Electronic Supplement– Background review Methods and Results

Methods.

Using PubMed, we conducted a background review of articles reporting RCTs for the treatment of acute or chronic pain in which there were outcomes related to opioid sparing (see details below). Included articles described trials of pain treatments in adults that included at least one outcome related to opioid sparing and were published in English. Study participants were not necessarily taking opioid medications in advance of the study and in some cases were excluded from participating if they were taking opioids. The search returned substantially more articles reporting on acute pain RCTs than on chronic pain RCTs. We included all chronic pain trials that were obtained (i.e., those articles published between 1966 and February 26, 2018). For acute pain RCTs, we limited inclusion to those published between January 1, 2010 and February 26, 2018 in order to evaluate the most recent research methods in opioid sparing trials. In order to supplement our search, the consensus meeting planning committee was asked to identify acute and chronic pain RCTs with opioid sparing outcomes. We evaluated the study objectives, intervention types, control types, inclusion and exclusion criteria, primary and secondary/exploratory outcomes, method of assessing opioid dosage, and reporting of clinically meaningful differences or relevance used in sample size determination or the interpretation of study results. Although we acknowledge that many RCTs that measured outcomes related to opioid sparing may have been missed by our search strategy, our examination of these trials provided information that identified important gaps that should be addressed when planning future studies.

Results.

The PRISMA diagram for the background review is shown in Figure below. The PubMed search identified 255 articles, of which 177 were ineligible, resulting in 73 eligible acute pain articles and 5 eligible chronic pain articles. The meeting planning committee

identified an additional 10 acute pain RCTs and an additional 17 chronic pain RCTs that were eligible. In total, 83 acute pain RCTs and 26 chronic pain RCTs reported in 22 articles were included in the review (see Electronic Supplement B for list of included articles).

The Supplemental Table presents the findings across the reviewed RCTs. Almost all acute pain RCTs investigated post-operative pain (98%), with opioid dosage reduction (47%) or opioid adverse events (AEs; 2%) being the primary outcome in about half of these trials. The most common interventions in the acute pain RCTs included anesthetic protocols (29%), non-steroidal anti-inflammatory drugs (20%), dexmedetomidine (10%), and anti-epileptic drugs (8%). The most common control conditions were placebo (60%), other active treatments (17%), and protocol-specified usual care or medication management (11%). The most common inclusion criterion was that participants had a specific procedure type scheduled (94%). Exclusion criteria included opioid or substance misuse or abuse (38%), taking selected chronic analgesic medications (35%), obesity (34%), chronic pain conditions (19%), psychological or psychiatric disorders (18%), recent involvement in other research (17%), or current use of opioid analgesics (17%).

Thirty-nine percent of the acute pain RCTs used a continuous measure of opioid dosage as the primary outcome, 13% used a pain outcome as primary, and 5% used a combination of the two as primary. Across these RCTs, the majority of secondary or exploratory outcomes included pain, opioid dosage, opioid reduction, and opioid AEs. Opioid dosage was captured primarily by patient-controlled analgesia devices (43%) or recorded in the medication administration record (41%). The majority of the acute pain RCTs (78%) did not discuss the clinical relevance of the assumptions made for the trial's sample size calculation or for interpretation of the study results. Of the studies that did discuss clinical relevance (22%), most provided no reference to support their interpretations of clinically relevant effects related to opioid sparing. When references were provided, we were unable to

determine the relevant basis for claims of clinical meaningfulness for which the articles had been referenced.

Only 31% of the identified chronic pain studies used an opioid sparing outcome as the primary outcome. Opioid-related study objectives were typically secondary or exploratory outcomes (i.e., opioid sparing 42%, opioid AEs 31%, opioid misuse, abuse, and withdrawal 19%). Interventions were primarily pharmacologic treatments (62% in total). Placebo controls were used in 38% of the chronic pain RCTs, 27% used other opioid control groups, 12% used an unspecified usual care/medication management condition, and 8% used a pre-specified usual care/medication management condition. Inclusion criteria related to current opioid usage were fairly common, such as a minimum length of time taking opioids (27%), around the clock opioid dosing (27%), or opioid dosage above (19%) or below (19%) a minimum cutoff. Some trials also had pain-related inclusion criteria, such as a minimum pain intensity (46%), specific chronic pain conditions (42%), poorly controlled pain (19%), or maximum pain intensity below a cutoff (15%). Exclusion criteria in these trials included mental health disorders (54%), an expectation of increased pain (e.g., from an upcoming surgery; 35%), opioid or other substance misuse or abuse (35%), current use of opioid analgesics (23%), or recent involvement in other research (19%).

Unlike the acute pain RCTs in which opioid dosage was the most frequent primary outcome, pain outcomes were the most frequent primary outcome in the chronic pain RCTs (31%), followed by continuous measures of opioid dosage (27%), with nearly one-quarter of the studies not reporting the primary outcome (23%). Pain outcomes were frequently secondary or exploratory measures (81%) as well, along with continuous measures of opioid dosage (31%), opioid-related AEs (method not reported; 27%), dichotomized opioid reduction (i.e., below or above a specified cut-off) (15%), opioid withdrawal (15%), self-reported opioid-related AEs (12%), or opioid misuse or abuse (12%). Opioid dosage was primarily captured by

self-report (42%), with one-fifth of the studies not reporting the method used to capture opioid dosage (19%). The majority of the chronic pain RCTs (73%) did not discuss the clinical relevance of the trial's results. Of the studies that did discuss clinical relevance (27%), none provided a reference to support the interpretation of clinical meaningfulness used in discussing the study results.

Search strategy

((opioid sparing[Text Word]) OR narcotic sparing[Text Word]) OR morphine sparing[Text Word] Sort by: PublicationDate Filters: Clinical Trial; Humans; English

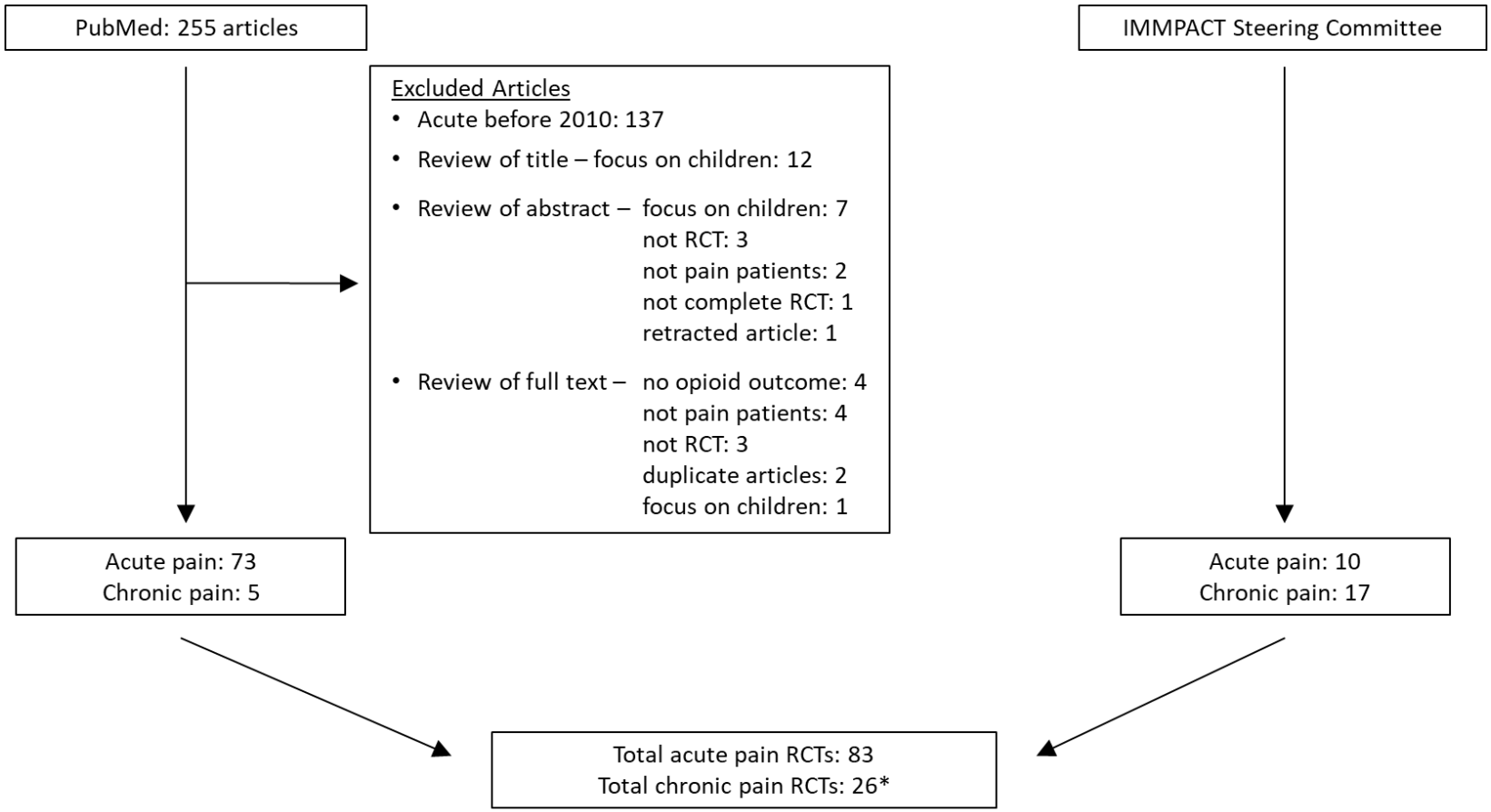
Criteria for inclusion

- RCT
- Treatment of acute or chronic pain
- Adults 18+
- Opioid-related outcome (e.g., opioid sparing/reduction in opioid dose; opioid side effects or adverse events)

Included articles

Authors	Publication Details
Bjorkman R, Ullman A, Hedner J.	Eur J Clin Pharmacol. 1993;44(1):1-5.
Blondell RD, Ashrafioun L, Dambra CM, Foschio EM, Zielinski	J Addict Med. 2010
Cowan DT, Wilson-Barnett J, Griffiths P, Vaughan DJ, Gondhia	Pain Med 2005
Fallon MT, Albert Lux E, McQuade R, Rossetti S, Sanchez R, Sun W, Wright S, Lichtman AH, Kornyeyeva E.	Br J Pain. 2017 Aug;11(3):119-133. doi: 10.1177/2049463717710042. Epub 2017 May 17.
Galer BS, Lee D, Ma T, Nagle B, Schlagheck TG.	Pain. 2005 Jun;115(3):284-95. Epub 2005 Apr 20.
Garland EL, Manusov EG, Froeliger B, Kelly A, Williams JM,	J Consult Clin Psychol. 2014
Hooten and Warner	Addict Behav 2015
Jamison RN, Ross EL, Michna E, Chen LQ, Holcomb C, Wasan	Pain 2010
Katz NP.	J Pain Symptom Manage. 2000 Jan;19(1 Suppl):S37-41.
Lichtman AH, Lux EA, McQuade R, Rossetti S, Sanchez R, Sun W, Wright S, Kornyeyeva E, Fallon MT.	J Pain Symptom Manage. 2018 Feb;55(2):179-188.e1. doi: 10.1016/j.jpainsymman.2017.09.001. Epub 2017 Sep 18.
Meyering SH, Stringer RW, Hysell MK.	West J Emerg Med. 2017 Apr;18(3):373-381. doi: 10.5811/westjem.2016.12.29218. Epub 2017 Feb 27.
Mishra S, Bhatnagar S, Goyal GN, Rana SP, Upadhya SP.	Am J Hosp Palliat Care. 2012 May;29(3):177-82. doi: 10.1177/1049909111412539. Epub 2011 Jul 10.
Naylor MR, Naud S, Keefe FJ, Helzer JE.	J Pain 2010
Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, McQuade R, Wright S, Fallon MT.	J Pain. 2012 May;13(5):438-49. doi: 10.1016/j.jpain.2012.01.003. Epub 2012 Apr 5.
Raptis E, Vadalouca A, Stavropoulou E, Argyra E, Melemeni A, Siafaka I.	Pain Pract. 2014 Jan;14(1):32-42. doi: 10.1111/papr.12045. Epub 2013 Mar 6.
Roux P, Sullivan MA, Cohen J, Fugon L, Jones JD, Vosburg SK, Cooper ZD, Manubay JM, Mogali S, Comer SD.	Pain 2013
Sullivan MD, Turner JA, DiLodovico C, D'Appollonio A,	J Pain. 2017 Mar;18(3):308-313
Webster L, Gruener D, Kirby T, Xiang Q, Tzanis E, Finn A.	Pain Med 2016
Williams AC, Richardson PH, Nicholas MK, Pither CE, Harding VR, Ridout KL, Ralphs JA, Richardson IH, Justins DM,	Pain 1996
Zgierska AE, Burzinski CA, Cox J1, Kloke J, Singles J, Mirgain S, Stegner A, Cook DB, Bačkonja M.	J Altern Complement Med. 2016
Zheng Z, Guo RJ, Helme RD, Muir A, Da Costa C, Xue CC.	Eur J Pain 2008
Green = reported 2 RCTs	
Blue = reported 3 RCTs	

PRISMA diagram



* 2 chronic pain RCT articles reported on 2 trials and 1 chronic pain RCT article reported on 3 trials.

Supplemental Table. Details of acute and chronic pain RCTs

Acute Pain RCTs	n (% out of 83)
Types of acute pain RCTs	
Post-operative pain	81 (98%)
Post-operative up to 1 year	1 (1%)
Severe acute pain in emergency department	1 (1%)
Opioid-related study objectives	
Opioid sparing objective	39 (47%)
Opioid sparing secondary / exploratory objective	43 (52%)
Opioid AEs primary outcome	2 (2%)
Opioid AEs secondary / exploratory outcome	56 (67%)
Intervention types	
Anesthetic protocol (e.g., epidural, regional anesthesia)	24 (29%)
NSAID	17 (20%)
Dexmedetomidine	8 (10%)
Anti-epileptics	7 (8%)
Acetaminophen, paracetamol	3 (4%)
Opioid (e.g., novel method of administering)	2 (2%)
Other pharmacologic	14 (17%)
Device	2 (2%)
Other	6 (7%)

Chronic Pain RCTS	n (% out of 26)
Types of chronic pain RCTs	
Tapering current opioid use	13 (50%)
Randomization to novel opioid/administration vs. standard opioid/administration	11 (42%)
Reduction of misuse or abuse	2 (8%)
Opioid-related study objectives	
Opioid sparing primary outcome	8 (31%)
Opioid sparing secondary / exploratory outcome	11 (42%)
Opioid AEs primary outcome	0 (0%)
Opioid AEs secondary / exploratory outcome	8 (31%)
Opioid misuse, abuse, or withdrawal secondary / exploratory outcome	5 (19%)
Intervention types	
Morphine sulfate/dextromethorphan hydrobromide combination	5 (19%)
Behavioral	4 (15%)
Cannabinoid	4 (15%)
Buprenorphine	3 (12%)
Multidisciplinary care	2 (8%)
Other	6 (23%)

Control types		Control types	
Placebo control	50 (60%)	Placebo control	10 (38%)
Other active treatment	14 (17%)	Other opioid	7 (27%)
Usual care/medication management (protocol specified)	9 (11%)	Usual care/medication management (not specified)	3 (12%)
Other	11 (13%)	Usual care/medication management (protocol specified)	2 (8%)
		Other	3 (12%)
Common inclusion criteria		Common inclusion criteria	
Specific procedure type	78 (94%)	*Opioid-related*	
Number of expected hospital days	6 (7%)	Minimum length of time using opioids	7 (27%)
Minimum pain intensity	5 (6%)	Around the clock opioid dosing	7 (27%)
		Opioid dosage above minimum cutoff	5 (19%)
		Opioid dosage below minimum cutoff	5 (19%)
		Opioid dependent, withdrawal symptoms	3 (12%)
		Willing to modify current opioid use	2 (8%)
		Pain-related	
		Minimum pain intensity	12 (46%)
		Specific chronic pain condition(s)	11 (42%)
		Pain poorly controlled	5 (19%)
		Maximum pain intensity below cutoff	4 (15%)
		Consistent non-experimental analgesic dosing for minimum time period	2 (8%)
Common exclusion criteria		Common exclusion criteria	

Opioid/substance misuse or abuse	32 (38%)	Psychological or psychiatric disorders	14 (54%)
Selected chronic analgesics	29 (35%)	Expected cause/increase in pain	9 (35%)
Obese	28 (34%)	Opioid or other substance misuse or abuse	9 (35%)
Chronic pain conditions	16 (19%)	Current use of opioid analgesics	6 (23%)
Psychological or psychiatric disorders	15 (18%)	Recent investigational drug use or other research participation	5 (19%)
Recent investigational drug use or other research participation	14 (17%)		
Current use of opioid analgesics	14 (17%)		
Expected cause/increase in pain	3 (4%)		
Primary outcomes		Primary outcomes	
Opioid dosage (continuous)	32 (39%)	Pain outcome	8 (31%)
Pain outcome	11 (13%)	Opioid dosage (continuous)	7 (27%)
Opioid dosage (continuous) & pain	4 (5%)	Opioid dosage (continuous) & opioid AEs	1 (4%)
Opioid reduction (dichotomized)	2 (2%)	Opioid misuse/abuse & pain	1 (4%)
Opioid dosage (continuous) & hemodynamic response to intubation	1 (1%)	Opioid withdrawal	1 (4%)
Opioid AEs (self-report)	1 (1%)	Pain & function	1 (4%)
Opioid AEs (observed)	1 (1%)	Completion of 6 month treatment protocol	1 (4%)
Other	5 (6%)	Not reported	6 (23%)
Not reported	26 (31%)		
Common secondary/exploratory outcomes		Common secondary/exploratory outcomes	
Pain outcome	69 (83%)	Pain outcome	21 (81%)
Opioid dosage (continuous)	43 (52%)	Opioid dosage (continuous)	8 (31%)
Opioid AEs (method not reported)	36 (43%)	Opioid AEs (method not reported)	7 (27%)

Opioid AEs (observed)	17 (20%)	Opioid reduction (dichotomized)	4 (15%)
Time to first opioid dose	16 (19%)	Opioid withdrawal	4 (15%)
Opioid AEs (Y/N)	9 (11%)	Opioid AEs (self-report)	3 (12%)
Opioid reduction (dichotomized)	7 (8%)	Opioid misuse/abuse	3 (12%)
Opioid AEs (treatment of AEs/side effects)	7 (8%)		
Opioid AEs (self-report)	5 (6%)		
Opioid dosage capture methods		Opioid dosage capture methods	
Patient-controlled analgesia	36 (43%)	Self-report	11 (42%)
Recorded/administered in hospital	34 (41%)	Patient controlled analgesia	1 (4%)
Hospital recorded & patient-controlled analgesia	4 (5%)	Completion of opioid discontinuation or opioid replacement treatment	1 (4%)
Self-report	2 (2%)	Number taking opioid rescue during study visit	1 (4%)
Pill count	2 (2%)	IV dose during procedure	1 (4%)
Hospital recorded & self-report after discharge	2 (2%)	Earn oxycodone doses (admin by study staff) vs. earn money	1 (4%)
Not reported	3 (4%)	Not reported	5 (19%)
Opioid AE measures		Opioid AE measures	
Nausea numeric rating scale	2 (2%)	*Opioid withdrawal symptoms*	
Bristol stool scale	1 (1%)	Clinical Opiate Withdrawal Scale (COWS)	2 (8%)
Opioid-related symptom distress scale	1 (1%)	Subjective Opiate Withdrawal Scale (SOWS)	1 (4%)
Opioid side effects scale	1 (1%)	Self-report & observation of physiological symptoms	1 (4%)
Confusion assessment method (delirium)	1 (1%)		
		Opioid misuse/abuse measures	
		Current Opioid Misuse Measure (COMM)	1 (4%)
		Prescription Opioid Misuse Index (POMI)	1 (4%)

	Drug Misuse Index (urine drug screen, COMM, PDUQ)	1 (4%)
	Other opioid AE measures	
	Constipation numerical rating scale	3 (12%)

systematciRCT = randomized controlled trials, COMM = Current Opioid Misuse Measure; PDUQ = Prescription Drug Use Questionnaire