Line

Many RCTs have studied combination therapy for low back pain or neuropathic pain. However, the number of available studies for any one combination is limited. The current evidence is insufficient to make any specific recommendations about which combination to select.

Evidence and Limitations

Low Back Pain

One health technology assessment was identified that included some pharmacologic combination therapies for low back pain, but it did not specifically address combination therapy. Most of the trials reviewed were for monotherapy. Two SRs were identified that evaluated the effect of combination pharmacological therapy on low back pain (Song 2016, Mathieson 2019). The PRISMA flow chart can be seen in Figure 13.

Song et al. conducted a SR and meta-analysis of combination therapy for low back pain. They identified 12 RCTs that studied the effect of combination therapy on low back pain (6 for acute and 6 for chronic). Only 8 of those RCTs compared combination therapy to monotherapy, whereas the remaining 4 compared combination therapy to placebo. The trials used a variety of outcomes to measure treatment effect, so the meta-analysis converted outcomes to a SMD for the sake of comparison. For chronic low back pain, only 2 RCTs reported change in pain intensity from baseline. One compared pregabalin plus an NSAID to NSAID plus placebo or acetaminophen plus placebo in 20 patients, whereas the other compared NSAID plus opioid to NSAID plus placebo in 35 patients. Both RCTs showed statistically significant reductions in pain intensity from baseline, with pooled SMD of combination therapy versus monotherapy being -0.84 (95% CI -1.12, -0.56). While statistically significant, the result is difficult to interpret clinically. There were no RCTs of combination therapy versus monotherapy for chronic low back pain reporting on change in physical function from baseline.

Adverse effects were treated as a dichotomous variable and reported as relative risks. In total, 8 RCTs of combination therapy versus monotherapy, for either chronic or acute low back pain, were evaluated for adverse effects. Of those, 2 used different dosages for the shared therapy in the combination and monotherapy arms. Pooling the results from only the RCTs that used the same dosages produced a relative risk of 1.72 (95% CI 1.28, 2.29), suggesting a statistically significant increased risk of experiencing adverse events with combination therapy versus monotherapy.

Mathieson et al. conducted a SR and meta-analysis of combination therapy for the management of sciatica and low back pain. They identified 27 studies to include in qualitative analysis and 11 for quantitative analysis. From these, there were 16 different combination therapies compared with monotherapy. For chronic low back pain, only one combination provided a significant reduction in pain intensity from baseline in an RCT of 44 patients. Transdermal buprenorphine plus pregabalin versus transdermal buprenorphine plus matching placebo led to a mean difference on a 100-mm VAS of -23.30 (95% CI -27.68, -18.92) after 1 week and -27.6 (95% CI -31.7, -23.5) after 3 weeks. The authors conclude that this is a clinically meaningful difference, but that the quality of evidence is low.

For adverse effects, the authors stated that there was no statistically significant difference between combination therapy and monotherapy. However, no pooled effect was presented, and there was considerable variability in findings between the included trials.

Limitations of the above SRs include the wide range of combination therapies evaluated, inclusion of therapies not readily available in clinical practice, studies with varying outcome measures, use of continuous outcomes instead of dichotomous outcomes, inclusion of non-blinded RCTs, and inclusion of few studies with an active comparator group, making evaluation of combination therapy versus monotherapy difficult.

Neuropathic Pain

Systematic Reviews

Nine SRs were identified for combination therapy for neuropathic pain. Two SRs were designed to evaluate the effect of combination pharmacological therapy on neuropathic pain (Chaparro 2012, Wiffen 2016). The PRISMA flow chart can be seen in Figure 12.

Chapparro et al. identified 21 double-blind RCTs with 9 different combinations. Meta-analysis of only two RCTs evaluating the combination of pregabalin/gabapentin with opioids was deemed appropriate. Combining of other studies was not deemed appropriate due to diverse pain conditions, diverse outcome measures, and single studies for a given combination. The combination of gabapentin with morphine versus gabapentin alone was evaluated in 423 patients with PHN and diabetic neuropathy (DN). Patients with PHN were included if a herpes zoster eruption occurred 6 months or more prior to enrolment. Moderate/good pain relief was achieved by 48% on combination therapy versus 37% on gabapentin alone [risk ratio (RR) 1.3, 95% CI 1.04, 1.61) with a number needed to treat NNT of 10.

The risk of dropout due to adverse events was evaluated in 433 patients and was 15% on combination vs 6% on gabapentin (RR 2.8, 95% CI 1.5, 5.2), with a number needed to harm (NNH) of 10. Limitation: one study only allowed for completer analysis which will make the efficacy data look better than intention to treat analysis.

Wiffen et al. planned a SR of acetaminophen with or without codeine for patients with neuropathic pain of various types. However, no RCTs could be found that met their inclusion criteria.

The remaining seven SRs evaluated combination therapy as a part of a larger review of pharmacological agents for neuropathic pain. It is challenging to apply the findings of these SRs to our question due to only a subset of studies including the relevant population (Finnerup 2015, Rudroju 2013);

absence of conclusions about combination therapy from qualitative review (Khadem 2013, Finnerup 2010); difficulty drawing conclusions for any specific combination (Selph 2011, Moisset 2020) or low-quality rating (Liampas 2020).

Randomized Controlled Trials

Given the difficulty in drawing conclusions about any specific combination, the RCTs from the above SRs were identified and an RCT search was run from 2015-2021. A decision was made to look at RCTs that examined combinations of pregabalin/gabapentin, serotonin and norepinephrine inhibitors (SNRIs), and TCAs, the most commonly prescribed first line agents for diabetic neuropathy and postherpetic neuralgia. Three RCTs were identified. See Figure 14 for the PRISMA flow chart. Risk of Bias Summary and Graph are shown in Figures 15 and 16 respectively.

Gilron et al. performed a double-blind crossover RCT in 45 patients with diabetic neuropathy (71%) and postherpetic neuralgia (29%). Patients with PHN had herpes zoster eruption 6 months or more prior to study enrolment. Patients were randomized to three treatment arms (gabapentin, nortriptyline or combination of both), and crossed to other arms after a six-week period with a 7-day washout in between each period. Outcomes were reported for the entire trial. Baseline pain on 11-point VAS was 5.4 in each group. Combination therapy improved pain more than gabapentin alone (VAS achieved: 2.3 combination versus 3.2 gabapentin, p=0.001) and more than nortriptyline alone (VAS achieved: 2.3 combination versus 2.9 nortriptyline, p=0.02). Dry mouth was more common with combination (60%, p<0.0001) and nortriptyline (58%, p<0.0001) when compared with gabapentin (17%). Difficulty concentrating was more common with gabapentin (11%) than nortriptyline (0%, p=0.03). Moderate pain relief was achieved by 65% on gabapentin, 76% on nortriptyline, and 84% on combination but no statistical analysis was provided.

Tesfaye et al. performed a double-blind RCT comparing the combination of duloxetine and pregabalin with duloxetine monotherapy and pregabalin monotherapy in 347 patients with diabetic neuropathy. This study consisted of two phases: initial therapy with either duloxetine or pregabalin, followed by a second phase of high-dose monotherapy or combination pregabalin and duloxetine therapy. Patients were randomized into one of four possible arms at study start: duloxetine/high-dose duloxetine, duloxetine/combination, pregabalin/high-dose pregabalin, or pregabalin/combination. After 8 weeks in the first phase, patients who did not respond to monotherapy continued in the study into the second phase. The proportion of patients achieving ≥30% or ≥50% pain relief was no different between high dose monotherapy and combination therapy groups. No differences in adverse effects were seen between groups. This study was limited by lack of randomization during the second phase of the study, removal of responders and lack of allocation concealment.

Simpson et al. performed a small parallel group study of 11 patients with diabetic neuropathy comparing gabapentin plus venlafaxine versus gabapentin plus placebo. This study suggested the combination was superior: difference on 11-point pain scale from baseline was -2.0 for combination versus -0.5 for monotherapy (p<0.001); proportion of patients with much/moderate improvement was 75% on combination versus 33% on monotherapy (p<0.01). However, it is limited by small sample size, short follow-up, and outcomes reported based on completer analysis. Responder analysis was not different when using ITT population (50% vs 20%, p=0.67, writer's calculations)

Osteoarthritis

No systematic reviews could be identified regarding combination therapy for osteoarthritis pain.

Context

Clinicians may recommend combination therapy to patients with chronic pain when monotherapy is limited in efficacy or tolerability. However, there is a lack of evidence supporting any specific drug combination. A trial of combination therapy may be reasonable if monotherapy fails but adverse effects may be more frequent. RCTs often have a small number of patients, vary in quality from low to moderate and measure pain using a variety of outcome measures. SRs are often descriptive and study combination therapy as a secondary objective.

Suggested Recommendation

We suggest the addition of another medication can be discussed if the original medication has only provided partial benefit (weak recommendation, very low quality evidence).

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Tapering Opioids in Chronic Pain

Clinical Question

Does tapering the dose of long-term opioids improve pain or function for patients with chronic pain?

Bottom Line

Randomized controlled trials have been unable to achieve statistically significant reductions in opioid use compared to control despite interventions specifically aimed at opioid reduction. However, doses do decrease from baseline. This is likely due to recruiting patients who were interested in reducing/tapering their opioid use. Many studies reported high drop-out rates. In a number of trials, both groups saw a modest decline in opioid use that was associated with stable, and at times slightly improved, outcomes. However, observational data suggest a possible link between tapering and risk of overdose, mental health crises and suicide. Tapering decisions must be discussed with patients and if tapering will commence, should be done slowly (e.g. 5-10% every 2-4 weeks).

Evidence and Limitations

The PRISMA diagram can been seen in Figure 17.

Table. Summary of Randomized, controlled trials (RCTs) (Eccleston 2017, Sullivan 2017, Garland 2014, Jamison 2010, Kurita 2018).

RCT	N	Intervention	Control	Duration	Opioid reduction?	Pain effects?	Physical function effects?	Psychological function effects?
Sullivan 2017	35	CBT	Usual care	22 weeks	NS	NS	Improved	NS
Garland 2014	115	CBT/ mindfulness	Support group	8 weeks	NR	Improved	Improved	NS
Jamison 2010	42	CBT/ mindfulness	Usual care	6 months	NR	NR	NS	Improved
Kurita 2018	35	Tapering	Control	4-6 weeks	NS	NS	NS	Improved
Zheng 2008	35	Electroacupuncture	Sham acupuncture	20 weeks	NS	NS	NR	NS

NS=not statistically different; NR=not reported.

One SR (without meta-analysis) of 4 RCTs and 278 mainly female patients (mean age 50) investigated methods to reduce or cease opioids for the management of chronic, non-cancer pain (Eccleston 2017). Each RCT will be discussed below and are summarized in the above table.

The first RCT utilized CBT to reduce opioid consumption versus usual care in 35 patients interested in reducing their opioid dosage (Eccleston 2017, Sullivan 2017). After 22 weeks of treatment, opioid use decreased in both groups from baseline, but was not statistically different between groups [baseline: 207mg morphine equivalent versus 245mg (usual care); final: 112mg versus 170mg (usual care)].

In terms of patient outcomes, there was no statistical difference in the proportion of patients who rated themselves at least "moderately better" on global impression of change: 56% versus 23% (usual care). There was also no statistical difference in pain severity on an 11-point scale [lower scores indicate less pain; baseline 5.7 versus 6.3 (usual care); final: 4.7 versus 5.8 (usual care)]. Nor was there any statistical difference in psychological function or depression and anxiety scores [baseline depression score ~12.4/27 where higher scores are worse; 8.9 versus 11.3 (usual care) at 22 weeks; baseline anxiety score ~8.6/21 where higher scores are worse; 5.9 versus 9.1 (usual care) at 22 weeks].

However, there was statistical improvement in patient's ability to manage pain on 60-point scale (higher=better), from 31 at baseline to 36 versus 30 (usual care) at 22 weeks, and a statistical improvement in physical function on an 11-point scale (lower=better), from 6 or 6.6 (usual care) at baseline to 4.6 versus 6.4 (usual care) at 22 weeks. Patients also had statistically fewer opioid "problems" on a 16-point scale (lower=better), from ~12 at baseline to 2.9 versus 7.5 (usual care) at 22 weeks.

Another RCT of a CBT/mindfulness program wanted to reduce opioid "misuse" scores (e.g. taking opioids in excessive doses or in ways other than how prescribed) in 115 patients with mixed pain types (Eccleston 2017, Garland 2014) compared to a support group. Approximately 72% of participants had opioid use disorder. However, after 8 weeks of treatment, opioid use itself was not measured. There was, however, a statistical trend towards fewer patients with opioid use disorder (based on scale data): 27% versus 49% (support group), p=0.05, with no difference in psychological functioning. The authors did find a statistical reduction in pain intensity scores of 4.9 versus 5.7 (control) on an 11-point scale (lower=better), which is of borderline clinical relevance. They also reported a statistical difference in physical function scores: 5.2 versus 6.9 (control) on 11-point scale (lower=better), which is likely a clinically relevant difference.

The third RCT of investigated CBT/mindfulness versus usual care to reduce "misuse" (use of medication in ways other than intended or prescribed) in 42 patients with chronic neck or back pain and at risk for, or with a history of, opioid misuse (Eccleston 2017, Jamison 2010). After 6 months, outcomes related to opioid use or pain intensity were not reported, and there was no difference in physical function. However, there were statistical changes in mean depression and anxiety scores on 21-point scales (lower=better) that were likely clinically important, with mean depression scores of 8.1 versus 9.1 (control), and mean anxiety scores of 6.1 versus 9.0 (control).

The last RCT of the Eccleston SR compared electroacupuncture to sham electroacupuncture in 35 patients with mixed pain types to reduce opioid consumption (Eccleston 2017). After 20 weeks, there was no difference in opioid use, pain intensity, psychological function between groups, and physical function was not measured.

One RCT has been published since the above SR. In Kurita 2018, 35 patients were stabilized on long-acting opioids before being randomized to tapering (10% per week until discontinued) or control. After 4-6 weeks, there was no difference in pain scores, however, 2 out of 15 patients in the taper arm dropped out due to pain, compared to 0 out of 20 in the control group. There was, however, a statistical increase in proportion of patients feeling "rested": 80% versus 35% control. No difference was found in opioid dose or other outcomes between groups. It should be noted that this study was statistically

underpowered due to high dropouts (planned for 130 patients, 75 included, 40 dropped out during stabilization).

In addition to the above RCT data, there are observational studies investigating outcomes such as overdose rates. A 2020 SR (without meta-analysis) that included observational data concluded the net balance of benefits/harms is unclear (Mackey 2020). Some example studies from this SR include a 2019 Vermont pre-post study of 694 patients. Over 60% of which had substance use disorder. Subsequently, 49% had an emergency department visit or hospitalization due to opioid poisoning or substance use disorder. Opioids were "most often" stopped without gradual taper.

Three other studies in the SR looked at overdose rates among people with opioid dose reductions. One found no difference in overdose rates and another found no overdoses. The third study of 572 people found overdose deaths in 4.9% of those who stopped opioids versus 1.75% who continued with prescription opioids.

A newer retrospective cohort study that was not included in the above SR investigated 113,618 patients identified through administrative claims data who were on stable, higher-doses of opioids in the USA (>= 50 mg morphine equivalents/day), 96% of whom had no overdoses in last year, ~53% with baseline depression/anxiety, who underwent tapering within a 7-month window (Agnoli 2021). The rate of overdose was 9.3% of those who tapered compared to 5.5% who did not taper. The risk of overdose was highest with doses ≥300mg/day, at 16.2% versus 7.4% (not tapered).

The study authors also looked at the speed of tapering on overdose risk. Compared to the 5.9% risk in those not tapered, the risk in those with a ≥50% monthly dose reduction was 9.4%, 10.1% in those with a 20-49% dose reduction, and 8.7% in those with a 10-19% dose reduction.

In contrast, the speed of taper did show a more linear relationship with mental health crises. A ≥50% monthly dose reduction carried a 12% risk, 20-49% dose reduction a 7.1% risk, and a 5.6% risk in those on a 10-19% dose reduction, compared to 3.5% risk in those not tapered. Looking at dose, the risk of a mental health crises was highest in people on ≥300mg/day, at 11.9% versus 3.8% in those not tapered. Overall, the risk of a mental health crisis was 7.6% versus 3.3% in those not tapered.

Finally, the study looked at the rate of suicide attempts. It was 0.4% versus 0.1% in those not tapered.

There are important limitations to this body of research. Most RCTs investigated methods to reduce opioid use, with effects on pain and function as secondary outcomes. Direct causality between reduced opioid dose and pain/function cannot be assumed. Additionally, the RCTs were generally underpowered to find a difference between groups, and the use of multiple comparisons increases the risk of finding spurious results. Observational studies may not be able to identify which patients have concurrent opioid use disorder or which patients were not motivated to taper and may not capture all potential confounding variables.

The Risk of Bias Summary and Graph are in Figures 18 and 19, respectively.

Context

Guidelines suggest tapering opioids should be considered for adults with chronic non-cancer pain on ≥90 mg morphine equivalent daily and that tapering should be done slowly (Busse 2017). However, if opioid use disorder is suspected, other treatments, such as opioid agonist treatment, may be indicated

(Korownyk 2019). The Prescription Opioid Misuse Index (POMI) may be useful in identifying patients taking prescription opioids who have opioid use disorder (Korownyk 2019). Any tapering decisions must be discussed with the patient first (United States Department of Health and Human Services).

Suggested Recommendation

For patients with chronic pain without opioid use disorder who are interested in tapering their long-term opioids, we suggest discussion of slow dose reductions, supported by CBT where possible. Best evidence suggests potential harm in patients who are not interested in tapering opioids. (weak recommendation, very low quality evidence).

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Chronic Pain and Cannabinoids

Clinical Question

How effective are cannabinoids for treating chronic (non-cancer) pain (osteoarthritis, low back pain, neuropathic pain)?

Bottom Line

Cannabinoids provide meaningful (≥30% pain reduction) relief in chronic neuropathic pain for approximately 39-40% of users versus 30% on placebo. Pain starting around 6.6 out of 10, improves to 5.4 with placebo and 4.7 with cannabinoids. The RCTs frequently have considerable bias. The neuropathic pain types studied are highly diverse and likely do not mirror neuropathic pain types seen in practice. Osteoarthritis and low back pain each have only one RCT: they are short (2-4 week), small (30-38 patients) and find limited benefit. Adverse events (like dizziness, nausea, cognitive disturbance, drowsiness, and confusion) are common and will cause around 10% to withdraw from therapy (versus 5% on placebo).

Evidence and Limitations

Most RCTs evaluating cannabinoids for chronic pain studied neuropathic pain. For this reason, we focused on SRs with meta-analysis for neuropathic pain. For osteoarthritis and chronic low back pain, the RCT evidence base was sparse, and therefore we expanded the inclusion to descriptive SRs without meta-analysis. Due to the number of SRs in the area of cannabinoids and chronic pain, we excluded those published over 10 years ago.

115 articles were identified, with two being duplicates, leaving 113. Title abstract review excluded 87 and full text review excluded another 13. This resulted in inclusion of 13 SRs (Allan 2018A, Andreae 2015, Aviram 2017, Fitzcharles 2016A, Fitzcharles 2016B, Johal 2020, Meng 2018, Mücke 2018, Petzke 2016, Rabgay 2020, Snedecor 2014, Stockings 2018, and Tsang 2016). A secondary search of Pubmed (March 25, 2021) for osteoarthritis OR chronic low back OR neuropathic pain AND cannabis OR cannabinoid, limited to SRs was conducted. This yielded 46 articles which identified one new article for inclusion (Wong 2020). Lastly, author records from past publications in the area were reviewed and one SR was added (Whiting 2015). The final list included 15 SRs (Allan 2018A, Andreae 2015, Aviram 2017, Fitzcharles 2016A, Fitzcharles 2016B, Johal 2020, Meng 2018, Mücke 2018, Petzke 2016, Rabgay 2020, Snedecor 2014, Stockings 2018, and Tsang 2016, Wong 2020, and Whiting 2015) (Figure 20 – PRISMA flow diagram).

The latest SR (Stockings 2018) to identify an RCT of low back pain (Pinsger 2006), was last searched in July 2017. We searched August 1, 2017 to April 14, 2021 with Cannabis OR cannabinoid AND low back pain, identifying 12 articles but no human RCTs.

The latest SR (Wong 2020) to identify a RCT of osteoarthritis (Huggins 2012), was last searched in December 2018. We searched January 1, 2019 to April 14, 2021 with Cannabis OR Cannabinoid AND

Osteoarthritis, identifying 28 articles but no human RCTs. The following results are statistically significant unless indicated.

Neuropathic Pain

If looking at responder results (percent of patients with ≥30% pain reduction), 39-40% of patients attained meaningful pain reduction on cannabinoids compared to 30% on placebo (study duration 2-26 weeks) (Mücke 2018 and Petzke 2016). If limited to inhaled cannabinoids, this changed to 47% versus 29% [relative risk 1.61 (1.21-2.14)] (Andreae 2015).

When ranking pain on a scale of 0-10: cannabinoid patients' pain was reduced -0.65 to -0.74 more than placebo (Meng 2018 and Wong 2020). One study (Meng 2018) had enough data for rough estimation of change from baseline pain score in both groups: starting at approximately 6.6 baseline pain, patients on placebo reached around 5.4 and patients on cannabinoid reached approximately 4.7. One review reported reduction versus placebo over differing time points: ≤2 weeks (-0.82); 2-8 weeks (-1.19); 2-6 months (-0.92) (Johal 2020). Combining differing pain scales yielded a SMD of -0.35 to -0.38 (Aviram 2017 and Mücke 2018). The clinical relevance was not interpretable.

One meta-analysis examining diabetic neuropathy ranked cannabinoids (nabiximol) last for improved pain scale and second last for attaining ≥30% improvement, based on one small (30 patient) RCT (Snedecor 2014).

Combined Chronic Pain

Looking for a ≥30% pain reduction (over 6 hours to 15 weeks, median 4 weeks): meaningful pain relief rates were 29-39% for cannabinoids versus 26-31% for placebo (Allan 2018A, Stockings 2018, and Whiting 2015). Ranking on a pain scale (0-10): cannabinoid patients pain reduced -0.46 to -0.71 more than placebo (Wong 2020 and Whiting 2015). Inadequate data was provided to estimate baseline pain scores or improvement with placebo. Combining differing pain scales yielded a SMD of -0.14 to -0.50 (Aviram 2017, Rabgay 2020, and Stockings 2018). The clinical relevance was not interpretable. The SMD specific to cancer pain was – 0.63 (-0.45 to -0.81) (Aviram 2017).

The majority of cannabinoids studied are pharmaceutically derived like nabiximols or nabilone. Route of administration or varying products seem to have similar effectiveness, but head to head comparisons are very limited (Allan 2018, Wong 2020, and Whiting 2015).

Chronic Back Pain

A cross-over RCT (with 4-week treatments) (Pinsger 200) of 30 patients looked at nabilone 0.25-1mg/day (in German, additional details from Fitzcharles 2016A) vs placebo. On a pain scale of 0-10, pain over weeks improved by 0.9 with nabilone versus 0.5 with placebo (p=0.2) and "current pain" improved 0.6 with nabilone versus 0.0 with placebo (p=0.002). No statistically significant improvement in quality of life or 2 headache outcomes were found. When the Cochrane Risk of Bias tool was applied to the chronic back pain data, all 7 items were rated as "unclear" risk of bias in Fitzcharles (Fitzcharles 2016A) and 7 out of 9 were unclear (2 low risk incomplete outcome and selective reporting) for Stockings (Stockings 2018).

Osteoarthritis (knee)

A single cross-over RCT (with 2-week treatments) (Huggins 2012) of 38 patients on PF-04457845 4mg/day vs placebo. PF-04457845 is "a potent and selective FAAH1 inhibitor" with endocannabinoid properties. The WOMAC Pain scale and the WOMAC pain and function scale showed no difference from placebo. As per the Cochrane Risk of Bias tool, this study was low risk for random sequence, allocation concealment selective reporting and other biases; and high risk for performance bias, detection bias and attrition bias. Thus, 3 of 7 at high risk of bias (Wong 2020).

Adverse Events

Total adverse events occur in ~80% on using cannabinoids versus ~60% on placebo (Mücke 2018 and Whiting 2015). Withdrawal due to adverse events were statistically more common with cannabinoids (Mücke 2018, Petzke 2016, Stockings 2018, and Whiting 2015), with estimated event rates around 10% for cannabinoids versus 5% for placebo (Mücke 2018 and Petzke 2016). Common adverse events included dizziness, nausea, cognitive disturbance, drowsiness, depressed mood, and confusion (Stockings 2018). Euphoria was also more common (Rabgay 2020) but dysphoria has similar risk increase (Allan 2018A). Table 4 provides comprehensive details on the adverse events and risks (Allan 2018B).

Table 4: Summary of results from Systematic Reviews

Study	Conditions	RCTs (patients)	Outcome	Effect	Event Rates	Discontinue due to adverse events	Notes
Allan 2018	Neuropathic/ Cancer	15 (1985)	≥30% pain reduction	RR 1.37 (1.14-1.64)	39% vs 30%		
Andrea 2015	Neuropathic	5 (178)	≥30% pain reduction	RR 1.61 (1.21-2.14) †	47% vs 29%	Not given	Inhaled (short studies)
Aviram 2017	Chronic Pain	40 (2345)	SMD (14 RCTs)	-0.39 (-0.29 to -0.49)	-	Not given	Adverse Events
	Neuropathic		SMD (11 RCTs)	-0.38 (-0.27 to -0.48)	-		
	Cancer		SMD (3 RCTs)	-0.63 (-0.45 to -0.81)	-		
Fitzcharles 2016a	Rheumatology	4 (160)	No meta		-		Spinal RCT
Fitzcharles 2016b	Rheumatology	4 (203)	No meta		-		Osteoarthritis RCT
Johal 2020	Chronic non-cancer pain	36 (4006)	VAS 0-10, ≤14 days (14 RCTs, neuropathic)	-0.82 (-0.46 to -1.18) over placebo	-		Any adverse event, 51% vs 43%
			VAS 0-10, 2-8 weeks (5 RCTs, neuropathic)	-1.19(-0.60 to -1.79) over placebo	-		
			VAS 0-10, 2-6 months (3 RCTs, neuropathic)	-0.92 (-0.03 to -1.80) over placebo	-		
Meng 2017	Neuropathic	11 (1219)	VAS 0-10 (10 RCTs)	- 0.65 (-0.23 to -1.06) over placebo	Baseline 6.6 (5.1 Cann vs 5.4 control)	No meta	Diff in PEER calc (0.39) due to random effects
Mucke 2018	Neuropathic	16 (1750)	≥30% pain reduction (10 RCTs)	Risk diff 9% (3-15%)	39% vs 33%	13 RCTs, Risk diff: 4% (2-7%), event rates 10.4% vs	Diff in events and Risk diff, random effects

						4.7% (random effects)	
			SMD (14 RCTs)	-0.35 (-0.09 to -0.60)			Any AE (7 RCTs, 1356 pts): risk diff 19% (12-27%); event rates 82% vs 66%
Petzke 2016	Neuropathic	15 (1619)	≥30% pain reduction (9 RCTs)	Risk Diff 10% (3-16)	38% vs 30%	(11 RCTs) Risk Diff 4% (1-7), event rates 11% vs 5%	severe side effects (11 RCTs) 6% vs 5% (NSS)
Rabgay 2020	Any Pain	39 (2270)	SMD (25 RCTs network meta) THC/CBD	-0.5 (-0.9 to -0.2)			Network Meta with lots on dose and route. Euphoria is a common side effect -example THC 7%, RR 1.74 (1.13 – 2.27)
Snedecor 2014	Diabetic Neuropathy	58 [1 Cannabinoid RCT (30)]	Rank for change in pain scale	Cannabinoid last of 19 treatments	Rank in ≥30% improvement, 2nd last of 19 treatments		Little value (only one small trial included)
Stockings 2018	Chronic non-cancer pain	46 (4719)	≥30% pain reduction (13 RCTs)	RR 1.31 (1.11-1.51)†	29% vs 25.9%	Odds Ratio 3.47 (2.64-4.56)	All Adverse events in odds ratio and without event rates cannot convert to RR.
			SMD (30 RCTs)	- 0.14 (-0.20 to -0.08)			Many odds Adverse events provided

			Patient Global Impression of Change (9 RCTs)	RR 1.51 (1.29 – 1.76)†	18.9% vs 11.8%		Dizziness, nausea, cognitive disturbance, drowsiness, depressed mood, confusion, intoxication
Tsang 2016	Nabilone for chronic pain	7 (251)	No meta				Spinal RCT
Wong 2020	Chronic Non-Cancer Pain	43 (3444)	Pain scale 0-10 over placebo (33 RCTs, Any Pain)	-0.71 (-0.88 to -0.53)			Longer RCT*s*, found less effect.
			Pain scale 0-10 (25 RCTs, neuropathic Pain)	-0.74 (-0.94 to -0.54)			Similar between route (inhaled vs oral, etc.)
			Pain scale 0-10 (8 RCTs, Non-neuropathic Pain)	-0.60 (-0.97 to -0.24)			Similar between medical cannabinoids and non.
Whiting 2015	Chronic pain	28 (2454)	≥30% pain reduction (8 RCTs)	RR 1.23 (0.98 – 1.56)†	37% vs 31%	Odds Ratio 2.94 (2.18 to 3.96)	No withdrawal AE event rates, could not convert
			Pain scale 0-10 (6 RCTs)	-0.46 (-0.11 to -0.80)			Total AE 1.30 (1.21 – 1.39), 81% vs 62%

Aviram 2017 – Other Adverse Events: CNS effects (SMD 2.8, 95% CI 2.2, 3.7); GI (SMD 1.9, 95% CI 1.4, 2.4); psychological (SMD 3.1, 95% CI 1.8, 5.3); Visual (SMD 3.1, 95% CI 2.0, 4.9); Hearing (SMD 3.3, 95% CI 1.6, 6.7)

† Note : Any Odds Ratio for treatment benefit converted to relative risk (https://clincalc.com/Stats/ConvertOR.aspx)

Limitations

The RCTs reviewed have multiple concerns including unblinding, enrolling patients with a history of cannabis use, small size, short duration, selective reporting risk, etc. A couple studies found that longer (Allan 2018A and Wong 2020) and larger studies (Allan 2018A) had less effect. Systematic reviews pooled various pain types, including multiple pain types within the neuropathic groups (in Mücke 2018 neuropathic pain in RCTs yielded 5 for Multiple Sclerosis, 3 of diabetic neuropathy, 1 brachial plexus injury, 1 spinal cord injury, 1 chemotherapy induced neuropathy, 1 HIV neuropathy, and 4 mixed neuropathy groups).

Context

Among individuals reporting medical cannabis use, chronic pain is cited 58-84% of the time as the reason for use (Park 2017). Our previous SRs associated with this chronic pain guideline focused on interventions for osteoarthritis, low back pain, and neuropathic pain (specifically diabetic neuropathy, post-herpetic neuralgia, and trigeminal neuralgia). Cannabinoids were not reviewed in detail in those SRs for reasons listed in the review. This updated review finds little evidence to modify recommendations from the 2018 "Simplified guideline for prescribing medical cannabinoids in primary care (Allan 2018B)."

So why might there be conflicting information in different sources around cannabinoids for chronic pain? The use of lower level, observational evidence presents a challenge. Some publications report cannabinoids to be highly effective. For example, surveys of medical cannabis users find greater than or equal to 70% feel it is working moderately well or better for their symptoms (Park 2017). This lower level, cross-sectional research is asking regular established cannabinoid users, if it is helping with their symptoms. It is flawed by design and likely exaggerates effectiveness.

Cannabinoids are therapeutics and their utility in the care of patients should be assessed using the same standard as all other therapeutics, through RCTs. Still, some conflicting information persists, creating confusion. Here are two examples from our review: from two descriptive SRs (lacking meta-analysis), cannabinoids are reported as working and not working for spinal pain. When summarizing the same study, Tsang and Giudice (2016) reported "small but significant reductions in pain" while Fitzcharles and colleagues (2016) reported "insufficient evidence for recommendation." While there are multiple differences in the SRs, Tsang and Giudice report only the statistically significant results (which was "improved pain currently") while Fitzcharles reported five pain/quality of life outcomes (four of five not statistically different). The selective reporting by Tsang and Giudice presents a different picture from full reporting. In Stockings (2018), the meta-analytic result for a greater than or equal to 30% improvement in chronic, non-cancer pain is presented as an odds ratio of 1.46 (95% CI 1.16, 1.84). This seems to imply that 46% more patients received a meaningful improvement in pain over placebo, however, odds ratios can exaggerate the effects when events are more common. When corrected to relative risk (https://clincalc.com/Stats/ConvertOR.aspx) it is found to be 1.30 or a 30% increase in those attaining meaningful improvement, which is similar to other studies.

We continue to support the recommendations from the 2018 "Simplified guideline for prescribing medical cannabinoids in primary care (Allan 2018B)." There remains insufficient evidence to recommend medical cannabinoids for osteoarthritis or low back pain.

From the 2018 guideline (Allan 2018B):

Neuropathic pain: We recommend against medical cannabinoids as first- or second-line therapy in neuropathic pain owing to limited benefits and high risk of harms (Strong Recommendation). Clinicians could consider medical cannabinoids for refractory neuropathic pain, with the following considerations (Weak Recommendation):

1. A discussion has taken place with patients regarding the benefits and risks of medical cannabinoids for pain.
2. Patients have had a reasonable therapeutic trial of greater than or equal to 3 prescribed analgesics and have persistent problematic pain despite optimized analgesic therapy.
3. Medical cannabinoids are adjuncts to other prescribed analgesics.

Palliative (end-of-life) cancer pain: We recommend against use of medical cannabinoids as first- or second-line therapy for palliative cancer pain owing to limited benefits and high risk of harms (Strong Recommendation). Clinicians could consider medical cannabinoids for refractory pain in palliative cancer patients, with the following considerations (Weak Recommendation):

1. A discussion has taken place with patients regarding the risks and benefits of medical cannabinoids for pain.
2. Patients have had a reasonable therapeutic trial of ≥ 2 prescribed analgesics and have persistent problematic pain despite optimized analgesic therapy.
3. Medical cannabinoids are adjuncts to other prescribed analgesics

Suggested Recommendations

We suggest the harms of cannabinoids likely outweigh the benefits and should be avoided for most patients with osteoarthritis and chronic low back pain (weak recommendation, very low quality evidence).

We suggest that cannabinoids could be discussed with patients with neuropathic pain when interventions with clear evidence of benefit have already been considered (weak recommendation, very low quality evidence).

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Psychological Strategies and Chronic Pain Management

Clinical Question

In adults with chronic pain (specifically, low back pain with or without radiculopathy, neuropathic pain, or osteoarthritis) do psychological interventions such as cognitive-behavioural therapy, behavioural therapy, acceptance and commitment therapy, mindfulness, or meditation improve pain outcomes compared to wait list, usual care, or no treatment?

Bottom Line

Psychological interventions lead to clinically significant reductions in chronic pain for some patients. Higher quality evidence suggests cognitive behavioural therapy and mindfulness-based stress reduction provide clinically meaningful improvement in pain for patients with chronic low back pain (around 30-60% at 18-52 weeks) and patients with neuropathic pain (approximately 60% at 12 weeks) compared to control (around 20-30%). For osteoarthritis pain, one small trial suggests internet-based pain coping skills training (based on CBT principles) provides pain improvement for 26% of patients (versus 9% with control) at 8 weeks, however these results were no longer significant at 24 and 52 weeks. The specific intervention chosen should likely be guided by patient preference and accessibility. Most interventions involve approximately eight weekly sessions.

Evidence and Limitations

See the PRISMA diagrams for the systematic reviews and randomized controlled trials in Figures 21 and 22 respectively.

Chronic low back pain

Two SRs, one umbrella review (UR), and three RCTs examining various psychological interventions for chronic low back pain were included (Table 2).

Mindfulness and meditation

Mindfulness-based stress reduction (MBSR) and meditation cognitive therapy (MCT) were evaluated in one SR of seven RCTs and 864 patients (Anheyer 2017). A meta-analysis found that MBSR and MCT resulted in statistically different pain intensity scores at 8-12 weeks compared to usual care or wait list (4 RCTs; SMD -0.48, 95% CI -0.82, -0.14).

One RCT with 342 patients found significantly more patients receiving MBSR (48.5%) achieved a clinically meaningful (≥30%) reduction in pain-bothersomeness score (rated 0-10) compared to those receiving usual care (31%) at 52 weeks (RR 1.56, 95% CI 1.14, 2.14) (Cherkin 2016). Similarly, a

statistical difference was seen in those reporting “much better” or “completely gone” pain on a global improvement scale (30% vs. 18%, RR 1.67, 95% CI 1.03, 2.71) at 52 weeks. No statistical difference was found at a 2-year follow up (Cherkin 2017).

Cognitive behavioural therapy

CBT alone was examined in one SR (Skelly 2020) and one UR (Chou 2017) which included three RCTs and one SR (5 RCTs) with 1050 and 239 patients respectively. Statistically lower pain scores were seen with CBT (see Table 5) for up to 34 months compared to wait list, usual care, or attention controls. Within the SR, one RCT with 701 patients found that 59% of patients considered themselves recovered after 12 months with CBT compared to 31% with control ($p<0.0001$) (Lamb 2010). Another RCT with 156 patients found that statistically more patients receiving CBT (49%) had a clinically relevant change in pain compared to control (26%) (Siemonsma 2013).

An RCT with 342 patients found more patients receiving CBT reported “much better” or “completely gone” improvement on a global impression of pain scale at 52 weeks (31.9% vs. 18%, RR 1.78, 95% CI 1.11, 2.85) (Cherkin 2016). A ≥30% reduction in pain-bothersomeness was not found to be statistically different between CBT and control at either 52 weeks or 2 years (Cherkin 2016 and Cherkin 2017).

Table 5. Systematic reviews of psychological interventions for chronic low back pain

Author year	Intervention	Control	Included studies	Patients enrolled	Mean age	Baseline	Duration	Outcome	Result
Anheyer 2017 (SR)	MBSR, MCT (8 weekly sessions, 1.5-2.5 hours; one trial included an optional 6-hour retreat)	UC/WL	4	454	40 to 78 years	NR	8-12 weeks	Pain improvement	SMD -0.48, 95% CI -0.82 to -0.14
			2	377	49 to 52 years		4.5-6.5 months	Pain improvement	SMD −0.45, 95% CI −3.83 to 2.93
Chou 2017 (UR, based on Henschke 2010)	CBT (when reported, 8-30 sessions, 1-2 hr, over 4-10 weeks)	WL	5	239	NR	NR	4-10 weeks	Pain improvement	SMD -0.60, 95% CI -0.97 to -0.22
Skelley 2020 (SR)	CBT (when reported, 8 group sessions over 6 to 8 weeks)	UC/AC	3	1050	47 to 54 years	NR	6-10.5 months	Pain improvement (change on 0-10 VAS)	MD -0.71 (95% CI -0.97 to -0.46)
							12-34 months	Pain improvement (change on 0-10 VAS)	MD -0.55 (95% CI -0.92 to -0.23)
	MBSR (8 weekly group sessions, 1.5-2.5 hours)	UC/ education	3 fair quality/5 total	549 (3 trials)/629 (5 trials)	49 to 78 years	NR	4-4.5 months	Pain, function scores	No difference
Cherkin 2016 & 2017 (RCTs)	MBSR (8 weekly group sessions, 2 hours; optional 6-hour retreat; home resources provided)	UC	-	342	49.3 years	Pain bothersomeness rating (0-10): 6.1 (MBSR) vs 6.0 (control)	52 weeks	≥30% reduction in pain bothersomeness Patient global impression of change	48.5% (MBSR) vs 31.0% (UC) RR 1.56, 95% CI 1.14 – 2.14

								(pain much better/completely gone)	30.0% (MBSR) vs 18.0% (UC), RR 1.67, 95% CI 1.03 – 2.71
							2 years	≥30% reduction in pain bothersomeness	41.2% (MBSR) versus 31.1% (UC) RR 1.32, 95% CI 0.95 – 1.85
	CBT (8 weekly group sessions, 2 hours; home resources provided)	UC	-	342	49 years	Pain bothersomeness rating (0-10): 6.0 (CBT and control)	52 weeks	≥30% reduction in pain bothersomeness Patient global impression of change (pain much better/completely gone)	39.6% (CBT) vs. 31.0% (UC), RR 1.28, 95% CI 0.91 – 1.79 31.9% (CBT) vs 18.0% (UC), RR 1.78, 95% CI 1.11 – 2.85
							2 years	≥30% reduction in pain bothersomeness	39.6% (CBT) versus 31.1% (UC) RR 1.27, 95% CI 0.90 – 1.79

Lamb 2010 and 2012 (RCTs)	CBT (6 group sessions, 1.5 hours)	UC/ education	-	701	53 to 54 years	Modified Von Korff scale (0-100): 59 (CBT and control)	12 months	Patients who considered themselves recovered	59% (CBT) vs 31% (control), p<0.0001
Siemonsma 2013 (RCT)	CBT (10-14 weekly individual sessions, 1 hour)	WL	-	156	45 to 47 years	VAS (1-100): 55.7 (CBT) vs 55.8 (control)	18 weeks	Patients with clinically relevant change (decrease of 18-24 mm on 100 mm VAS)	49% (CBT) vs 26% (control), OR 2.77 (95% CI 1.28 to 6.01)

Author, year	Intervention	Control	Included studies	Patients enrolled	Mean age	Baseline	Duration	Outcome	Result
Skelley 2020 (SR)	MI (1 initial session, 45-60 minutes; 5 additional sessions, 10-15 minutes) (Gilbert 2018)	NT	1	155	61 years (MI), 65 years (control)	WOMAC pain score (0-20): 5.9 (MI) vs. 5.5 (control)	3 months	WOMAC pain score (0-20)	5.2 (95% CI 4.6 to 5.8) versus 6.1 (95% CI 5.6 to 6.7) (control); MD 1.0 (95% CI 0.2 to 1.8)
							6-24 months	WOMAC pain score (0-20)	No difference
	iCBT (details not reported) (O'Moore 2018)	UC	1	67	63 years (iCBT), 60 years (control)	WOMAC pain (0-20): 9.9 (iCBT) vs. 9.4 (control)	3 months	WOMAC pain score (0-20)	7.4 versus 9.8 (control); MD −2.34 (95% CI −4.2 to −0.5), p<0.05
	Group CBT (18 group sessions, 1 hour, over 24 weeks, with homework) (Helminen 2015)	UC	1	111	65 years (CBT), 63 years (control)	WOMAC pain (0-100): 57.6 (CBT) vs. 56.4 (control)	1.5-10.5 months	WOMAC pain score (0-100)	35.6 versus 39.5(control); MD −3.9 (95% CI −11.8 to 4.0)
Bennell 2018 (RCT)	iPCST (8 modules, 35-45 minutes, completed 1	Education	-	135	61 years	WOMAC pain (0-20): 8.7 (iPCST) vs	8 weeks	Patients reporting improvement in pain	17/65 (26%) iPCST + EE vs. 6/70 (9%) control; RR 3.1,

	per week) + education					8.3 (control)			95% CI 1.28 – 7.26
	iPCST (8 modules, 35-45 minutes, completed 1 per week) + education + PT	Education + PT	-	128	61 years		24 weeks	Patients reporting improvement in pain	34/64 (53%) iPCST + EE vs. 38/64 (59%) control; NSS
		Education + PT		120	61 years		52 weeks	Patients reporting improvement in pain	26/61 (43%) iPCST + EE vs. 33/59 (56%) control; NSS

Results statistically different unless indicated. AC: attention control; CBT: cognitive behavioural therapy; CI: confidence interval; EE: education and exercise; iCBT: internet-based cognitive behavioural therapy; iPCST: internet-based pain coping skills training; MBSR: mindfulness-based stress reduction; MCT: meditation cognitive therapy; MI: motivational interviewing; MD: mean difference; MI: NR: not reported; NT: no treatment; PMR: progressive muscle relaxation; PT: physiotherapist-guided individualized exercise; RCT: randomized controlled trial; SMD: standard mean difference; SR: systematic review; UC: usual care; UR: umbrella review; VAS: visual analogue scale; WL: wait list.

Osteoarthritis

One SR and one RCT studying psychological interventions for the treatment of chronic osteoarthritis pain were included (Table 6). A meta-analysis of 2 RCTs (210 patients) found a statistically significant difference on a 20-point Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Score between groups that received motivational interviewing (MI) or internet-based CBT compared to usual care or no treatment at 3-month follow up (MD -0.60, 95% CI, 1.48, 0.08) (Skelly et al., 2020). A 0.6-point change on a 20-point WOMAC scale is likely not clinically significant (Newberry 2017).

An RCT with 144 patients with hip osteoarthritis found that when added to education and exercise, an internet-based pain coping skills training (iPCST) program, based on CBT, resulted in 26% of patients reporting improvement in pain at 8 weeks compared to 9% of controls (RR 3.1, 95% CI 1.28, 7.26). There was no significant difference after 24 and 52 weeks (Bennell 2018).

Table 6. Systematic reviews of psychological interventions for osteoarthritis

Author, year	**Intervention**	**Control**	**Included studies**	**Patients enrolled**	**Mean age**	**Baseline**	**Duration**	**Outcome**	**Result**
Skelley 2020 (SR)	MI (Gilbert 2018)	NT	1	155	61 years (MI), 65 years (control)	WOMAC pain score (0-20): 5.9 (MI) vs. 5.5 (control)	3 months	WOMAC pain score (0-20)	5.2 (95% CI 4.6 to 5.8) versus 6.1 (95% CI 5.6 to 6.7) (control); MD 1.0 (95% CI 0.2 to 1.8)
							6-24 months	WOMAC pain score (0-20)	No difference
	iCBT (O'Moore 2018)	UC	1	67	63 years (iCBT), 60 years (control)	WOMAC pain (0-20): 9.9 (iCBT) vs. 9.4 (control)	3 months	WOMAC pain score (0-20)	7.4 versus 9.8 (control); MD −2.34 (95% CI −4.2 to −0.5), p<0.05
	Group CBT (Helminen 2015)	UC	1	111	65 years (CBT), 63 years (control)	WOMAC pain (0-100): 57.6 (CBT) vs. 56.4 (control)	1.5-10.5 months	WOMAC pain score (0-100)	35.6 versus 39.5(control); MD −3.9 (95% CI −11.8 to 4.0)

Bennell 2018 (RCT)	iPCST + EE	EE	-	135	61 years	WOMAC pain (0-20): 8.7 (iPCST) vs 8.3 (control)	8 weeks	Patients reporting improvement in pain	17/65 (26%) iPCST + EE vs. 6/70 (9%) control; RR 3.1, 95% CI 1.28 – 7.26
	iPCST + EE + PT	EE + PT	-	128	61 years		24 weeks	Patients reporting improvement in pain	34/64 (53%) iPCST + EE vs. 38/64 (59%) control; NSS
		EE + PT		120	61 years		52 weeks	Patients reporting improvement in pain	26/61 (43%) iPCST + EE vs. 33/59 (56%) control; NSS

Results statistically different unless indicated. CBT: cognitive behavioural therapy; CI: confidence interval; iCBT: internet-based cognitive behavioural therapy; iPCST: internet-based pain coping skills training; MD: mean difference; MI: motivational interviewing; NSS: not statistically significant; NT: no treatment; PT: physiotherapist-guided individualized exercise; RCT: randomized controlled trial; RR: relative risk; SR: systematic review; UC: usual care; WOMAC: Western Ontario and McMaster Universities Pain Index; WPS: Walking Pain Scale.

Neuropathic pain

One SR and one RCT studied the benefits of psychological interventions in treating patients with chronic diabetic peripheral neuropathy (Table 7). A combination of psychological interventions, including lifestyle counselling, CBT, and MBSR, were examined at "short-term" (2-12 weeks) and "medium-term" (12-24 weeks) duration (Racaru 2020). At 2-12 weeks, a meta-analysis of four RCTs (212 patients) found a statistically significant benefit in pain severity (SMD -0.94, 95% CI -1.5, -0.37) with psychological interventions, compared to usual care or education. Similarly, pain severity was also improved with MBSR or CBT compared to usual care at 12-24 weeks (SMD -1.26, 95% CI -1.76, -0.77).

One RCT of 62 patients with diabetic neuropathy demonstrated a clinically important decrease of ≥1.0 in the Brief Pain Inventory (BPI) score in 63% of patients that underwent MBSR compared to 22% in a wait list control at 12-weeks (RR 2.2, 95% CI 1.0 to 4.6) (Nathan 2017).

Table 7. Systematic reviews of psychological interventions for neuropathic pain

Author, year	Intervention	Control	Included studies	Patients enrolled	Mean age	Baseline	Duration	Outcome	Result

Racaru 2020 (SR)	Mixed (lifestyle counselling, CBT, MBSR) (when reported, 8-12 group or individual weekly sessions, 1-2.5 hours; 1 trial had 1 additional 6-hour session)	UC, education	6	212	47 to 75 years	NR	2-12 weeks	Pain improvement	SMD -0.94, 95% CI -1.5 to -0.37
	Mixed (CBT, MBSR) (8-11 weekly sessions, group or individual, 1-2.5 hours; 1 trial had 1 additional 6-hour session)	UC	2	85	60 to 63 years	NR	12-24 weeks	Pain improvement	SMD -1.26, 95% CI -1.76 to -0.77
Nathan 2017 (RCT)	MBSR (8 weekly group sessions, 2.5 hours, with additional 6-hour session)	WL	-	62	60 years	Pain severity: 5.3 (MBSR) vs 4.9 (control)	12 weeks	Clinically important decrease in BPI	19/30 (63%) (MBSR) vs. 7/32 (22%) (control)

Results statistically different unless indicated. BPI: Brief Pain Inventory; CBT: cognitive behavioural therapy; CI: confidence interval; MBSR: mindfulness-based stress reduction; RCT: randomized controlled trial; SMD: standard mean difference; SR: systematic review; UC: usual care; WL: wait list.

Limitations

Due to the small number of trials in included SRs, publication bias was not assessed in funnel plots. In general, overall heterogeneity was high, with reviews including a multitude of psychological interventions, with varying frequencies and modifications in delivery. Further, a multitude of pain outcomes were utilized, resulting in reporting of standard SMDs, which have little to no clinical utility. Table 8 outlines the RCTs including responder outcome data. The authors could not find suitable

evidence for some of the interventions searched, such as acceptance commitment therapy, therefore only the above-mentioned psychological interventions were reviewed. Within the RCTs, blinding of participants was not attempted. Refer to Figures 23 and 24 for the Risk of Bias Summary and Graph, respectively.

Table 8. Randomized controlled trials that included responder outcome data

Condition	Study	Intervention	Outcome	Duration	Intervention event rate	Control event rate
Chronic low back pain	Cherkin 2016	MBSR	≥30% reduction in pain bothersomeness	52 weeks	48.5%	31.0%
		MBSR	Patient global impression of change	52 weeks	30.0%	18.0%
		CBT	≥30% reduction in pain bothersomeness	52 weeks	Not statistically different	
		CBT	Patient global impression of change	52 weeks	31.9%	18.0%
	Siemonsma 2013	CBT	Patients with clinically relevant change (decrease of 18-24 mm on 100 mm VAS)	18 weeks	49%	26%
	Lamb 2010, 2012	CBT	Patients who considered themselves recovered	52 weeks	59%	31%
Osteoarthritis	Bennell 2018	iPCST	Patients reporting improvement in pain	8 weeks	26%	9%
Neuropathic pain	Nathan 2017	MBSR	Clinically important decrease in BPI (≥1)	12 weeks	63%	22%

CBT: cognitive behavioural therapy; iPCST: internet-based pain coping skills training; MBSR: mindfulness-based stress reduction. Results statistically different unless indicated.

Context

In those studies that commented on adverse events, none were reported. Psychological services vary significantly in cost and accessibility and may require significant time and effort on the part of the patient. Multiple delivery models are available (e.g. online, in-person) and there is little evidence to recommend one over another, so patient preference should likely guide the specific therapy chosen. As all the studies in this review provided psychological interventions by a trained professional, primary care providers could consider taking additional training to provide this within their own practice or they could refer to another health care professional with this training.

Suggested Recommendation

We suggest cognitive behavioural therapy (CBT) or mindfulness-based stress reduction be offered to patients to help manage chronic pain, when access to services allow (weak recommendation, low quality evidence).

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Topical Treatments for the Management of Chronic Pain

Clinical Question

Are topical TCAs, nitrates, ketamine, muscle relaxants or combinations effective in osteoarthritis, chronic low back pain, or chronic neuropathic pain?

Bottom Line

Available evidence suggests no benefit from topical antidepressants, topical clonidine, topical ketamine or esketamine, and combined topical therapies. Evidence from two small RCTs in diabetic neuropathy (pain decrease ranging from 2.5 to 3.0 on a 0-10 VAS relative to placebo which decreased pain ranging from 0.5 to 0.6) and one small RCT in OA (pain decreasing by 0.6 on a 0-10 VAS relative to placebo which increased pain by 0.24) suggest using topical nitrates may improve pain scores.

Evidence and Limitations

Included therapies: TCAs (amitriptyline, doxepin), gabapentin, muscle relaxants (baclofen, cyclobenzaprine), clonidine, and ketamine. Nitrates were added based on the results of our literature search.

To be included, trials had to be randomized and controlled and had to include patients with one of the following conditions: osteoarthritis, chronic low back pain, or neuropathic pain (trigeminal neuralgia, diabetic neuropathy, post-herpetic neuralgia, or mixed neuropathic pain). Trials specifically looking at different pain conditions were excluded. Withdrawal enrichment trials were also excluded.

Literature search focusing on SRs yielded 313 articles, 18 of them being included to extract RCTs. A grey literature search yielded 27 more articles. In total, 17 RCTs were included (See Figure 25 for PRISMA flow chart).

Topical TCAs

Amitriptyline

One RCT (35 patients, mean age 57) compared 5% topical amitriptyline, 5% topical lidocaine and a placebo, all twice a day in participants suffering from postsurgical neuropathic pain, postherpetic neuralgia or diabetic neuropathy in a crossover double-blind RCT testing each treatment for one week, with a one-week washout period between each treatment (Ho 2008). Topical amitriptyline resulted in a non-statistically significant increase in pain of 0.9 on a 0-100 VAS, with lidocaine (mean reduction of 5.7) and placebo (mean reduction of 7.6) both being statistically superior to amitriptyline. A similar proportion of participants in each group rated their satisfaction as ¨good¨ or ¨excellent¨.

One RCT (102 patients, mean age 56) compared 2% topical amitriptyline and 0.75% topical capsaicin, both three times a day, in participants suffering from diabetic neuropathy in a 12-week double-blind RCT (Kiani 2015A) . Amitriptyline and capsaicin resulted in a similar improvement on a 0-10 VAS of around 3.5 (exact numbers not given). Amitriptyline and capsaicin both lead to a ≥ 50% pain improvement in a similar proportion of participants (43.1% and 37.3% respectively; p=0.545). Adverse

events were more common with capsaicin than amitriptyline (56.9% and 25.5% respectively), with amitriptyline causing mainly dryness (8.8%) and itching (4.4%).

One RCT (20 patients, mean age 59) compared 1% topical amitriptyline, 0.5% topical ketamine, combined amitriptyline and ketamine, and a placebo applied 4 times a day for 2 days in a cross-over double-blind RCT in participants with diabetic neuropathy, postherpetic neuralgia, or postsurgical/posttraumatic neuropathic pain (Lynch 2003). There was no difference in pain on a VAS between groups.

A similar RCT (92 patients, median age 52) compared 2% topical amitriptyline, 1% topical ketamine, combined topical amitriptyline and ketamine, and a placebo applied three times a day for 3 weeks in participants with diabetic neuropathy, postherpetic neuralgia, or postsurgical/posttraumatic neuropathic pain (Lynch 2005). No treatment was superior to placebo, with a 1.1-1.5 points reduction on a 0-10 pain VAS in all groups. There was no statistically significant difference in responder rates (≥ 30% or ≥ 50% pain reduction) between groups**.**

Doxepin

One RCT (82 patients, mean age 45-48) looked at the effect of topical 3.3% doxepin, topical 0.025% capsaicin, a combination of topical 3.3% doxepin and 0.025% capsaicin, and a placebo three times a day for 6 weeks on chronic neuropathic pain (McCleane 2000B). All treatment groups showed a significant and similar decrease of about 1 point on a 0-10 VAS from baseline pain to pain at 4 weeks while there was no significant change in the placebo group (numbers not given for placebo and no statistical comparison between treatments and placebo).

A second RCT (30 patients, mean age 49) looked at the effect of topical 5% doxepin and a placebo twice a day for 6 weeks on chronic neuropathic pain (McCleane 2000C). The doxepin group showed a significant decrease in mean pain over the last 10 days of the study compared to placebo (-1.87 points on a 0-10 VAS; $p<0.05$).

This last trial was the only trial that showed a positive outcome for a TCA in 30 out of 361 patients in the TCA RCTs.

Topical clonidine

One RCT (179 patients, mean age 59) looked at the effect of topical 0.1% clonidine gel and a placebo applied three times a day for 12 weeks in diabetic neuropathy (Campbell 2012). There was no significant difference in the clonidine group compared to placebo on a 0-10 Numeric Pain Rating Scale (NPRS) at 12 weeks.

A second RCT (139 patients, mean age 57) investigated topical clonidine 0.1% vs. 0.75% topical capsaicin three times a day for 12 weeks in diabetic neuropathy (Kiani 2015B). There was no significant difference between the clonidine and capsaicin groups at 12 weeks.

Topical ketamine

In two trials described earlier including 112 participants comparing topical ketamine to topical amitriptyline, a combination of both, or placebo, there was no statistically significant difference on a pain VAS or responder rates (Lynch 2003 and Lynch 2005).

One RCT (12 patients, mean age 72) compared 1% topical esketamine and placebo applied four times a day for 15 days in a cross-over double-blind RCT in participants suffering from postherpetic neuralgia (Barros 2012). Esketamine was not superior to placebo.

One RCT (17 patients, mean age 65) compared 5% topical ketamine and a placebo applied three times a day for a month in a double-blind RCT in participants suffering from diabetic neuropathy (Dworkin 2008A). Ketamine was not superior to placebo. (Mahoney 2012).

Topical nitrate

One RCT (43 patients, mean age 58-59) looked at 0.4 mg of glyceryl trinitrate spray (GTN) applied topically at bedtime to each leg in patients with diabetic neuropathy for 4 weeks, then crossed over to placebo for 4 weeks (or vice versa) (Agrawal 2007). There was a significant decrease in pain with topical GTN (ranging from 2.5 to 3.0) compared to placebo (ranging from 0.6-0.7) on a 0-10 VAS score after 4 weeks.

One RCT (40 patients, mean age 58-62) looked at 0.4 mg of GTN spray applied topically versus placebo (in addition to either oral sodium valproate or oral placebo) in a 4-arm study (Agrawal 2009). There was a significant decrease in pain (2.8) in the topical GTN/oral placebo compared to topical/oral placebo group (0.45).

One RCT looked at 30 mg isosorbide dinitrate topical spray for patients (22 patients, mean age 49) with diabetic neuropathy applied topically at bedtime to each foot for 4 weeks followed by a cross-over to placebo for 4 weeks (Yuen 2002). There was a significant decrease in pain (2) compared to placebo (no change) represented by a 0-10 VAS score in the treatment arm.

One RCT (167 patients, mean age 49) looked at 1.33% topical GTN cream with radiologically proven osteoarthritis of the hip, knee, shoulder, or hand who have failed oral anti-inflammatories (McCleane 2000A). Participants applied the cream to the most painful joint four times per day for 6 weeks. There was a significant pain decrease (0.59) in the GTN measured by a 0-10 VAS in the treatment arm relative to placebo (increase by 0.24).

Adverse events were similar between the 3 trials that reported them with no serious adverse events (Agrawal 2007, Agrawal 2009, and Yuen 2002). Headaches were reported in 5-9% of study participants receiving topical GTN and 2% receiving placebo. Palpitations or tachycardia were reported in ~5% of patients receiving GTN and none in the placebo group (Agrawal 2007). Minor faintness was reported in a single patient who also experienced palpitations and headache, and subsequently withdrew from the study (Agrawal 2007).

Topical Combination treatment

In two RCTs described earlier including 112 participants comparing combined topical ketamine and amitriptyline to topical ketamine, topical amitriptyline, or placebo, there was no statistically significant difference on a pain VAS or responder rates (Lynch 2003 and Lynch 2005).

One RCT (360 patients, mean age 53) compared a 4% amitriptyline and 2% ketamine combination, oral gabapentin, and an oral and topical placebo for 4 weeks in a double-blind RCT in participants suffering from postherpetic neuralgia (Dworkin2008B). Topical amitriptyline and ketamine combination were statistically superior to placebo on a 1-10 VAS with a change difference of 0.55 points (p=0.04). The difference does not seem to be clinically significant.

A similar RCT (226 patients, mean age 56) compared a 4% amitriptyline and 2% ketamine combination, and a placebo for 4 weeks in a double-blind RCT in participants with diabetic neuropathy (Brutcher 2019). There was no difference between groups on a 0-10 pain VAS.

One RCT (399 patients, median age 51) compared three different topical combinations to a placebo based on the pain type as classified by each patient's treating physician (ketamine, gabapentin, clonidine, and lidocaine for neuropathic pain; ketoprofen, baclofen, cyclobenzaprine, and lidocaine for nociceptive pain; ketamine, gabapentin, diclofenac, baclofen, cyclobenzaprine, and lidocaine for mixed pain) in a double-blind RCT for 1 month (Mahoney 2012). No treatment was shown superior to placebo.

The Risk of Bias Summary and Graph can be found in Figures 26 and 27 respectively.

Context

Topical lidocaine and capsaicin are readily available in Canada and have been shown to be effective in multiple chronic pain conditions. Nitroglycerin spray is readily available in Canada and costs under $10 for two hundred 0.4mg doses. Topical TCAs, clonidine, and ketamine are not readily available in Canada but can be prepared by compounding pharmacies. Costs vary widely.

Suggested Recommendation

We suggest topical nitrate spray on the affected area has unclear evidence and could be discussed with patients when interventions with clear evidence of benefit have already been considered (weak recommendation, low quality evidence).

We suggest other topical treatments (ketamine, amitriptyline, doxepin and combination products) have evidence of no benefit, but could be discussed with patients when interventions with clear evidence of benefit have already been considered (weak recommendation, moderate quality evidence).

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Tricyclic Antidepressants and Chronic Pain Management

Clinical Question

How effective are tricyclic antidepressants in the treatment of osteoarthritis and chronic low back pain?

Bottom Line

Randomized trials identified by one high quality SR suggest TCAs provide a clinically meaningful reduction in pain for patients with chronic low back pain [Mean difference (MD) -11.17, 95% CI -21.35, -1.00], and for those with sciatica (MD -16.99, 95% CI -29.25, -4.72). It is unknown whether TCAs are effective in osteoarthritis.

Evidence and Limitations

One high-quality SR looked at the efficacy of antidepressants, including tricyclic antidepressants, in osteoarthritis and chronic low back pain (Ferreira 2021). This review included all RCTs, parallel or cross-over, comparing any antidepressant versus placebo in patients with neck pain, low back pain (with or without radicular symptoms), hip or knee osteoarthritis, or both, where a mean difference in on-treatment pain scores could be determined (see Figure 28 for PRISMA flow diagram).

The synthesis of this review required transforming all pain scales into a common pain scale that ranged from 0 to 100. The authors defined 10 points on the transformed scale as the minimum clinically important difference. All antidepressant classes were evaluated separately; however we will be focusing on reporting results for TCAs.

Chronic Low Back Pain (Non-radicular)

Eight RCTs evaluating TCAs (973 patients) were identified and meta-analyzed by the review (Figure 29). See Table 9 for a summary of study characteristics of studies on low back pain included in the SR. The authors primary analysis separated results out by duration of therapy, allowing individual studies to contribute to multiple time points to explore the effect over time. However, they did not aggregate all studies into one meta-analysis except in a post-hoc sensitivity analysis in which the RCT showing greatest benefit was removed for an exploration of heterogeneity. With removal of this RCT (212 patients; examining amitriptyline 5mg/day for neck pain) (Maarrawi 2018), the pooled analysis (332 patients) found statistically significant, homogeneous, but clinically unimportant pain relief (MD -5.37, 95% CI −9.93, −0.80).

Table 9: Study characteristics of studies on low back pain included in the systematic review.

Author Year	Condition	Sample	Duration	Intervention Control	Outcomes
Hameroff 1985	Chronic low back and/or neck pain (duration not reported)	60	6 weeks	1. Doxepin 300mg/day 2. Placebo	Visual Analogue Scale (0-100)
Jenkins 1976	Chronic low back pain (duration not reported)	44	4 weeks	1. Imipramine 75mg/day 2. Placebo	Visual Analogue Scale (0-10)
Schliessbach 2018	Chronic low back pain (≥3 months)	90	Single dose	1. Imipramine 75mg/day 2. Active Placebo (Tolterodine 1mg/day)	Numeric Pain Rating Scale (0-10)
Maarrawi 2018	Chronic Neck pain (≥3months)	332	8 weeks	1. Amitriptyline 5mg/day 2. Placebo	Visual Analogue Scale (0-10)
Atkinson 1998	Chronic low back pain (≥6 months)	78	8 weeks	1. Nortriptyline 100mg/day 2. Placebo	Descriptor Differential Scale (0-21)
Gould 2020	Chronic low back pain (≥6 months)	142	12 weeks	1. Desipramine 20-60mg/day 2. Active Placebo (Benztropine 0.125mg/day)	Descriptor Differential Scale (0-21)
Atkinson 2007	Chronic low back pain (≥6 months)	121	12 weeks	1. Desipramine 50-150ng/ml 2. Active placebo (Benztropine 0.5mg/day)	Descriptor Differential Scale (0-21)
Urquhart 2018	Chronic low back pain (≥3 months)	146	26 weeks	1. Amitriptyline 25mg/day 2. Active Placebo (Benztropine 1mg/day)	Visual Analogue Scale (0-100)

In order to obtain a pooled estimate of effect from all available trials we needed to perform our own meta-analysis. In doing so we excluded one RCT whose intervention was a single one-time dose of TCA, as we felt this was not consistent with the management of chronic back pain (Schliessbach 2018). Our meta-analysis found that TCAs significantly reduced pain with a mean difference of -11.17 (95% CI, -21.35, -1.00) in favour of TCAs (Figure 30). This difference is statistically significant and meets the definition of clinical significance used by the authors of this SR. The authors cite multiple references

supporting their 10-point threshold for clinical significance (Abdel 2016, Chou 2017, Ferreira 2013, and Machado 2017).

Meta-analysis of responder data (Table 10) from 5 RCTs included in this SR was also performed (Figures 32 & 33) (Atkinson 1998, Atkinson 2007, Gould 2020, and Urquhart 2018), and demonstrated significantly more TCA recipients, compared to placebo recipients, reporting clinically meaningful benefit. We performed this meta-analysis both with (RR 1.67, 95% CI 1.36, 2.06), and without (RR 1.31, 95% CI 1.02, 1.68) one RCT (Maarawi 2018; 212 patients; amitriptyline 5mg/day) (Maarrawi 2018), which demonstrated a larger benefit to TCAs than other studies, and which had a population (neck pain sufferers) which did not clearly represent back pain. We conservatively used the lower of these relative risks as our estimate of effect.

Table 10: Study characteristics of studies on low back pain with a responder analysis.

Author Year	Condition	Sample	Duration	Intervention Control	Responder Outcome
Maarrawi 2018	Chronic Neck pain (≥3months)	332	8 weeks	1. Amitriptyline 5mg/day 2. Placebo	Responders with 50% Improvement
Atkinson 1998	Chronic low back pain (≥6 months)	78	8 weeks	1. Nortriptyline 100mg/day 2. Placebo	At least some improvement or more on a Clinical Global Impression scale.
Gould 2020	Chronic low back pain (≥6 months)	142	12 weeks	1. Desipramine 20-60mg/day 2. Active Placebo (Benztropine 0.125mg/day)	Attaining 30% reduction on a Descriptor Differential Scale
Atkinson 2007	Chronic low back pain (≥6 months)	121	12 weeks	1. Desipramine 50-150ng/ml 2. Active placebo (Benztropine 0.5mg/day)	Attaining a 75% reduction on a Descriptor Differential Scale
Urquhart 2018	Chronic low back pain (≥3 months)	146	26 weeks	1. Amitriptyline 25mg/day 2. Active Placebo (Benztropine 1mg/day)	Proportion attaining a minimal clinically important difference (15/100)

Although not definitive, results also suggest that TCAs are less effective in durations less than 3 weeks (Figure 29).

Sciatica (radicular pain)

Three included RCTs (175 patients) explored TCAs to treat sciatica. See Table 11 for study characteristics. When broken up into different time periods, only the longer duration subgroups are statistically significant (Figure 33). When all three studies are combined using data from the longest follow up, the mean difference is -16.99 (95% CI, -29.25, -4.72), which is clinically and statistically significant (Figure 34).

Table 11: Study characteristics of studies on sciatica included in the systematic review.

Author Year	Condition	Sample	Duration	Intervention Control	Outcomes
Vanelderen 2015	Sciatica (duration not reported)	60	2 weeks	1. Amitriptyline 25mg/day 2. Placebo	Numeric Pain Rating Scale (0-10)
Pirbudak 2003	Acute Sciatica (< 3 months)	60	26 weeks	1. Amitriptyline 50mg/day plus epidural corticosteroid injections 2. Placebo plus epidural corticosteroid injections	Visual Analogue Scale (0-10)
Khoromi 2007	Chronic sciatica (≥3 months)	55	2 weeks	1. Nortriptyline 100mg/day 2. Placebo	Visual Analogue Scale (0-10)

Osteoarthritis

We were unable to find RCTs that compared TCAs and placebo in chronic osteoarthritis conditions and reported on pain outcomes.

Adverse Events

TCAs in the included trials did not find a statistically significant difference with any adverse events (22% vs 13% for placebo), serious adverse events (2.6% vs 0% for placebo) or withdrawal due to adverse events (11% versus 4.6% for placebo). However, the incidence rates for safety outcomes that

were reported suggest that adverse events need to be considered when prescribing TCAs for these chronic conditions.

Context

The current National Institute for Health and Care Excellence (NICE) guidelines advise against offering tricyclic antidepressants for the management of low back pain, with or without sciatica, but provide no specific rationale for this recommendation (Listed 2020).

The SR upon which our synthesis is based only examined TCAs within the three treatment duration subgroups. This resulted in lower power and failure to demonstrate statistical significance at any of these time points. As a result, they too, did not recommend TCAs for treatment of chronic low back pain.

Suggested Recommendation

We recommend treatments with evidence of benefit (like TCAs in chronic low back pain) be considered and discussed first as options (strong recommendation, moderate quality evidence).

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Weight Loss for Osteoarthritis

Clinical Question

Will diet-induced weight loss reduce osteoarthritic knee pain in overweight and obese adults?

Bottom Line

Observational data suggests that obesity may be a risk factor for developing osteoarthritis, however trials reporting diet-induced weight loss alone (e.g. 5% weight loss) demonstrate limited, likely clinically insignificant improvements in osteoarthritic pain (~5 points on 100-point pain scale) compared to control. Studies are limited by the small magnitude of weight loss.

Evidence and Limitations

The highest quality SR and meta-analysis included 4 RCTs of 676 patients with a BMI~35 (Chu 2018). The mean diet induced weight loss was 8% (8.5kg) versus 3% (2.7kg) in the control group. There was a statistical improvement in pain scales with diet-induced weight loss, with an effect size of 0.33. This effect size is equivalent to ~5 points on a 100-point scale (Christensen 2005), with a range from 2-9 out of 100. The minimal clinically detectable difference for this scale is 9-10 (Ehrich 2020, Bellamy 2015).

An additional SR and meta-analysis also looked at diet induced weight loss versus control in participants with a BMI~34 (Hall 2019). In this case, the change in pain scales from diet-induced weight loss alone was not statistically different from control (5 RCTs, 616 patients). However, diet-induced weight loss plus exercise resulted in statistical improvement in pain scales over control (3 RCTs, 264 patients), with an effect size of 0.37. The improvement on 100-point pain scale ranged from 2-11. However, an important limitation is that some relevant studies were excluded.

Context

A meta-analysis of 22 cohort studies found that patients with BMI >30 were twice as likely to have knee osteoarthritis (OR 2.66) (Silverwood 2015). One RCT, with a mean BMI ~35, reported that intensive diet and exercise interventions prevented development of knee pain at one year in a secondary analysis (White 2015). There are no published RCTs of more substantial forms of weight loss (i.e. bariatric surgery) and knee pain.

Guidelines recommend education and exercise programs with or without dietary weight management for knee osteoarthritis, citing insufficient evidence for dietary management alone (Bannuru 2019). Exercise results in 47% of osteoarthritis patients achieving a 30% reduction in pain compared to 21% in control (Ton 2020).

Observational data suggests surgically induced weight loss of ~15-35% resulted in ~75% of people experiencing some benefit in knee pain (Groen 2015). There are no published RCTs of more substantial forms of weight loss (i.e. bariatric surgery) and knee pain.

There is no one size fits all diet. If weight loss is desired, patients should choose a diet they can adhere to (Ting 2018).

Suggested Recommendation

We suggest that the goal of exercise is pain management, independent of weight loss (weak recommendation, low quality evidence).

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Figures

Figure 1: Modified AMSTAR – Quality Assessment of all Systematic Reviews

Topic	Author Year	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Were the methods used to combine the findings of studies appropriate?	Was the conflict of interest stated?	Was publication bias formally assessed?
Acute to Chronic Pain	Alper 2000	No	Yes	Yes	Yes	No	No	No
Acute to Chronic Pain	Bay 2018	Yes	Yes	Yes	Yes	No	Yes	No
Acute to Chronic Pain	Berube 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Acute to Chronic Pain	Chang 2020	Yes	Yes	Yes	Yes	Yes	Yes	No
Acute to Chronic Pain	Chaparro 2013	Yes	Yes	Yes	Yes	Yes	Yes	No
Acute to Chronic Pain	Chen 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Acute to Chronic Pain	Choi 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Acute to Chronic Pain	Crooks 1991	No	No	Yes	No	No	No	No
Acute to Chronic Pain	Dennis 2020	No	Yes	Yes	Yes	Yes	Yes	No
Acute to Chronic Pain	Han 2013	Yes	Yes	Yes	Yes	Yes	Yes	No
Acute to Chronic Pain	Huang 2020	Yes	Yes	Yes	Yes	Yes	Yes	No
Acute to Chronic Pain	Jackson 1997	No	No	Yes	No	No	No	No
Acute to Chronic Pain	Jessen 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Acute to Chronic Pain	Lancaster 1995	No	Yes	Yes	Yes	Yes	Yes	No
Acute to Chronic Pain	Martinez 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Acute to Chronic Pain	Rai 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Acute to Chronic Pain	Schmader 1989	No	No	No	Yes	No	No	No
Acute to Chronic Pain	Shiri 2018	No	Yes	Yes	Yes	No	Yes	Yes
Acute to Chronic Pain	Steffens 2016	Yes	Yes	Yes	Yes	Yes	Yes	No
Acute to Chronic Pain	Verret 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Acute to Chronic Pain	Wang 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Acute to Chronic Pain	Watson 2010	No	Yes	No	Yes	No	Yes	No
Acute to Chronic Pain	Whale 2019	No	Yes	Yes	Yes	No	Yes	No
Acute to Chronic Pain	Wong 2014	Yes	Yes	Yes	Yes	No	Yes	No
Acute to Chronic Pain	Wood 1996	No	No	No	No	Yes	No	No
Acute to Chronic Pain	Wylde 2018	No	Yes	Yes	Yes	No	Yes	No
Acute to Chronic Pain	Xing 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Assisting People to Exercise	Davergne 2019	No	Yes	Yes	Yes	Yes	Yes	No
Assisting People to Exercise	Oliveira 2016	Yes	Yes	Yes	Yes	Yes	No	No
Assisting People to Exercise	Nicolson 2017	Yes	Yes	Yes	Yes	No	Yes	No
Cannabinoids	Allan 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Cannabinoids	Andreae 2015	Yes	Yes	Yes	Yes	Yes	Yes	No
Cannabinoids	Aviram 2017	No	Yes	Yes	Yes	No	Yes	No
Cannabinoids	Fitzcharles 2016A	Yes	Yes	Yes	Yes	No	Yes	Yes
Cannabinoids	Fitzcharles 2016B	Yes	Yes	Yes	Yes	No	Yes	No
Cannabinoids	Johal 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cannabinoids	Meng 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cannabinoids	Mucke 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cannabinoids	Petzke 2016	Yes	Yes	Yes	Yes	Yes	No	Yes
Cannabinoids	Rabgay 2020	Yes	Yes	Yes	Yes	Yes	Yes	No
Cannabinoids	Snedecor 2014	Yes	Yes	Yes	No	Yes	Yes	No
Cannabinoids	Stockings 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cannabinoids	Tsang 2016	No	Yes	Yes	No	No	No	No
Cannabinoids	Wong 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cannabinoids	Whiting 2015	Yes	Yes	Yes	Yes	Yes	Yes	No

Drug Combinations	Chaparro 2012	Yes	Yes	Yes	Yes	Yes	Yes	No
Drug Combinations	Finnerup 2010	No	Yes	Yes	No	No	Yes	No
Drug Combinations	Finnerup 2015	Yes	Yes	Yes	Yes	No	Yes	Yes
Drug Combinations	Khadem 2013	No	Yes	Yes	No	No	Yes	No
Drug Combinations	Liampas 2020	No	No	No	Yes	No	Yes	No
Drug Combinations	Mathieson 2019	Yes	Yes	Yes	Yes	No	Yes	No
Drug Combinations	Moisset 2020	No	Yes	Yes	Yes	No	Yes	No
Drug Combinations	Rudroju 2013	Yes	Yes	Yes	No	No	Yes	No
Drug Combinations	Selph 2011	Yes	Yes	Yes	Yes	No	Yes	No
Drug Combinations	Song 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Drug Combinations	Wiffen 2016	Did not identify any randomized controlled trials, therefore cannot be assessed.						

Effective Exercise	Bystrom 2013	Yes	No	Yes	Yes	No	Yes	No
Effective Exercise	Chang 2016	No	No	No	Yes	N/A	No	No
Effective Exercise	Chou 2016	Yes	Yes	Yes	Yes	N/A	Yes	No
Effective Exercise	Coudeyre 2016	Yes	No	Yes	Yes	No	Yes	No
Effective Exercise	Dong 2018	Yes	Yes	Yes	Yes	No	Yes	No
Effective Exercise	Goh 2019	No	Yes	Yes	Yes	Yes	Yes	No
Effective Exercise	Kamioka 2016	Yes	Yes	Yes	Yes	N/A	Yes	No
Effective Exercise	Kong 2016	Yes	No	No	No	No	Yes	No
Effective Exercise	Lauche 2019	Yes	Yes	Yes	Yes	No	Yes	No
Effective Exercise	Lawford 2016	Yes	Yes	Yes	Yes	N/A	Yes	No
Effective Exercise	Lee 2007	Yes	Yes	Yes	Yes	N/A	No	No
Effective Exercise	Lin 2016	Yes	No	Yes	Yes	N/A	No	No
Effective Exercise	Macedo 2009	Yes	Yes	Yes	Yes	Yes	No	No

Effective Exercise	Niederer 2020	Yes	Yes	Yes	Yes	No	Yes	Yes
Effective Exercise	Owen 2019	Yes	Yes	No	Yes	Yes	Yes	Yes
Effective Exercise	Saragiotto 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Effective Exercise	Smith 2014	Yes	Yes	Yes	Yes	Yes	Yes	No
Effective Exercise	Uthma 2013	Yes	Yes	No	No	Yes	Yes	No
Effective Exercise	Van Middlekoop 2011	Yes	Yes	Yes	Yes	N/A	Yes	No
Effective Exercise	Wieland 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Effective Exercise	Yamato 2016	Yes	Yes	Yes	Yes	Yes	Yes	No
Effective Exercise	Zhang 2019	Yes	Yes	Yes	Yes	Yes	Yes	No
Effective Exercise	Zhu 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Psychological Supports	Anheyer 2017	Yes	Yes	Yes	Yes	Yes	Yes	No
Psychological Supports	Chou 2017	Yes	Yes	Yes	Yes	Yes	Yes	No

Psychological Supports	Pitsillides 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Psychological Supports	Racaru 2020	Yes	Yes	Yes	Yes	Yes	Yes	No
Psychological Supports	Skelley 2020	Yes	Yes	Yes	Yes	Yes	Yes	No
TCAs	Ferreira 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Weight Loss and OA	Chu 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Weight Loss and OA	Hall 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Figure 2: Preventing Chronic Pain in Primary Care: PRISMA

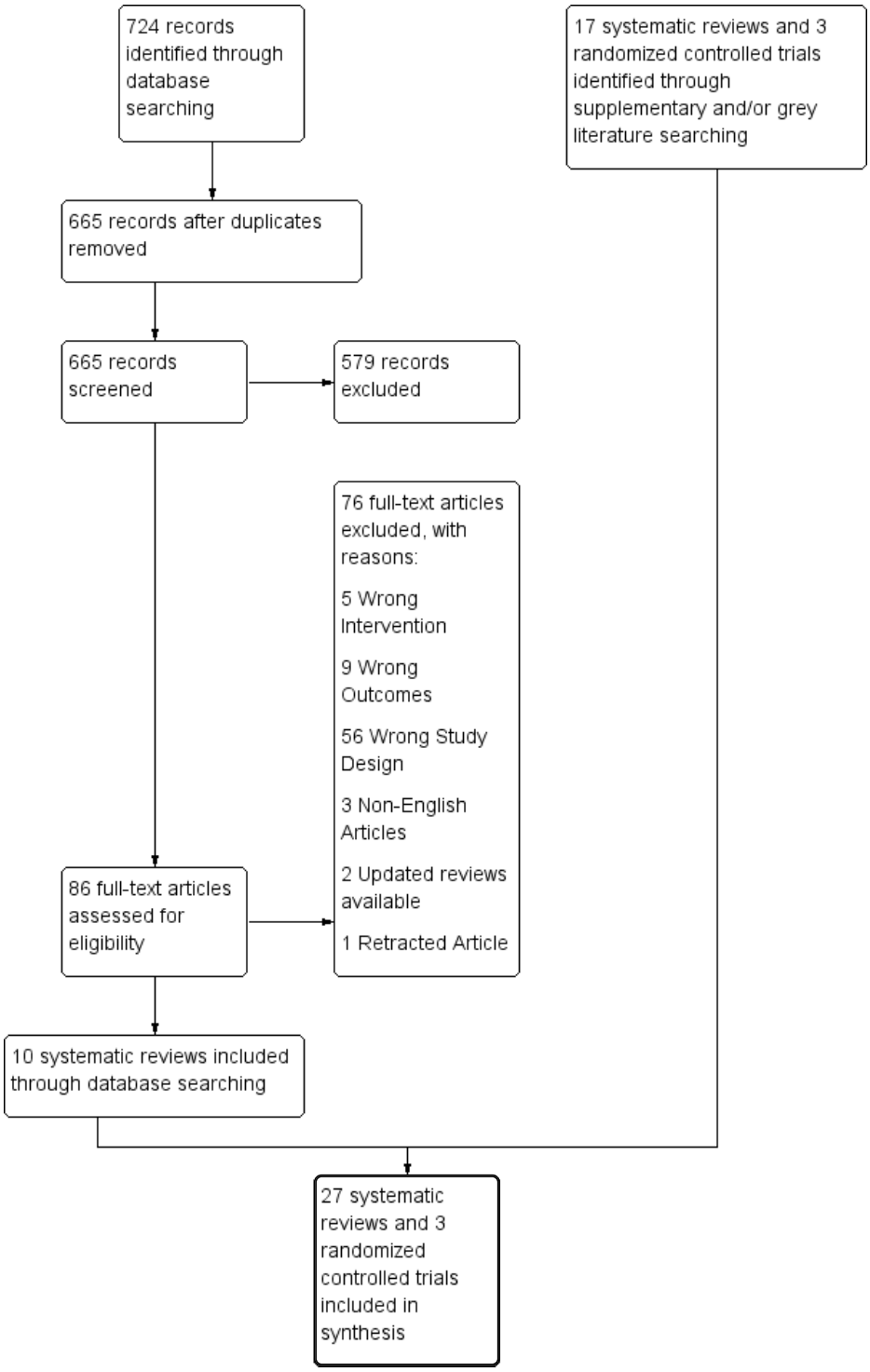


Figure 3: Preventing Chronic Pain in Primary Care: Risk of Bias Summary

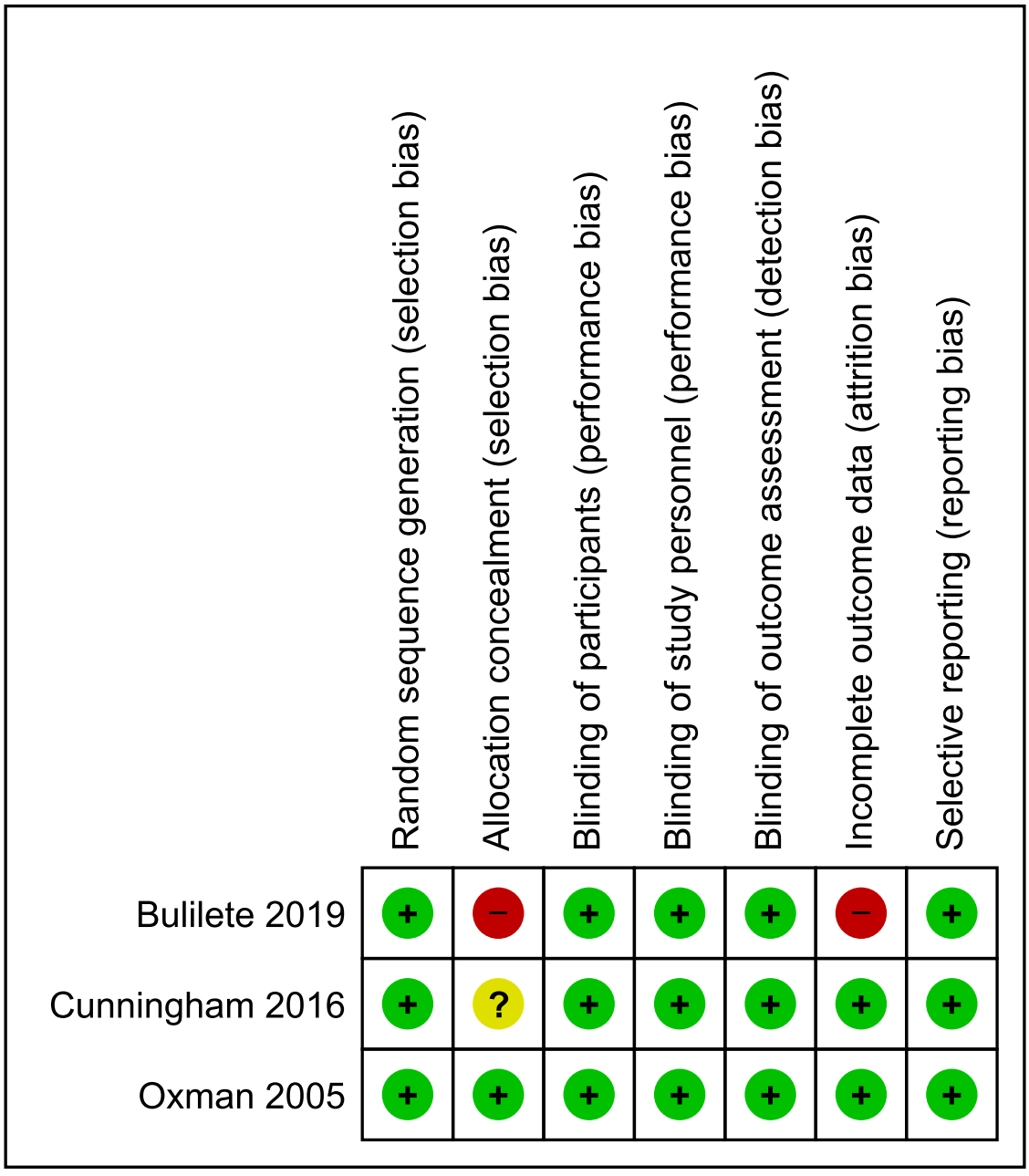


Figure 4: Preventing Chronic Pain in Primary Care: Risk of Bias Graph

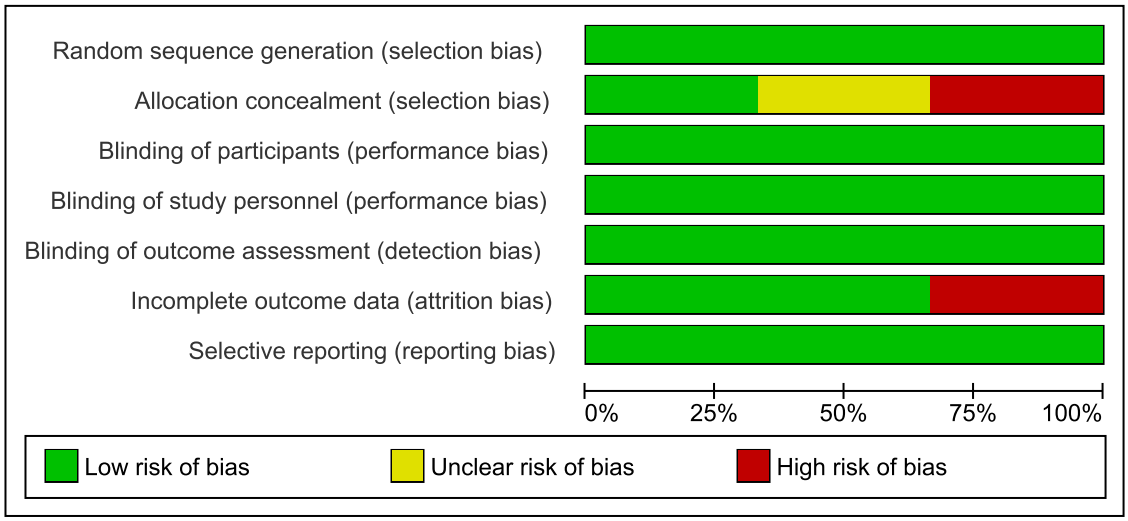


Figure 5: Encouraging Exercise with Chronic Pain – PRISMA (Systematic Reviews)

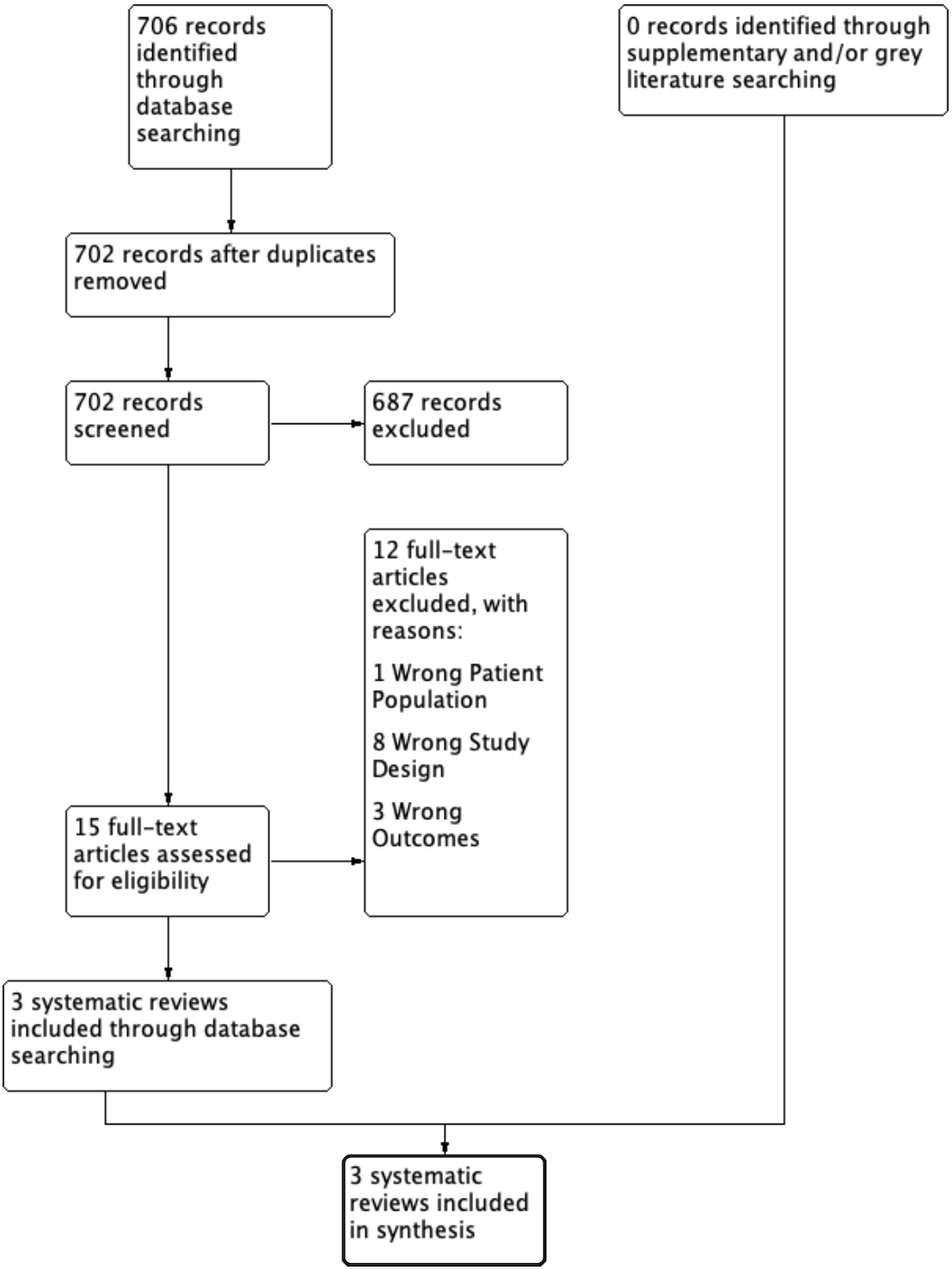


Figure 6: Encouraging Exercise with Chronic Pain – PRISMA (Randomised Controlled Trials)

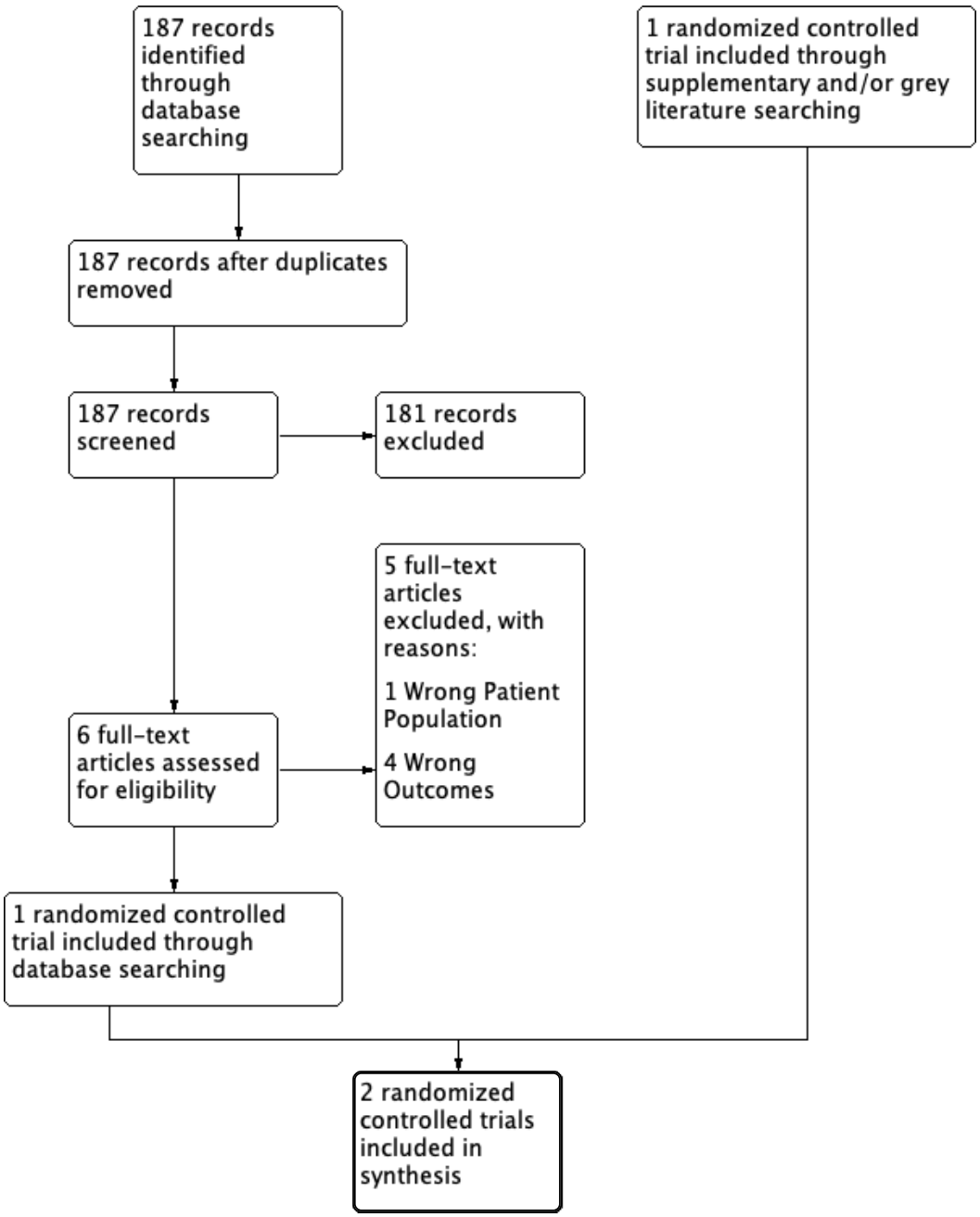


Figure 7: Encouraging Exercise with Chronic Pain – Risk of Bias Summary

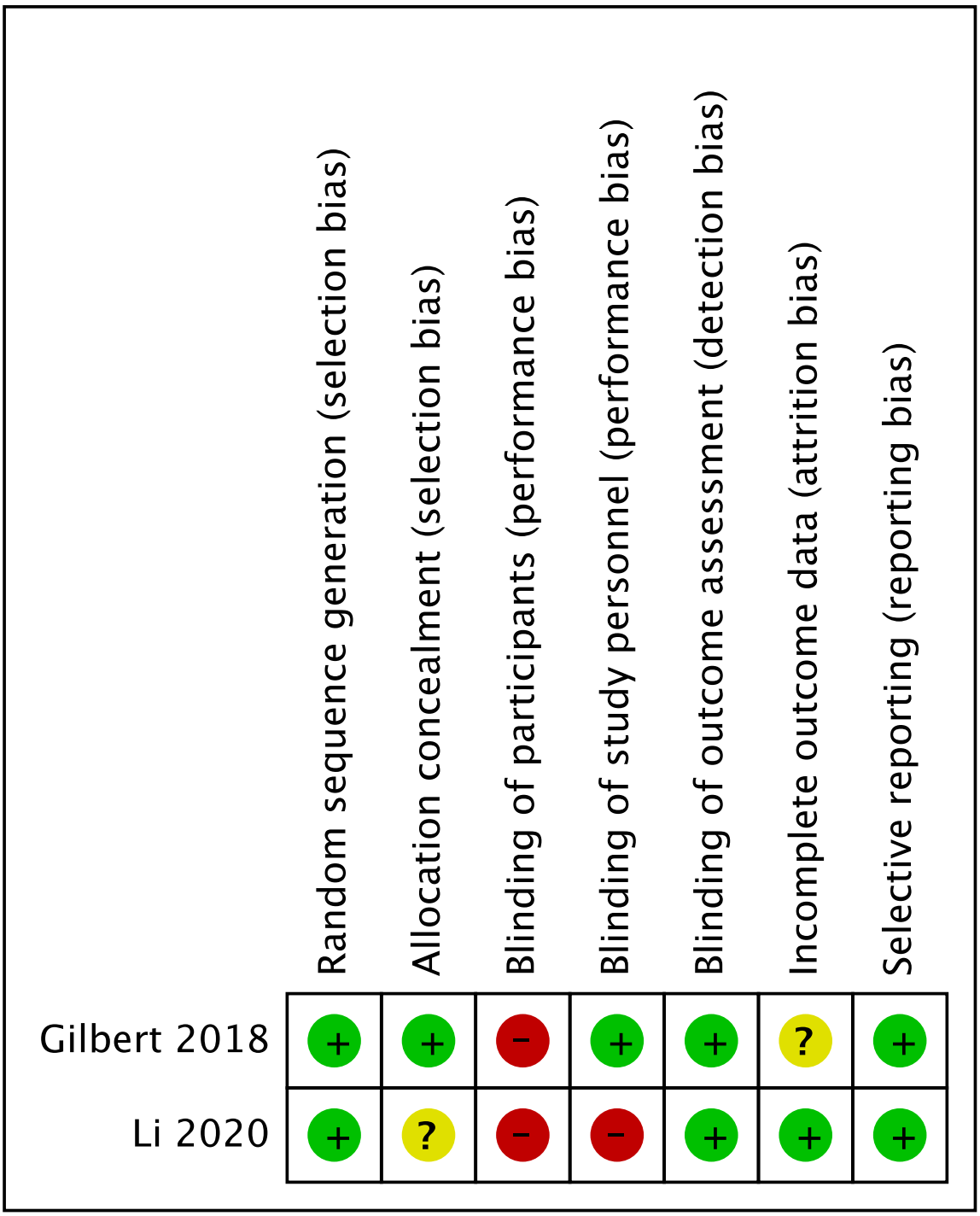


Figure 8: Encouraging Exercise with Chronic Pain – Risk of Bias Graph

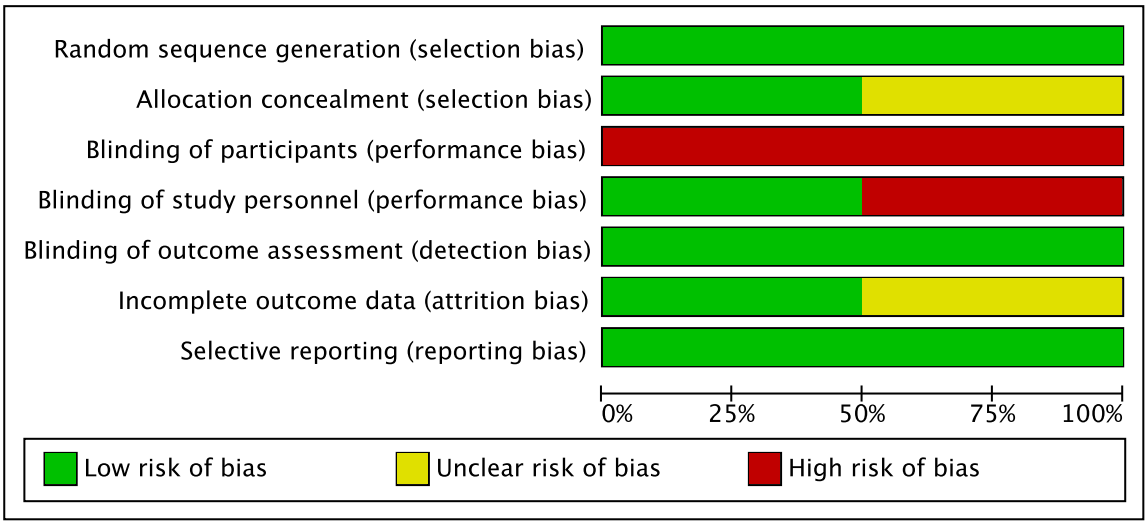


Figure 9: Effective Exercises for Chronic Pain – PRISMA

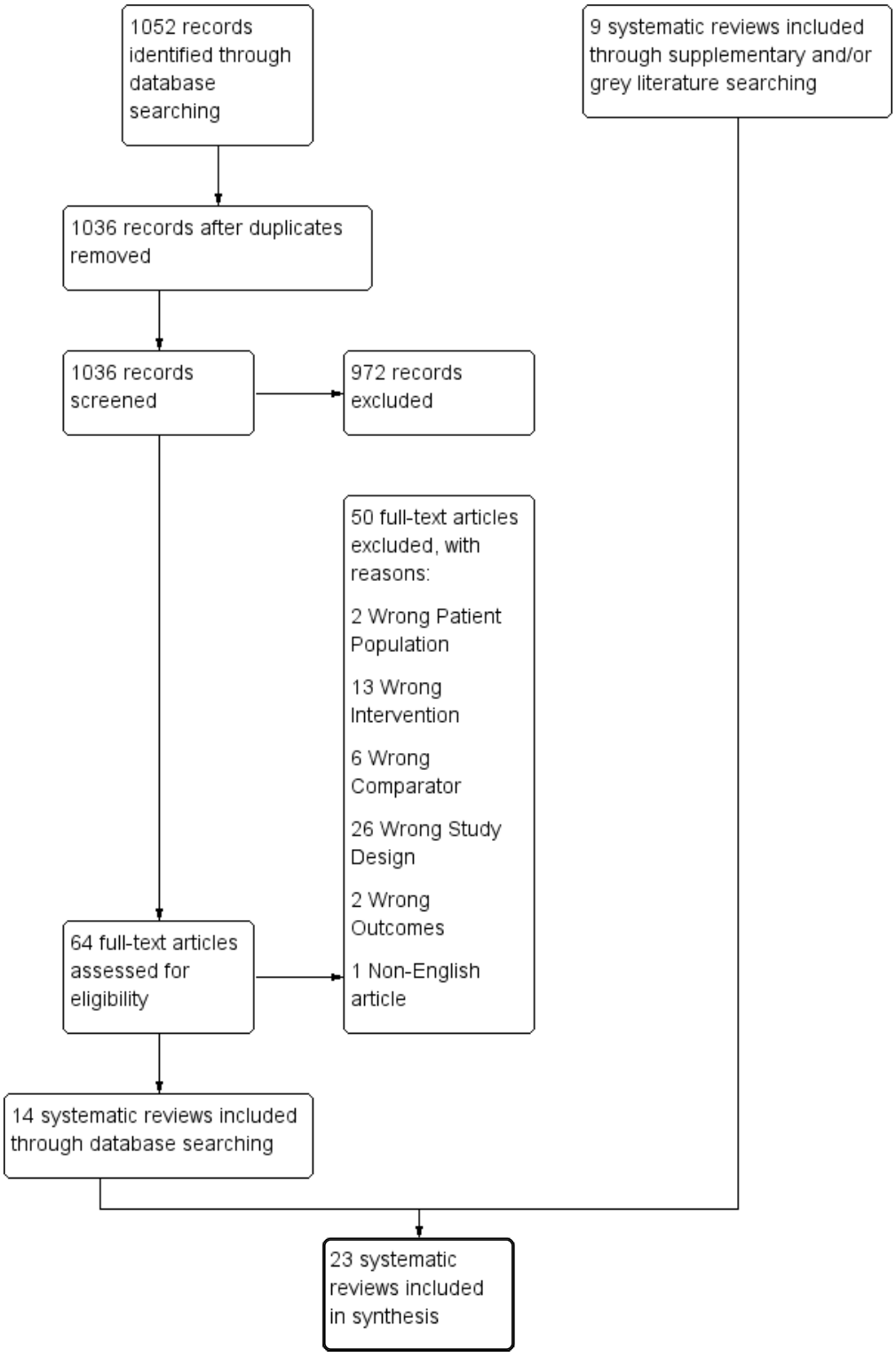


Figure 10: Exercise and Chronic Neuropathic Pain – PRISMA

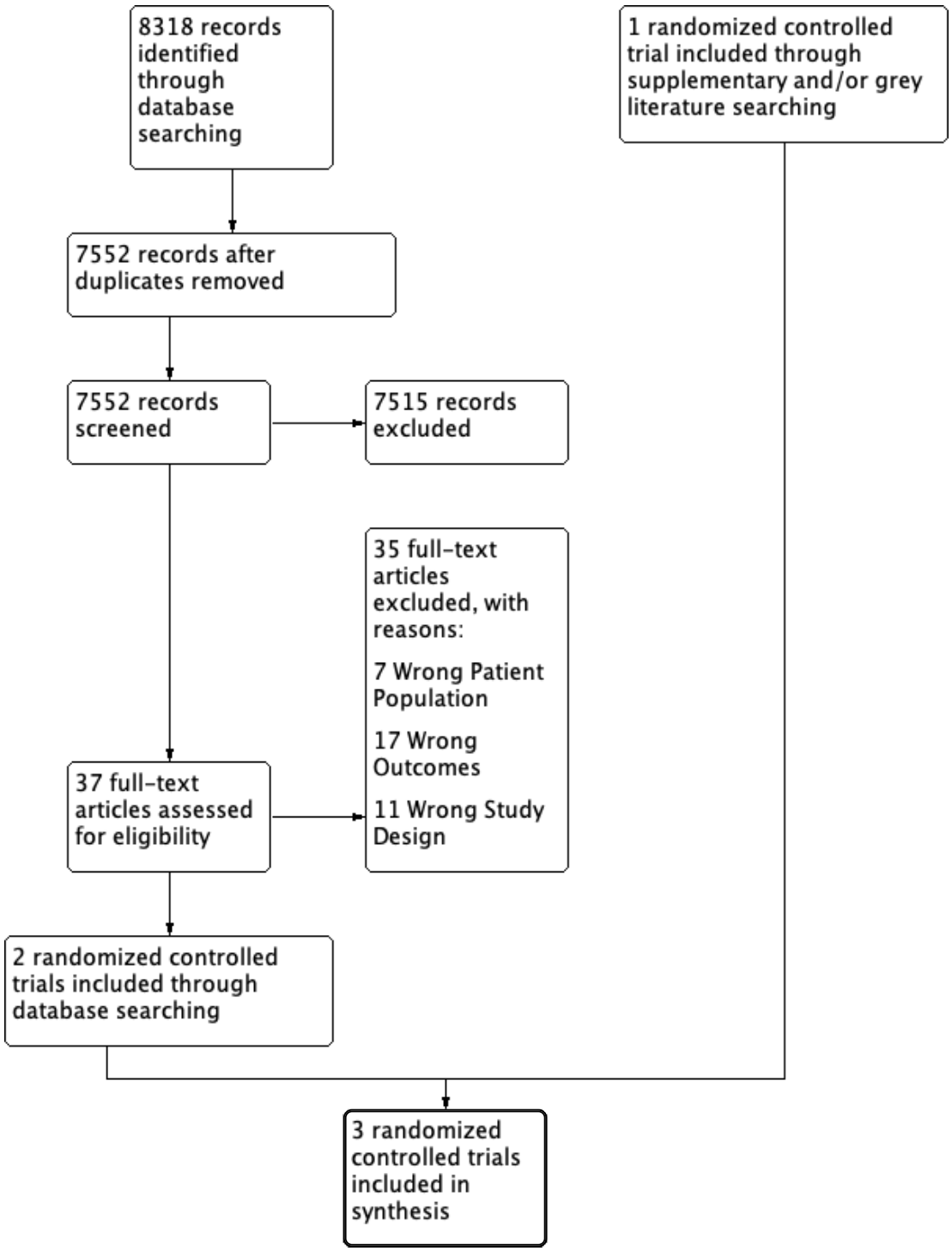


Figure 11: Exercise and Chronic Neuropathic Pain – Risk of Bias Summary

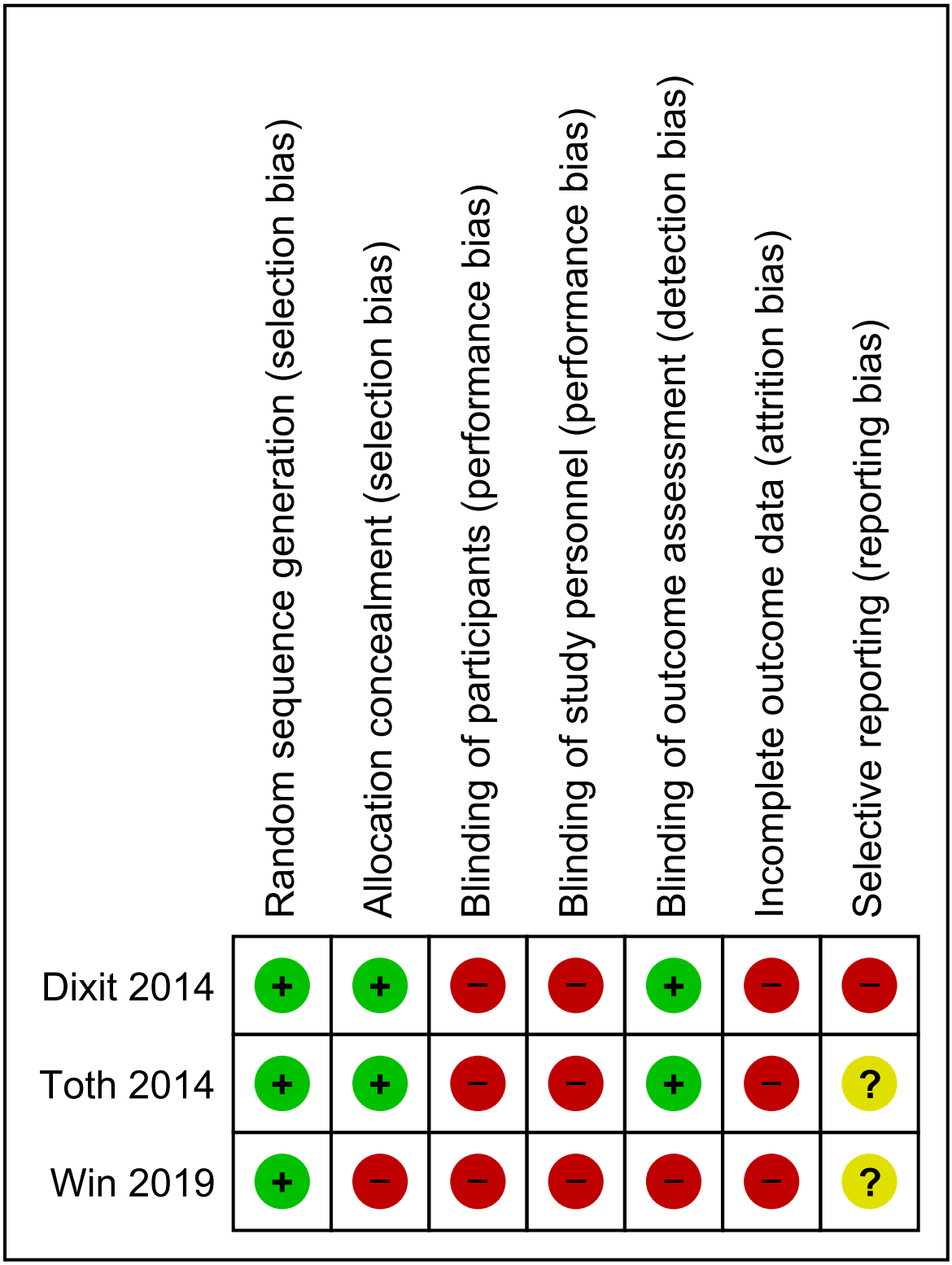


Figure 12: Exercise and Chronic Neuropathic Pain – Risk of Bias Graph

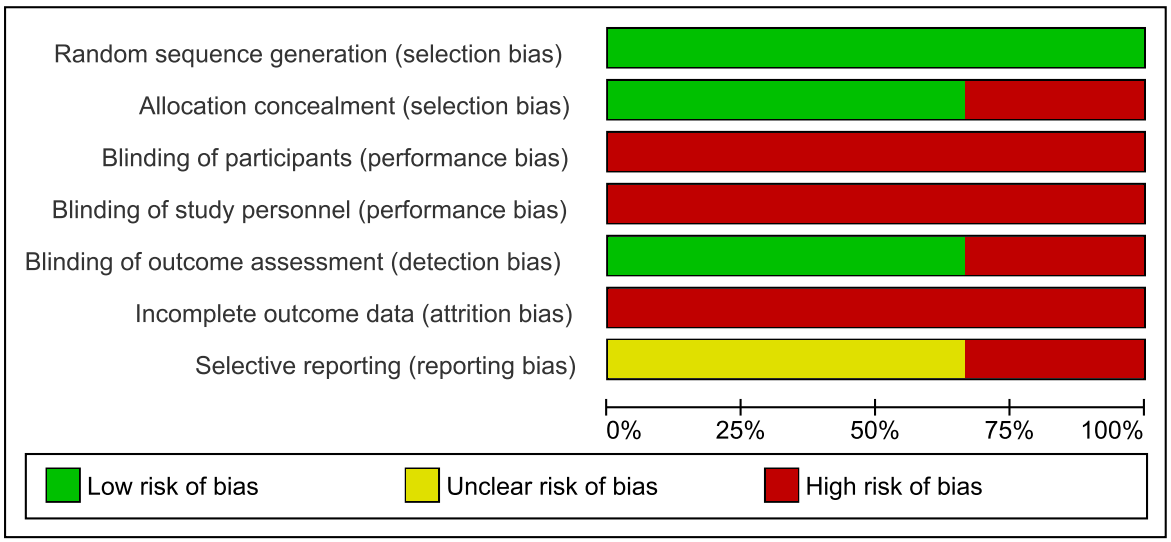


Figure 13: Chronic Pain and Drug Combinations – PRISMA (Systematic Reviews)

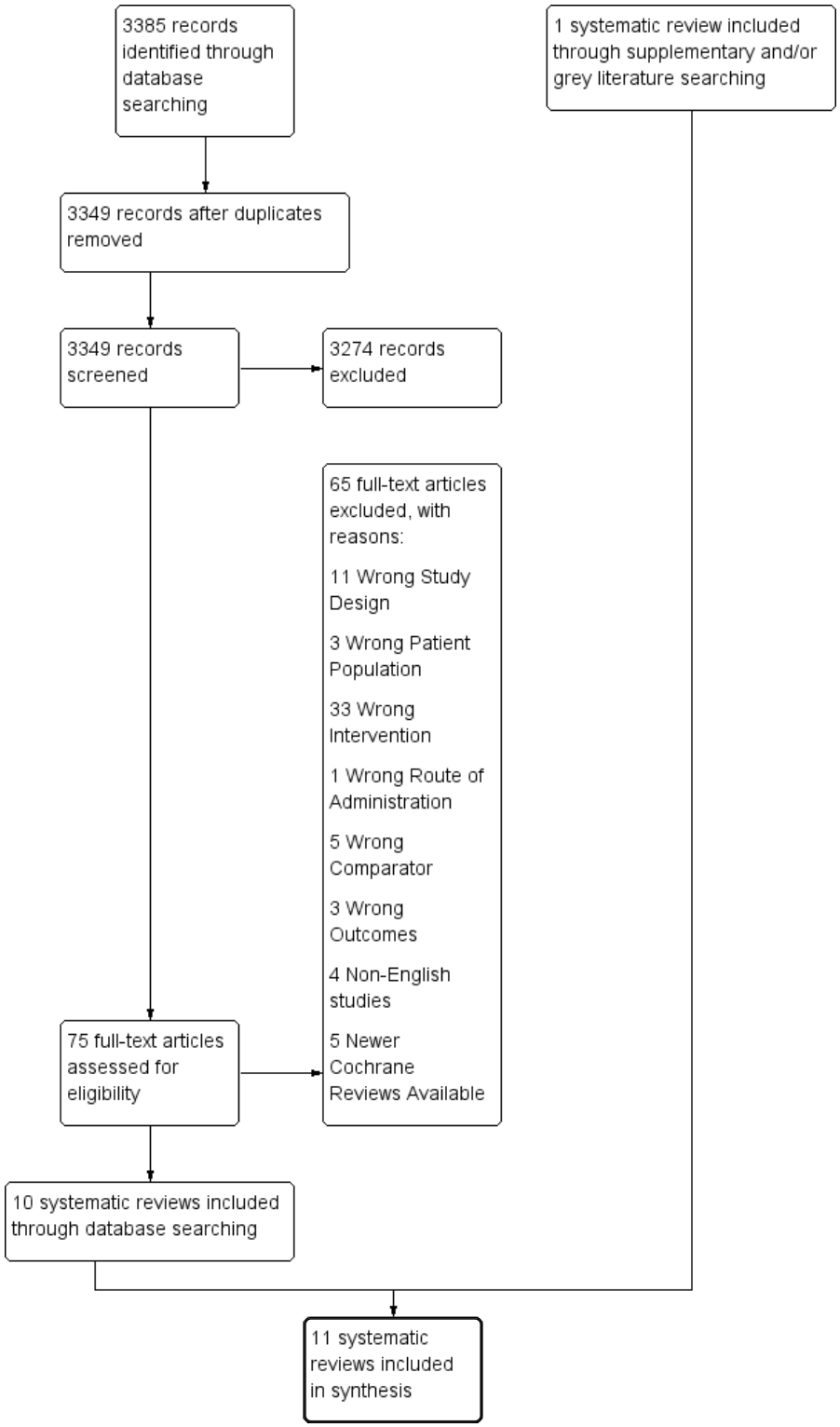


Figure 14: Chronic Pain and Drug Combinations – PRISMA (Randomised Controlled Trials)

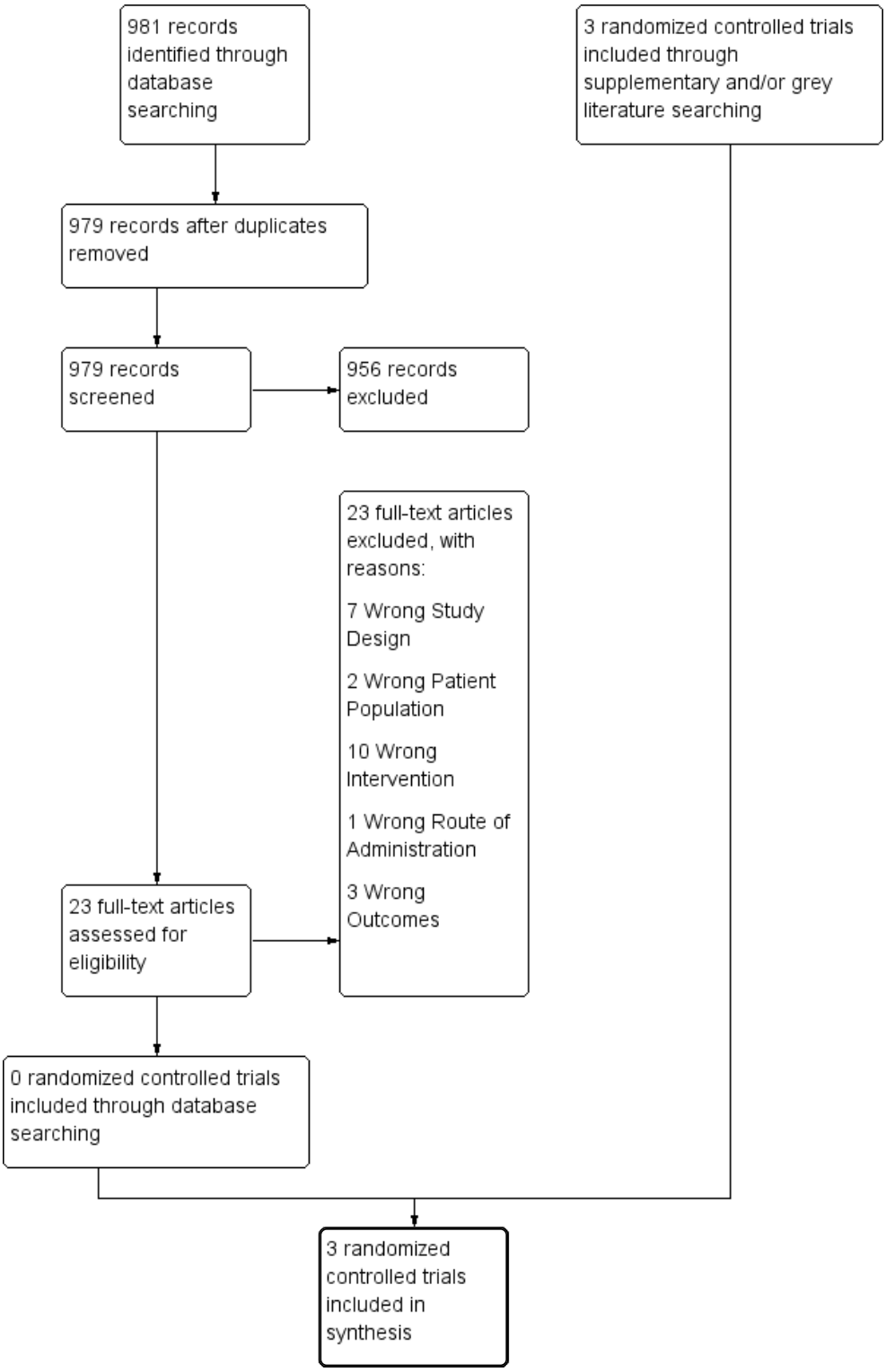


Figure 15: Chronic Pain and Drug Combinations – Risk of Bias Summary

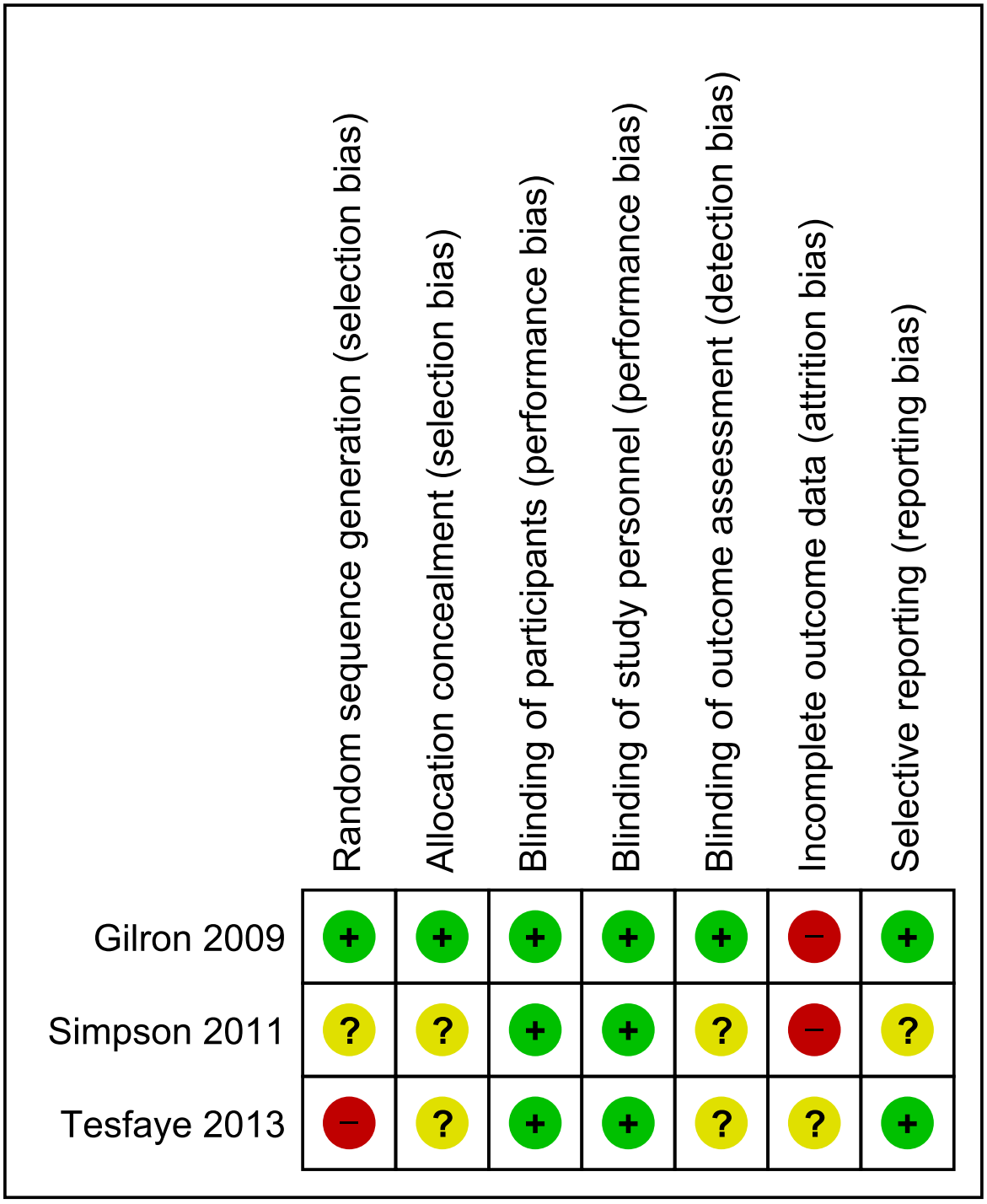


Figure 16: Chronic Pain and Drug Combinations – Risk of Bias Graph

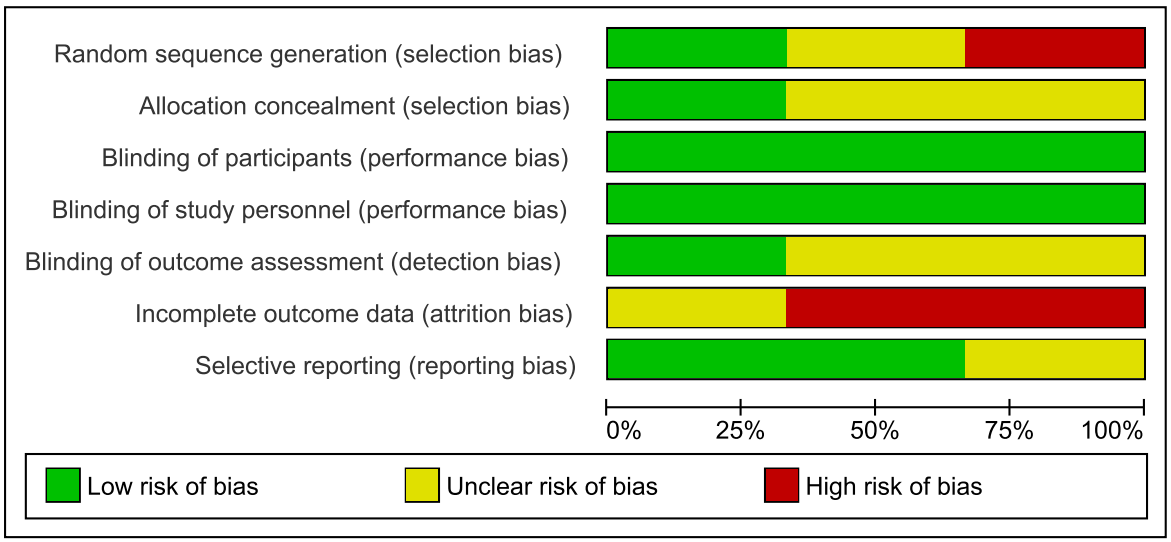


Figure 17: Opioid Tapering in Chronic Pain – PRISMA

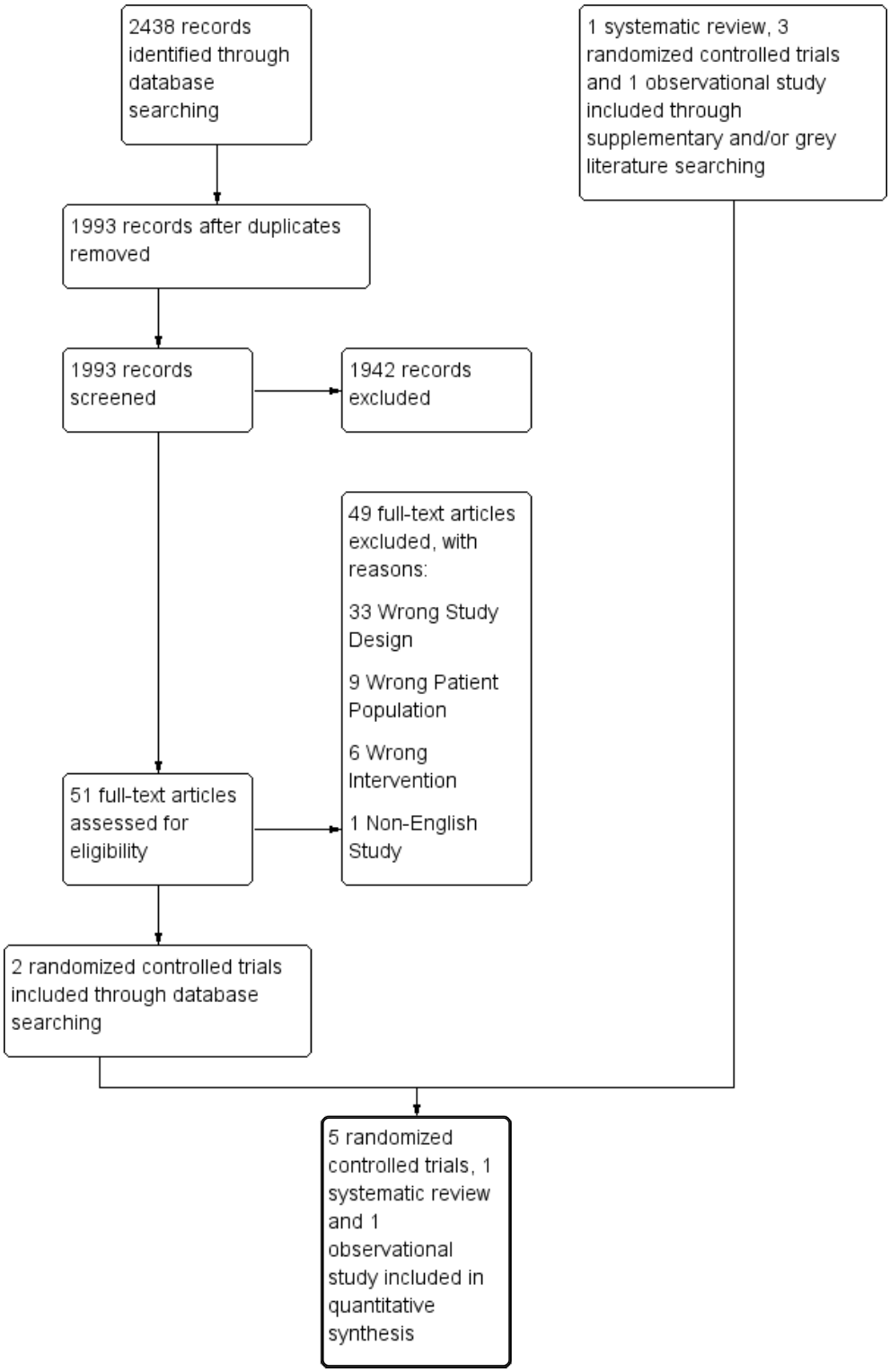


Figure 18: Opioid Tapering in Chronic Pain – Risk of Bias Summary

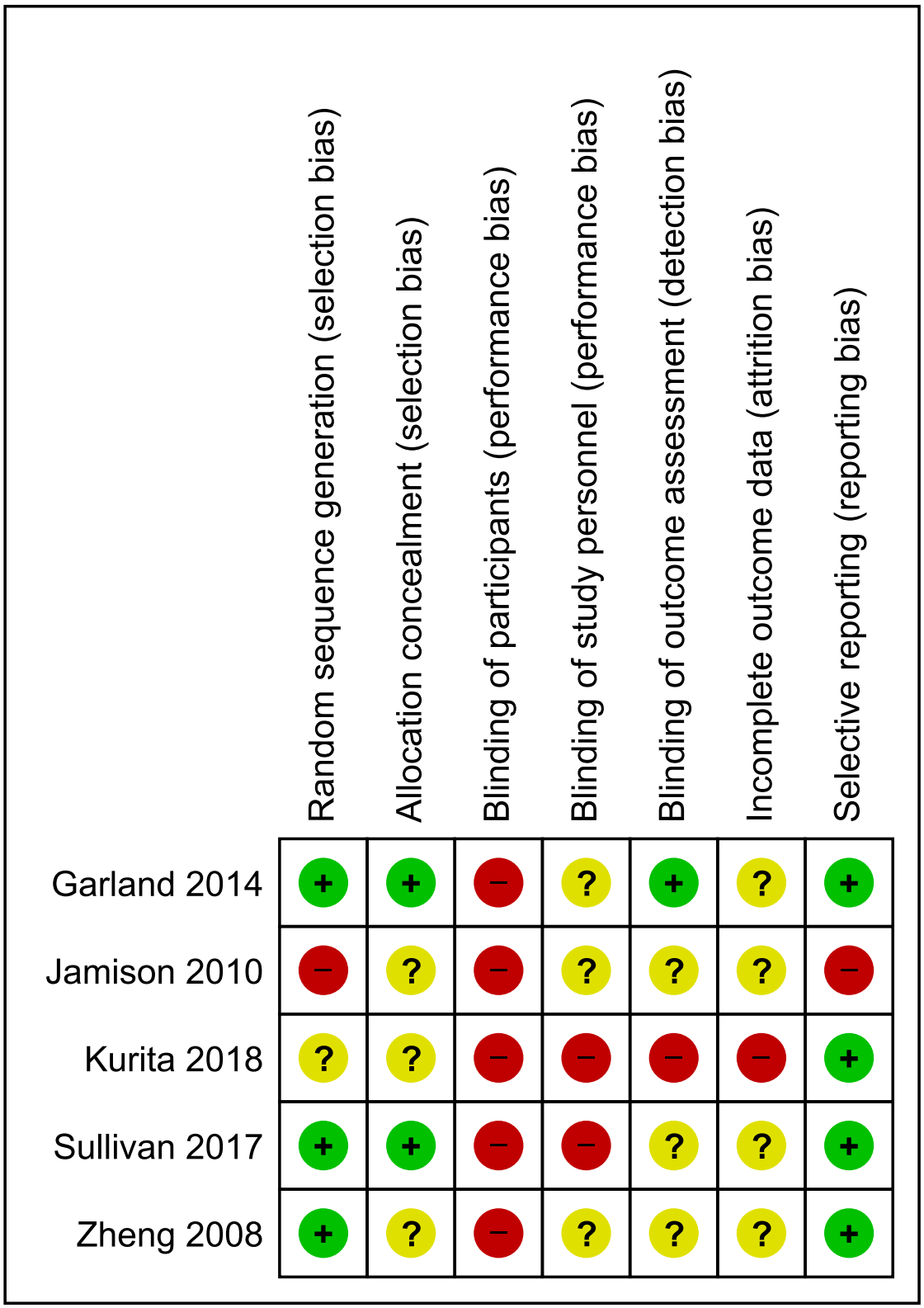


Figure 19: Opioid Tapering in Chronic Pain – Risk of Bias Graph

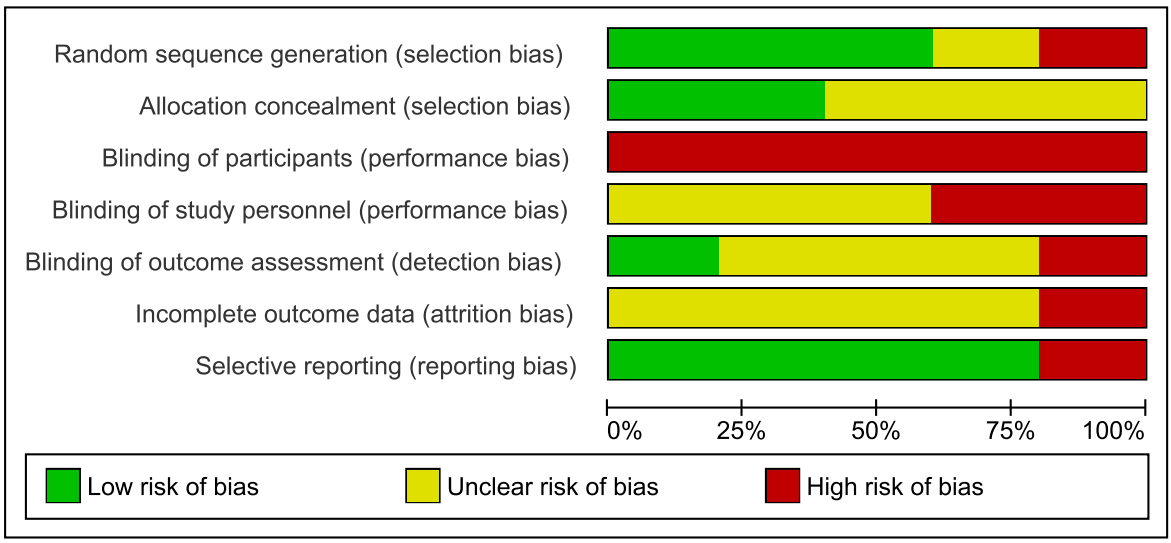


Figure 20: Chronic Pain and Cannabinoids - PRISMA

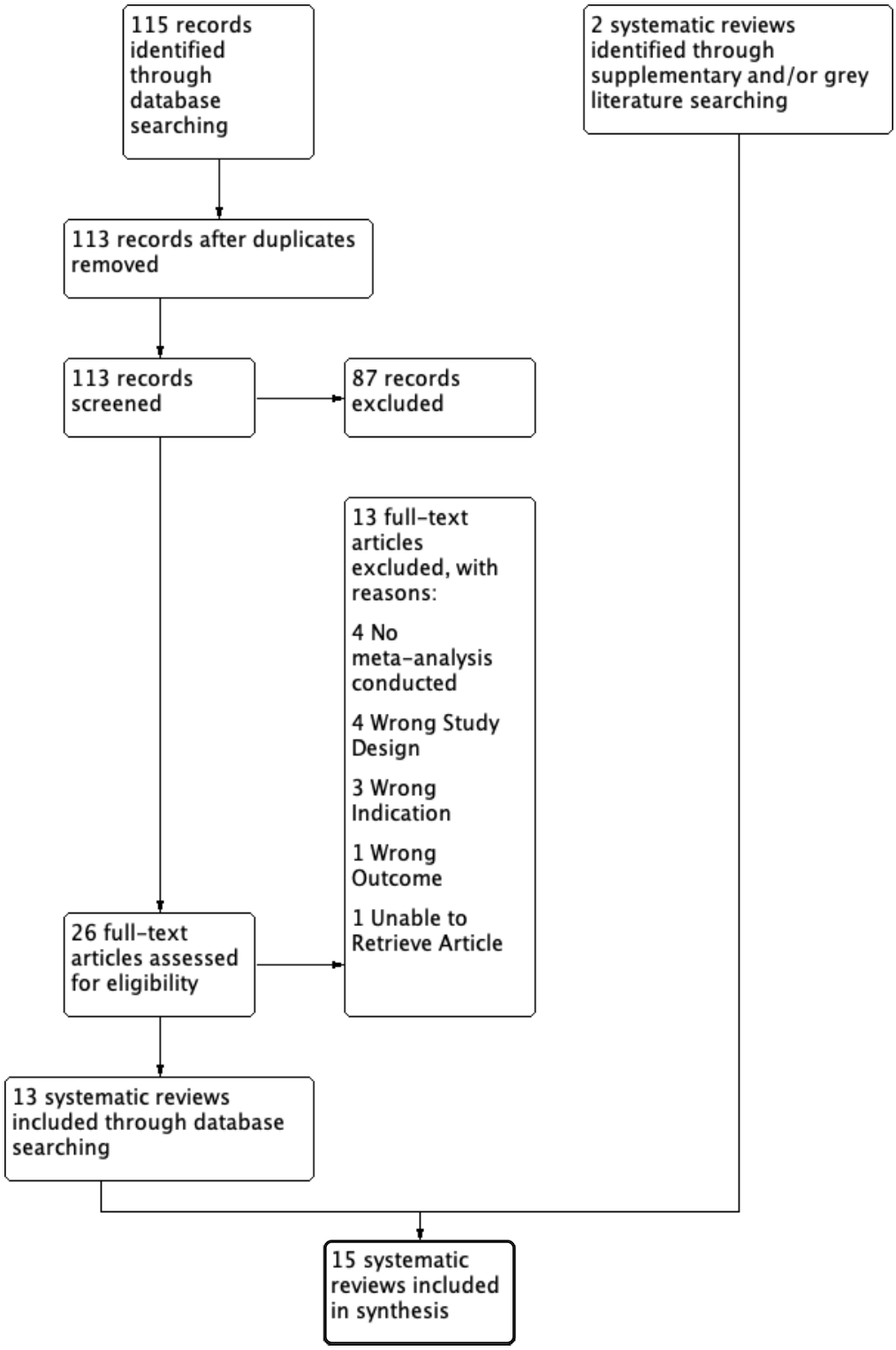


Figure 21: Psychological Strategies and Chronic Pain Management – PRISMA (Systematic Reviews)

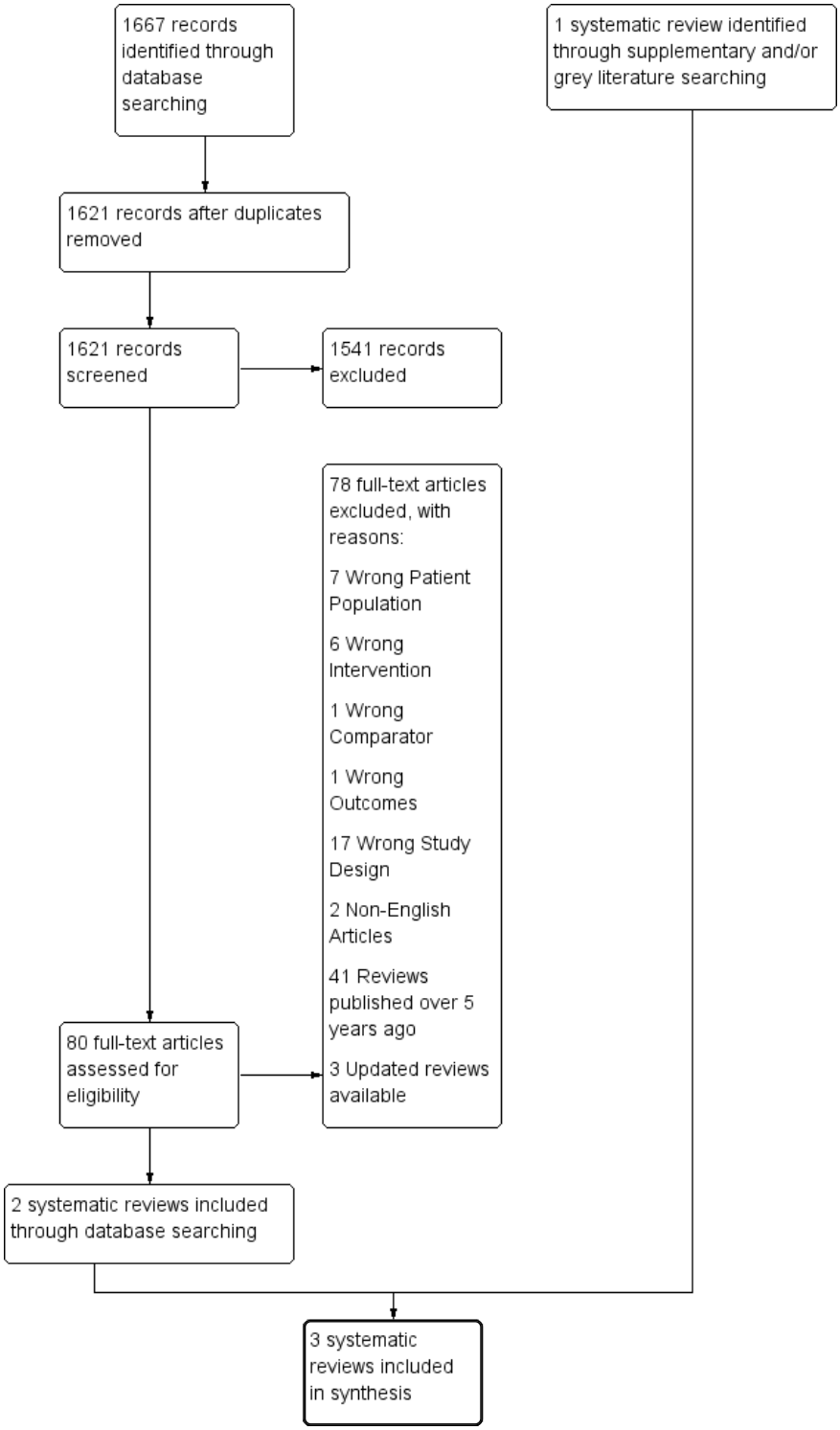


Figure 22: Psychological Strategies and Chronic Pain Management – PRISMA (Randomised Controlled Trials)

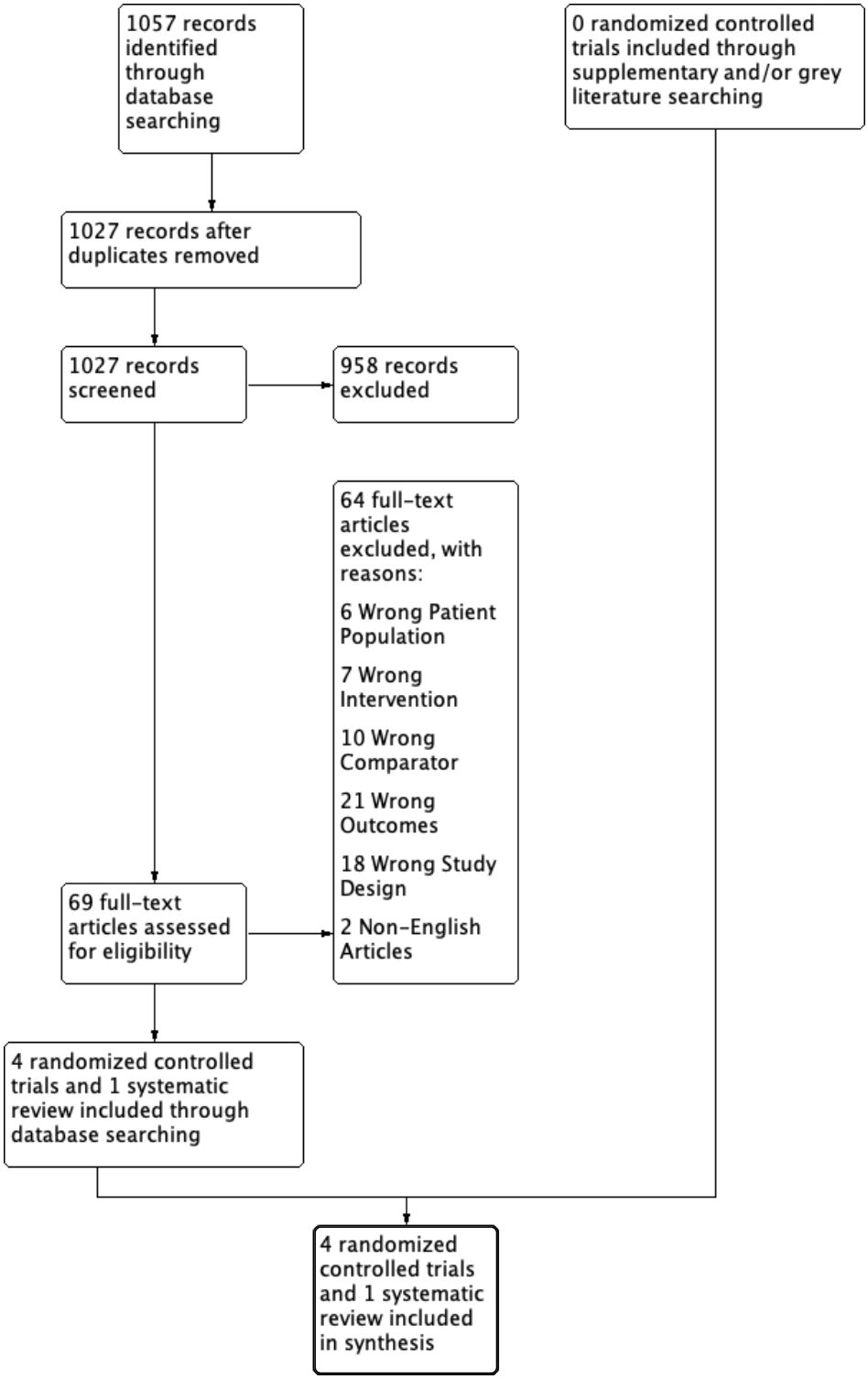


Figure 23: Psychological Strategies and Chronic Pain Management – Risk of Bias Summary

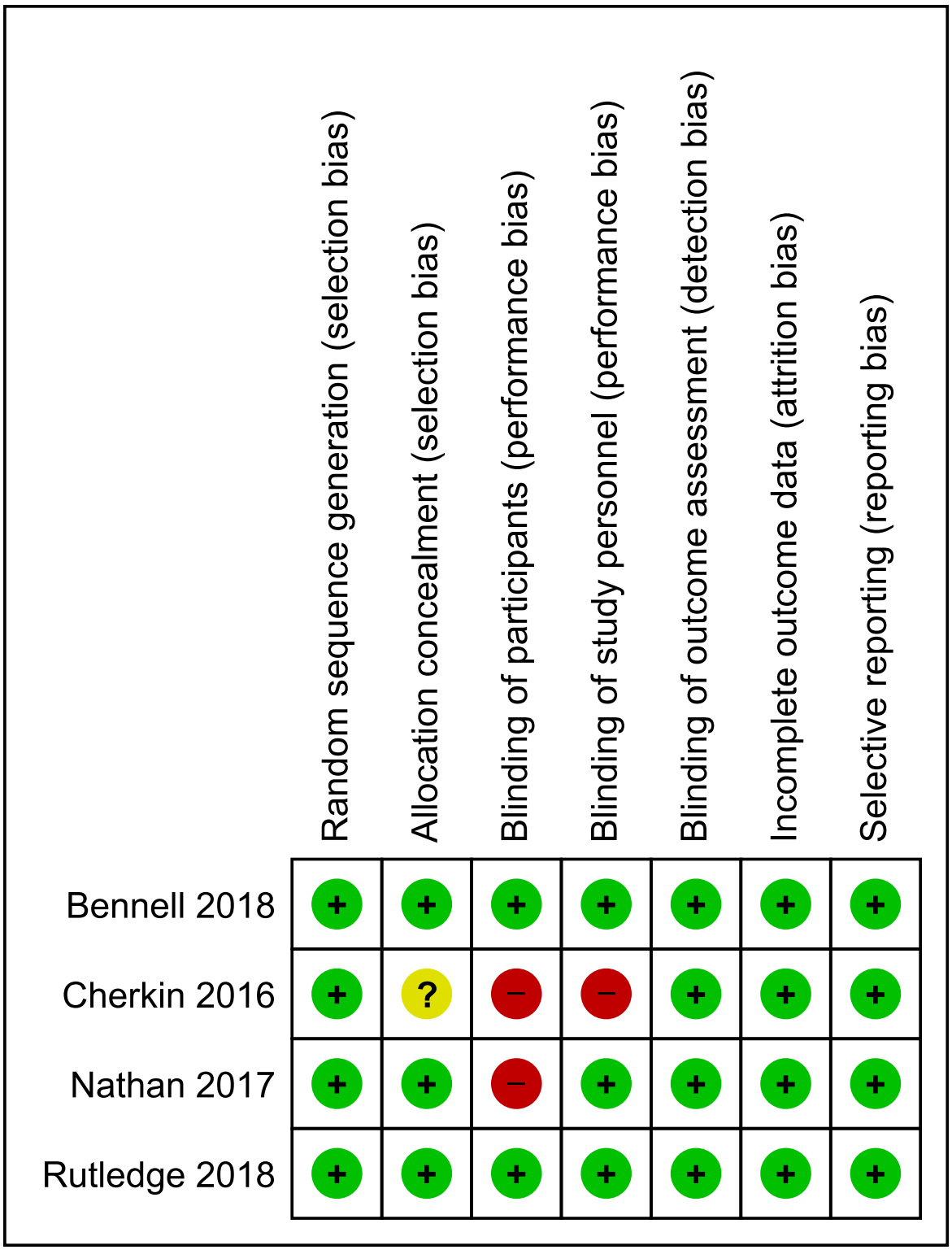


Figure 24: Psychological Strategies and Chronic Pain Management – Risk of Bias Graph

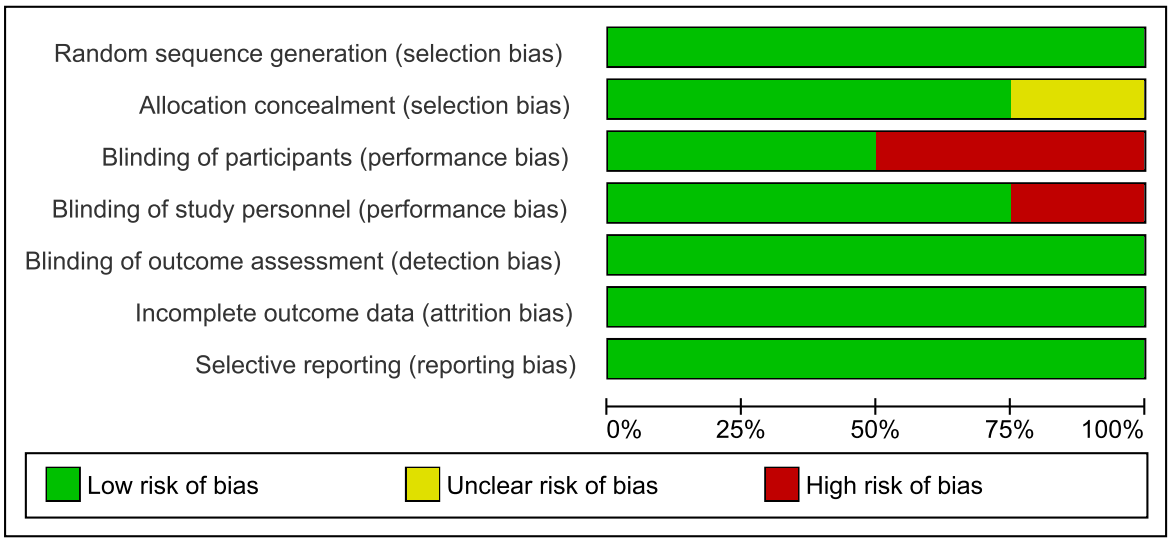


Figure 25: Topical Treatments for the Management of Chronic Pain – PRISMA

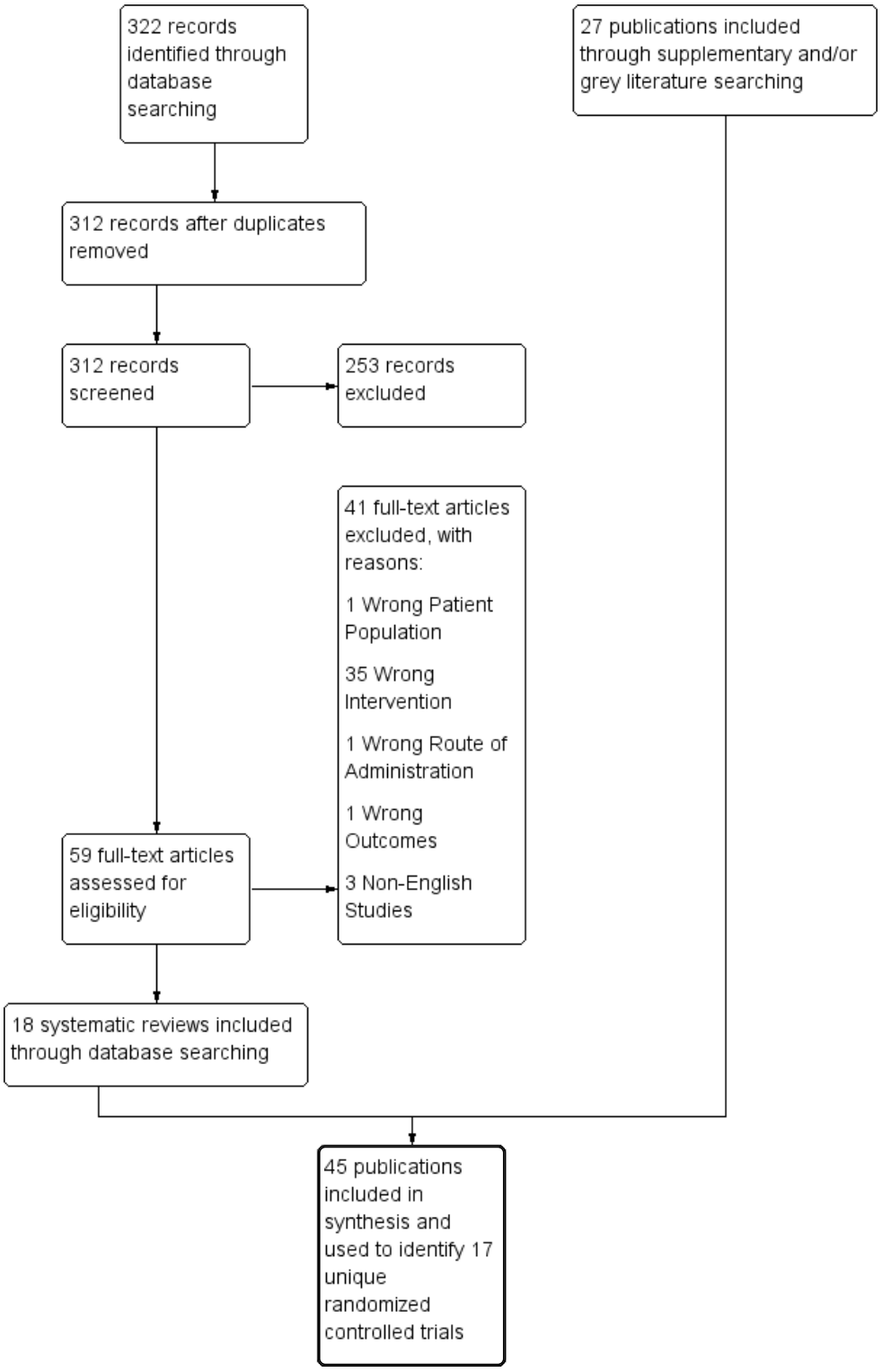


Figure 26: Topical Treatments for the Management of Chronic Pain – Risk of Bias Summary

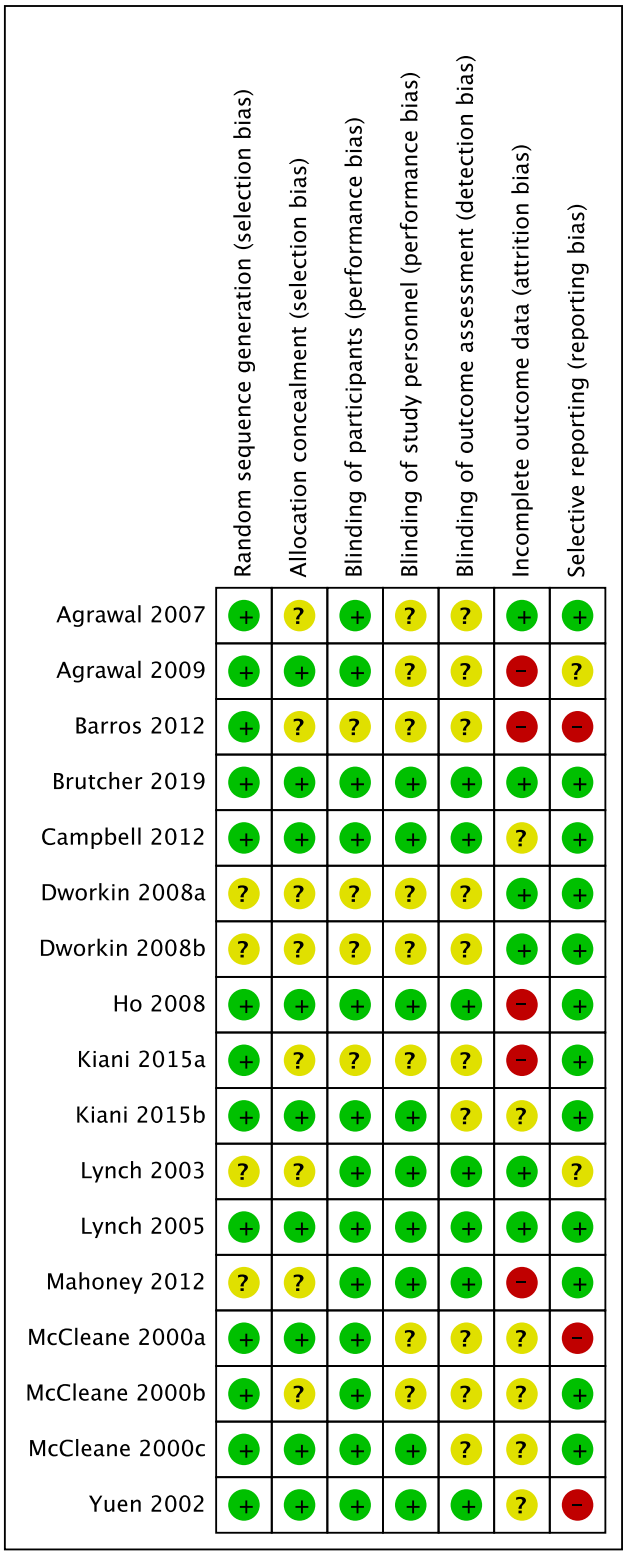


Figure 27: Topical Treatments for the Management of Chronic Pain – Risk of Bias Graph

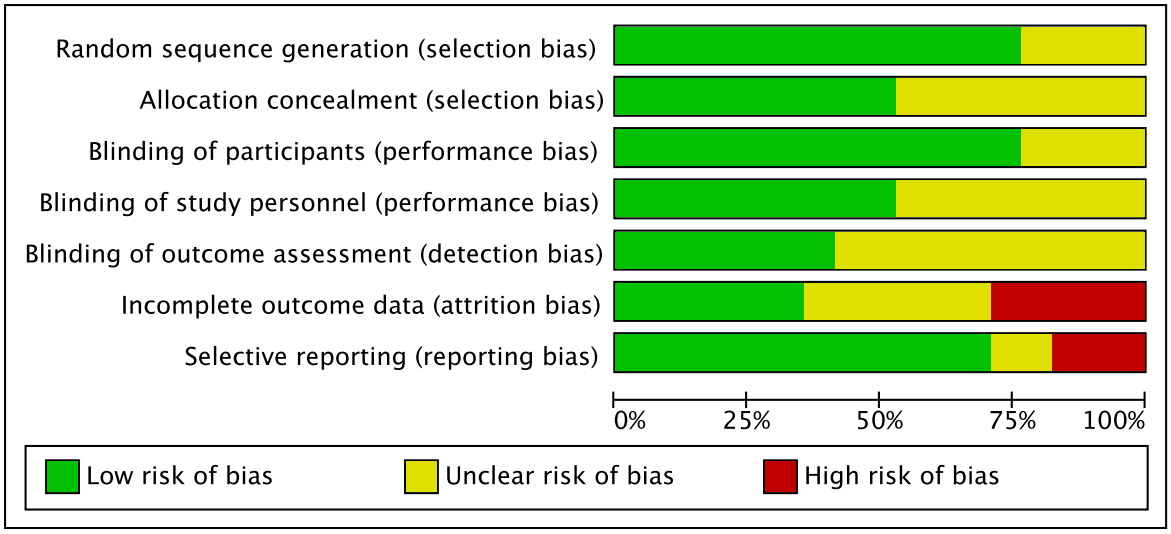


Figure 28: Tricyclic Antidepressants and Chronic Pain Management – PRISMA

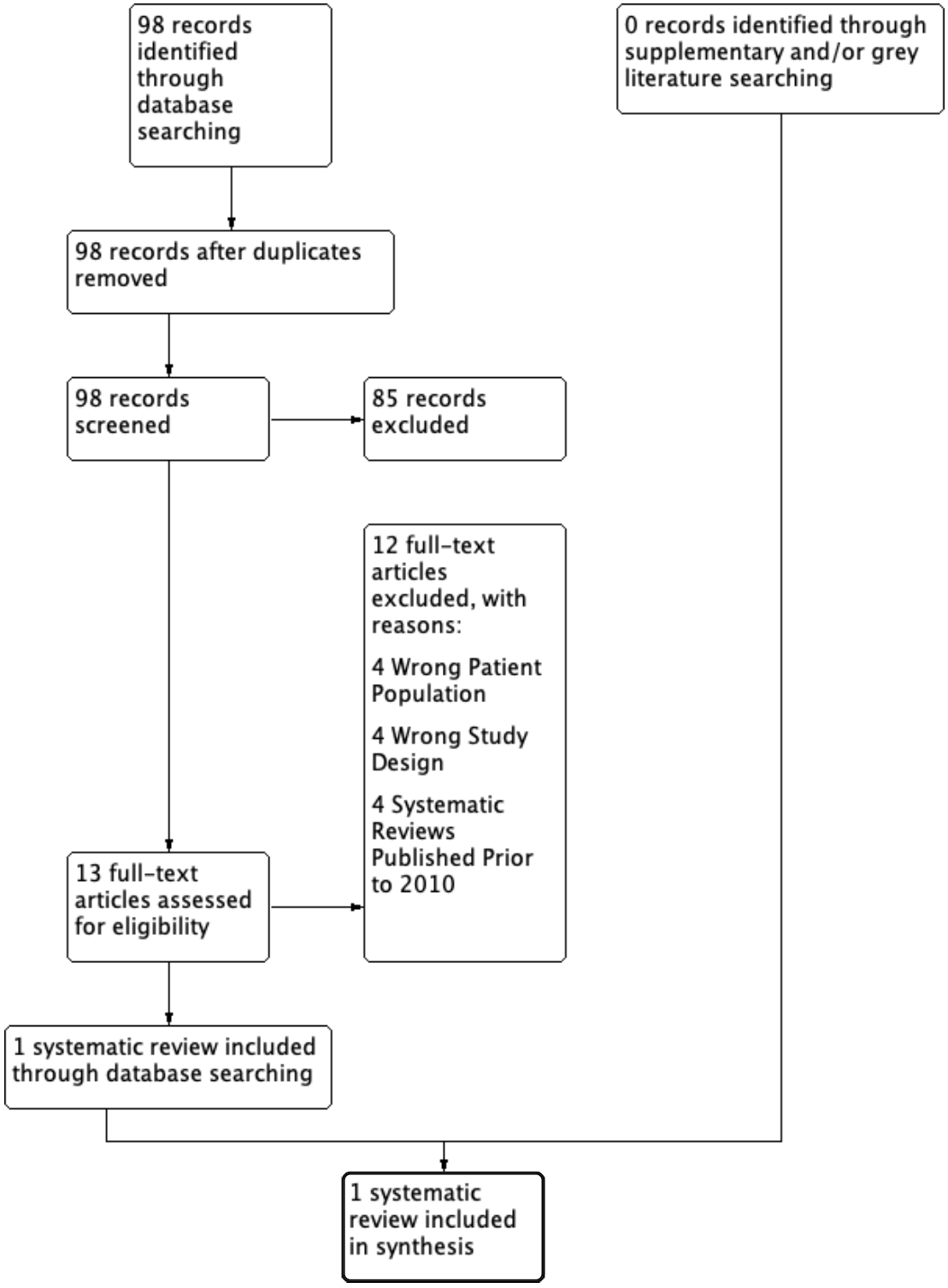


Figure 29: Mean difference for pain in trials that assessed efficacy of tricyclic antidepressants for chronic low back pain. Studies ordered by effect size.
TCA = Tricyclic Antidepressants, SE = Standard Error, IV = Inverse Variance.

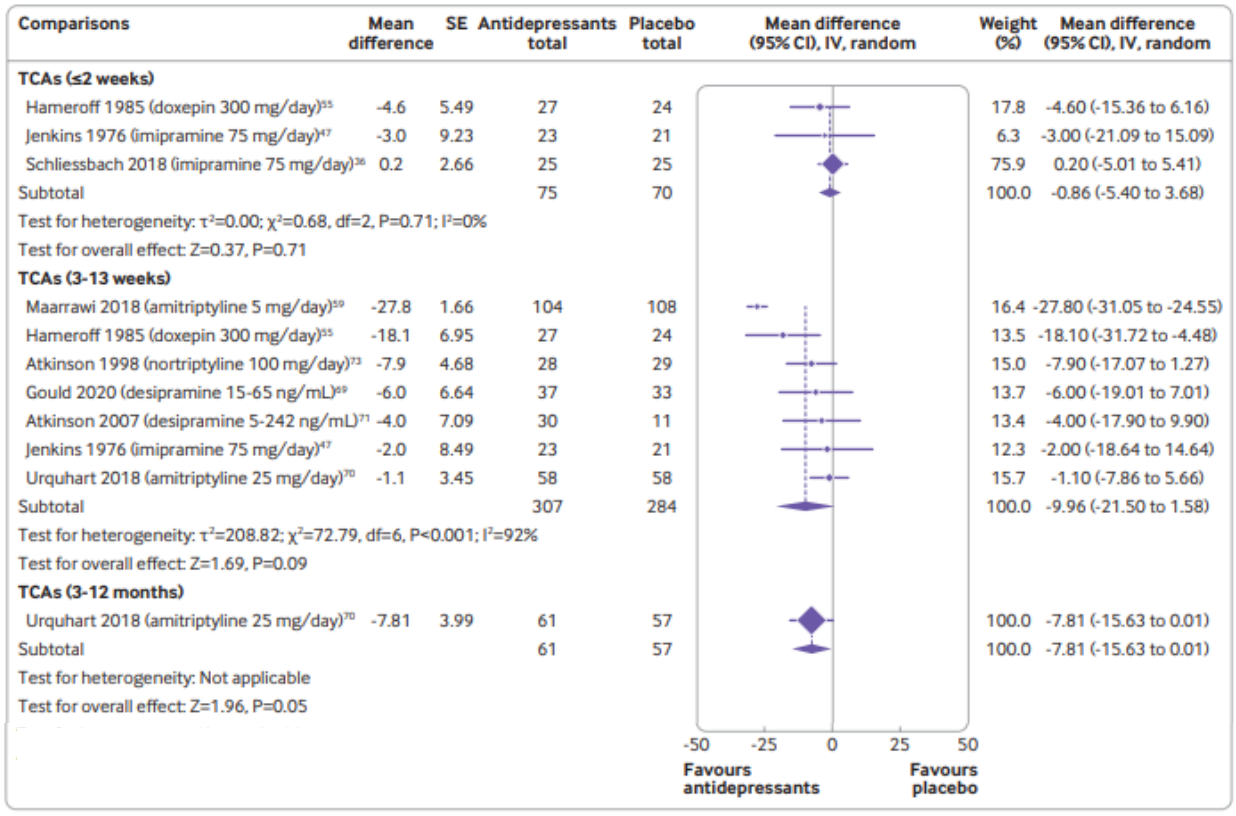


Figure 30: Mean difference for pain in trials that assessed efficacy of tricyclic antidepressants for low back pain using the longest time point and removal of a single dose study.

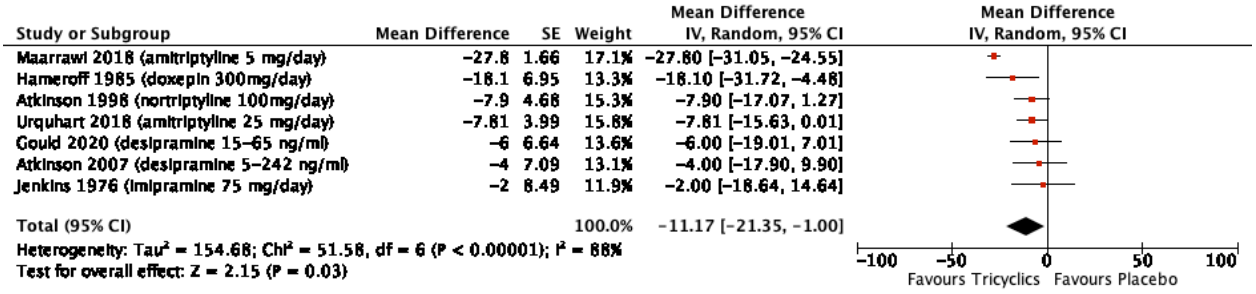
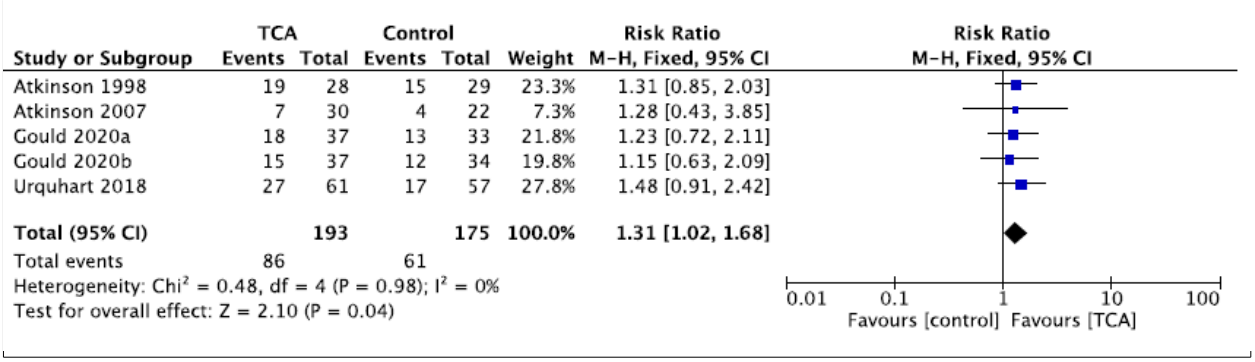
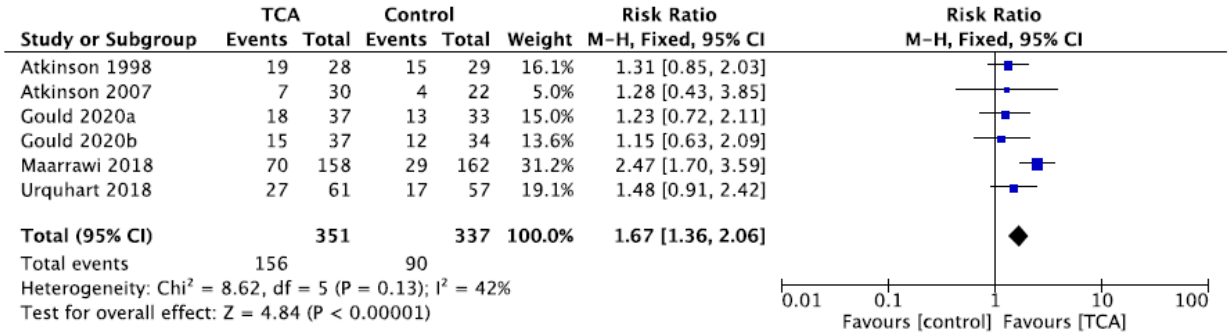


Figure 31: Patients who achieved a meaningful pain reduction in trials that reported responder data for tricyclic antidepressants versus control excluding Maarawi 2018.



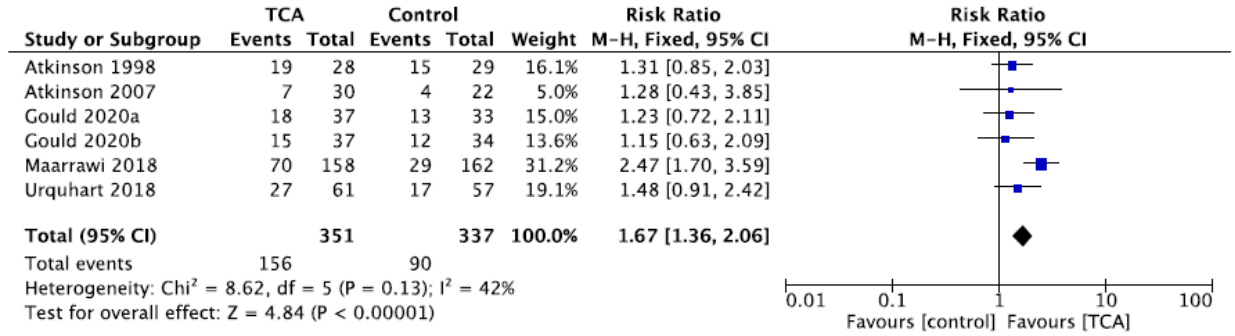
TCA = Tricyclic Antidepressants

Figure 32: Patients who achieved a meaningful pain reduction in trials that reported responder data for tricyclic antidepressants versus control including Maarrawi 2018.



TCA = Tricyclic Antidepressants

Figure 33: Mean difference for pain in trials that assessed efficacy of tricyclic antidepressants for sciatica.



TCA = Tricyclic Antidepressants, SE = Standard Error, IV = Inverse Variance.

Figure 34: Mean difference for pain in trials that assessed efficacy of tricyclic antidepressants for sciatica using data from the longest timepoint.