Evidence Brief: Managing Acute Pain in Patients with Opioid Use Disorder on Medication-assisted Treatment

Supplementary Materials

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Health Services Research & Development Service
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Veterans Health Administration
Health Services Research & Development Service

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APPENDIX A. SEARCH STRATEGIES

1. Search for current systematic reviews **Date Searched: 4/23/19**	
Source:	**Strategy:**
AHRQ	Search: opioid, opiate
CADTH	Search: opioid, opiate
NICE	Search: opioid use disorder and "acute pain"; opiate use disorder and "acute pain";
ECRI Institute	Search: opioid, opiate
VA Products: VATAP, PBM, HSR&D publications, VA ART Database	A. http://www.hsrd.research.va.gov/research/default.cfm B. http://www.research.va.gov/research_topics/ C. http://art.puget-sound.med.va.gov/default.cfm Search: opioid, opiate
Cochrane Database of Systematic Reviews	Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 17, 2019> Search Strategy: --- 1 (Opioid Related Disorder* or Opioid-Related Disorder* or Opioid Addiction* or Opioid Dependence* or Opioid Abuse* or Opiate Abuse* or Opiate Dependence* or Opiate Addiction* or Narcotic Dependence* or Narcotic Abuse* or Narcotic Addiction*).ti,ab. (21) 2 (buprenorphine or Probuphine or Sublocade).ti,ab. (24) 3 (Revia or Vivitrol or naltrexone).ti,ab. (14) 4 (Bunavail or Cassipa or Suboxone or Subutex or Zubsolv).ti,ab. (0) 5 (medicat* adj2 assist* adj2 (treat* or therap* or regimen* or interven* or program*)).ti,ab. (0) 6 ((opiate* or opioid* or narcotic*) adj2 (substitut* or replac* or maint*) adj2 (treatment* or therap* or regimen* or program* or interven*)).ti,ab. (5) 7 (Opiate Substitution Treatment* or Opioid Substitution Treatment* or Opiate Substitution Therap* or Opioid Substitution Therap* or Opiate Replacement Therap* or Opioid Replacement Therap* or Medication Assisted Treatment* or Medication Assisted Therap*).ti,ab. (4) 8 (Methadone or Biodone or Dolophine or Metadol or Metasedin or Symoron or Methadose or Methex or Phenadone or Physeptone or Phymet or Pinadone or Amidone or Methaddict).ti,ab. (27) 9 or/2-8 (48) 10 Acute Pain*.ti,ab. (49) 11 1 and 9 and 10 (0) **********

2. Systematic reviews currently under development (forthcoming reviews & protocols) **Date Searched: 4/23/19**	
Source:	**Strategy:**
PROSPERO (SR Registry)	Search: opioid, opiate
DoPHER (SR Protocols)	Search: opioid, opiate

3. Current Guidelines **Date Searched: 4/23/19**	
Source:	**Strategy:**
VA/DoD Clinical Practice Guidelines	Search: NA
Guidelines Trust	Search: opioid, opiate
Guideline Central	Search: opioid, opiate

4. Current Primary Literature **Date Searched:**	
Source:	**Strategy:**
MEDLINE	Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to April 22, 2019> Search Strategy: --- 1 exp Opioid-Related Disorders/ (24042) 2 (Opioid Related Disorder* or Opioid-Related Disorder* or Opioid Addiction* or Opioid Dependence* or Opioid Abuse* or Opiate Abuse* or Opiate Dependence* or Opiate Addiction* or Narcotic Dependence* or Narcotic Abuse* or Narcotic Addiction*).ti,ab. (6815) 3 1 or 2 (26883) 4 exp Opiate Substitution Treatment/ (2433) 5 exp Opioid-Related Disorders/dt, rh (9639) 6 exp Buprenorphine/ or (buprenorphine or Probuphine or Sublocade).ti,ab. (6795) 7 exp Naltrexone/ or (Revia or Vivitrol or naltrexone).ti,ab. (9567) 8 exp Buprenorphine, Naloxone Drug Combination/ or (Bunavail or Cassipa or Suboxone or Subutex or Zubsolv).ti,ab. (373) 9 (medicat* adj2 assist* adj2 (treat* or therap* or regimen* or interven* or program*)).ti,ab. (497) 10 ((opiate* or opioid* or narcotic*) adj2 (substitut* or replac* or maint*) adj2 (treatment* or therap* or regimen* or program* or interven*)).ti,ab. (1335) 11 (Opiate Substitution Treatment* or Opioid Substitution Treatment* or Opiate Substitution Therap* or Opioid Substitution Therap* or Opiate Replacement Therap* or Opioid Replacement Therap* or Medication Assisted Treatment* or Medication Assisted Therap*).ti,ab. (1270) 12 exp Methadone/ (11934) 13 (Methadone or Biodone or Dolophine or Metadol or Metasedin or Symoron or Methadose or Methex or Phenadone or Physeptone or Phymet or Pinadone or Amidone or Methaddict).ti,ab. (12911) 14 or/4-13 (32994) 15 exp Acute Pain/ (1721) 16 Acute Pain*.ti,ab. (7766) 17 15 or 16 (8710) 18 3 and 14 and 17 (46) 19 limit 18 to english language (42) **********
PsycINFO	Database: PsycINFO <1806 to April Week 3 2019> Search Strategy: --- 1 exp Drug Abuse/ or exp Drug Dependency/ or exp Opiates/ or exp Drug Addiction/ (123405) 2 (Opioid Related Disorder* or Opioid-Related Disorder* or Opioid Addiction* or Opioid Dependence* or Opioid Abuse* or Opiate Abuse* or Opiate Dependence* or

	Opiate Addiction* or Narcotic Dependence* or Narcotic Abuse* or Narcotic Addiction*).ti,ab. (3956) 3 1 or 2 (123779) 4 exp Drug Therapy/ (137456) 5 exp Methadone Maintenance/ (3515) 6 exp Buprenorphine/ or (buprenorphine or Probuphine or Sublocade).ti,ab. (2543) 7 exp Naltrexone/ or (Revia or Vivitrol or naltrexone).ti,ab. (3314) 8 exp Buprenorphine, Naloxone Drug Combination/ or (Bunavail or Cassipa or Suboxone or Subutex or Zubsolv).ti,ab. (105) 9 (medicat* adj2 assist* adj2 (treat* or therap* or regimen* or interven* or program*)).ti,ab. (295) 10 ((opiate* or opioid* or narcotic*) adj2 (substitut* or replac* or maint*) adj2 (treatment* or therap* or regimen* or program* or interven*)).ti,ab. (847) 11 (Opiate Substitution Treatment* or Opioid Substitution Treatment* or Opiate Substitution Therap* or Opioid Substitution Therap* or Opiate Replacement Therap* or Opioid Replacement Therap* or Medication Assisted Treatment* or Medication Assisted Therap*).ti,ab. (794) 12 exp Methadone/ (1773) 13 (Methadone or Biodone or Dolophine or Metadol or Metasedin or Symoron or Methadose or Methex or Phenadone or Physeptone or Phymet or Pinadone or Amidone or Methaddict).ti,ab. (7068) 14 or/4-13 (145089) 15 Acute Pain*.ti,ab. (1707) 16 3 and 14 and 15 (85) 17 limit 16 to english language (85) **********
CCRCT	Database: EBM Reviews - Cochrane Central Register of Controlled Trials <March 2019> Search Strategy: --- 1 exp Opioid-Related Disorders/ (1694) 2 (Opioid Related Disorder* or Opioid-Related Disorder* or Opioid Addiction* or Opioid Dependence* or Opioid Abuse* or Opiate Abuse* or Opiate Dependence* or Opiate Addiction* or Narcotic Dependence* or Narcotic Abuse* or Narcotic Addiction*).ti,ab. (1302) 3 1 or 2 (2536) 4 exp Opiate Substitution Treatment/ (263) 5 exp Opioid-Related Disorders/dt, rh (4) 6 exp Buprenorphine/ or (buprenorphine or Probuphine or Sublocade).ti,ab. (2178) 7 exp Naltrexone/ or (Revia or Vivitrol or naltrexone).ti,ab. (2173) 8 exp Buprenorphine, Naloxone Drug Combination/ or (Bunavail or Cassipa or Suboxone or Subutex or Zubsolv).ti,ab. (76) 9 (medicat* adj2 assist* adj2 (treat* or therap* or regimen* or interven* or program*)).ti,ab. (93) 10 ((opiate* or opioid* or narcotic*) adj2 (substitut* or replac* or maint*) adj2 (treatment* or therap* or regimen* or program* or interven*)).ti,ab. (318) 11 (Opiate Substitution Treatment* or Opioid Substitution Treatment* or Opiate Substitution Therap* or Opioid Substitution Therap* or Opiate Replacement Therap* or Opioid Replacement Therap* or Medication Assisted Treatment* or Medication Assisted Therap*).ti,ab. (188) 12 exp Methadone/ (1138) 13 (Methadone or Biodone or Dolophine or Metadol or Metasedin or Symoron or Methadose or Methex or Phenadone or Physeptone or Phymet or Pinadone or Amidone or Methaddict).ti,ab. (2522) 14 or/4-13 (6437)

	15 exp Acute Pain/ (462) 16 Acute Pain*.ti,ab. (2289) 17 15 or 16 (2546) 18 3 and 14 and 17 (5) 19 limit 18 to english language (2) **********
CINAHL	Database: CINAHL Plus with Full Text via EBSCOhost Search Strategy: --- S1 (MH "Analgesics, Opioid+") (30707) S2 (MH "Substance Abuse+") (59260) S3 (MH "Substance Dependence+") (82500) S4 TI ((Opioid Related Disorder* or Opioid-Related Disorder* or Opioid Addiction* or Opioid Dependence* or Opioid Abuse* or Opiate Abuse* or Opiate Dependence* or Opiate Addiction* or Narcotic Dependence* or Narcotic Abuse* or Narcotic Addiction*)) OR AB ((Opioid Related Disorder* or Opioid-Related Disorder* or Opioid Addiction* or Opioid Dependence* or Opioid Abuse* or Opiate Abuse* or Opiate Dependence* or Opiate Addiction* or Narcotic Dependence* or Narcotic Abuse* or Narcotic Addiction*)) (3021) S5 S1 OR S2 OR S3 OR S4 (143323) S6 (MH "Drug Therapy+") (149586) S7 (MH "Methadone") (4360) S8 (MH "Buprenorphine") (2680) S9 (MH "Naltrexone") (1677) S10 TI ((buprenorphine or Probuphine or Sublocade or Revia or Vivitrol or naltrexone or Bunavail or Cassipa or Suboxone or Subutex or Zubsolv)) OR AB ((buprenorphine or Probuphine or Sublocade or Revia or Vivitrol or naltrexone or Bunavail or Cassipa or Suboxone or Subutex or Zubsolv)) (5277) S11 TI ((medicat* N2 assist* N2 (treat* or therap* or regimen* or interven* or program*))) OR AB ((medicat* N2 assist* N2 (treat* or therap* or regimen* or interven* or program*))) (529) S12 TI (((opiate* or opioid* or narcotic*) N2 (substitut* or replac* or maint*) N2 (treatment* or therap* or regimen* or program* or interven*))) OR AB (((opiate* or opioid* or narcotic*) N2 (substitut* or replac* or maint*) N2 (treatment* or therap* or regimen* or program* or interven*))) (915) S13 TI ((Opiate Substitution Treatment* or Opioid Substitution Treatment* or Opiate Substitution Therap* or Opioid Substitution Therap* or Opiate Replacement Therap* or Opioid Replacement Therap* or Medication Assisted Treatment* or Medication Assisted Therap*)) OR AB ((Opiate Substitution Treatment* or Opioid Substitution Treatment* or Opiate Substitution Therap* or Opioid Substitution Therap* or Opiate Replacement Therap* or Opioid Replacement Therap* or Medication Assisted Treatment* or Medication Assisted Therap*)) (969) S14 TI ((Methadone or Biodone or Dolophine or Metadol or Metasedin or Symoron or Methadose or Methex or Phenadone or Physeptone or Phymet or Pinadone or Amidone or Methaddict)) OR AB ((Methadone or Biodone or Dolophine or Metadol or Metasedin or Symoron or Methadose or Methex or Phenadone or Physeptone or Phymet or Pinadone or Amidone or Methaddict)) (4400) S15 S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 (159110) S16 (MH "Acute Pain (Saba CCC)") OR (MH "Acute Pain Control (Saba CCC)") (2) S17 TI Acute Pain* OR AB Acute Pain* (3202) S18 S16 OR S17 (3202) S19 S5 AND S15 AND S18 (202) S20 limit 19 to Academic Journals (162) S21 limit 20 to english language (158)

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5. Primary literature currently under development (forthcoming studies & protocols) **Date Searched: 4/23/19**	
Source:	**Strategy:**
Clinicaltrials.gov	Search: opioid and "acute pain"; opiate and “acute pain” Effect of Buprenorphine/Naloxone Continuation on Pain Control and **Opioid** Use

APPENDIX B. LIST OF EXCLUDED STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible timing, 6=Ineligible study design, 7=Ineligible publication type 8=Outdated or ineligible systematic review

#	Citation	Exclude reason
1	Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Annals of Internal Medicine. 2006;144(2):127-134.	E7
2	Anderson TA, Quaye ANA, Ward EN, Wilens TE, Hilliard PE, Brummett CM. To Stop or Not, That Is the Question: Acute Pain Management for the Patient on Chronic Buprenorphine. Anesthesiology. 2017;126(6):1180-1186.	E7
3	Bean HK, Gannon R. Treatment of acute pain in opioid tolerant patients. Connecticut Medicine. 2010;74(3):143-148.	E7
4	Book SW, Myrick H, Malcolm R, Strain EC. Buprenorphine for postoperative pain following general surgery in a buprenorphine-maintained patient. American Journal of Psychiatry. 2007;164(6):979.	E7
5	Broglio K, Matzo M. CE: Acute Pain Management for People with Opioid Use Disorder. American Journal of Nursing. 2018;118(10):30-38.	E7
6	CADTH. Research Gaps: Acute Pain Management: Non-Opioid Treatments (Pharmacologic and Non-Pharmacologic). 2018.	E7
7	Chapman C, Davis J, Donaldson GW, Naylor J, Winchester D. Postoperative pain trajectories in chronic pain patients undergoing surgery: The effects of chronic opioid pharmacotherapy on acute pain. Journal of Pain. 2011;12(12):1240-1246.	E1
8	Chua K-P, Brummett CM, Waljee JF. Opioid Prescribing Limits for Acute Pain: Potential Problems With Design and Implementation. JAMA: Journal of the American Medical Association. 2019;321(7):643-644.	E7
9	Compton P, McCaffery M. Treating acute pain in addicted patients. Nursing. 2001;31(1):17.	E7
10	De Pinto M, Cahana A. Medical management of acute pain in patients with chronic pain. Expert Review of Neurotherapeutics. 2012;12(11):1325-1338.	E7
11	Dever C. Treating Acute Pain in the Opiate-Dependent Patient. Journal of Trauma Nursing. 2017;24(5):292-299.	E7
12	Eyler EC. Chronic and acute pain and pain management for patients in methadone maintenance treatment. American Journal on Addictions. 2013;22(1):75-83.	E7
13	Gorman E, Warfield CA. The opioid-dependent patient with acute pain. Hospital Practice. 1987;22(11):113, 115, 117-120.	E7
14	Hay JL, White JM, Bochner F, Somogyi AA. Antinociceptive effects of high-dose remifentanil in male methadone-maintained patients. European Journal of Pain. 2008;12(7):926-933.	E1
15	Huxtable CA, Macintyre PE. An alternative way of managing acute pain in patients who are in buprenorphine opioid substitution therapy programs. European Journal of Anaesthesiology. 2013;30(11):717-718.	E7
16	Kraft L, Wiechula R, Conroy T. The effectiveness of acute pain management for opioid tolerant or opioid dependent patients: a systematic review protocol. JBI Database System Rev Implement Rep. 2015;13(9):120-135.	E7
17	Manfredi PL, Gonzales GR, Cheville AL, Kornick C, Payne R. Methadone analgesia in cancer pain patients on chronic methadone maintenance therapy. Journal of Pain and Symptom Management. 2001;21(2):169-174.	E1
18	Mehta V, Langford R. Acute Pain Management in Opioid Dependent Patients. Rev Pain. 2009;3(2):10-14.	E7

#	Citation	Exclude reason
19	Mehta V, Langford RM. Acute pain management for opioid dependent patients. Anaesthesia. 2006;61(3):269-276.	E7
20	Mercadante S, Ferrera P, Arcuri E, Mercadante S, Ferrera P, Arcuri E. The use of fentanyl buccal tablets as breakthrough medication in patients receiving chronic methadone therapy: an open label preliminary study. Supportive Care in Cancer. 2011;19(3):435-438.	E1
21	Mercadante S. Opioid titration in cancer pain: A critical review. European Journal of Pain. 2007;11(8):823-830.	E1
22	Nielsen RV, Fomsgaard JS, Siegel H, et al. Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: a randomized, blinded trial. Pain. 2017;158(3):463-470.	E1
23	Paschkis Z, Potter ML. CE: Acute Pain Management for Inpatients with Opioid Use Disorder. American Journal of Nursing. 2015;115(9):24-32; quiz 33, 46.	E7
24	Rapp SE, Ready LB, Nessly ML. Acute pain management in patients with prior opioid consumption: a case-controlled retrospective review. Pain. 1995;61(2):195-201.	E1
25	Schug SA. Acute pain management in the opioid-tolerant patient. Pain Manag. 2012;2(6):581-591.	E7
26	Shah S, Kapoor S, Durkin B. Analgesic management of acute pain in the opioid-tolerant patient. Current Opinion in Anaesthesiology. 2015;28(4):398-402.	E1
27	Streltzer J. Pain management in the opioid-dependent patient. Curr Psychiatry Rep. 2001;3(6):489-496.	E7
28	Stromer W, Michaeli K, Sandner-Kiesling A. Reply to: an alternative way of managing acute pain in patients who are in buprenorphine opioid substitution therapy programmes. European Journal of Anaesthesiology. 2013;30(11):718-719.	E7
29	Tauben D, Klein JW, Merrill JO, Gordon DB. Acute Pain Management in Patients with Opioid Use Disorder. NIH.	E7
30	Taveros MC, Chuang EJ. Pain management strategies for patients on methadone maintenance therapy: a systematic review of the literature. BMJ supportive & palliative care. 2017;7(4):383-389.	E1
31	Wilson JL, Poulin PA, Sikorski R, Nathan HJ, Taljaard M, Smyth C. Opioid use among same-day surgery patients: Prevalence, management and outcomes. Pain Research & Management. 2015;20(6):300-304.	E1

APPENDIX C. EVIDENCE TABLES

DATA ABSTRACTION OF INCLUDED OBSERVATIONAL STUDIES

Study and Patient Characteristics

Author, Year N	Study design Setting Duration	Type of MAT Type of condition	Population and comparator
Hansen, 2016[1] N = 51	Retrospective matched cohort study Tertiary care institution Avg. follow-up 27.2 months	Methadone or buprenorphine/naloxone Elective surgery	Cases: 17 patients taking either methadone or buprenorphine/naloxone for history of drug addiction Controls: 34 patients matched to cases based on procedure type, sex, diagnosis, age, and BMI without history of buprenorphine/naloxone
Harrington, 2010[2] N = 1	Case study Hospital 6 days	Buprenorphine/naltrexone Emergent condition	Case: 30-year-old male with brain, liver, spleen, renal, elbow, and rib injuries from a motorcycle accident; had history of opiate abuse; on maintenance buprenorphine/naloxone (2 mg/.5 mg) No comparator
Hines, 2008[3] N = 134	Retrospective matched cohort study Hospital Cases: Median 7 days; Controls: Median 4 days	Methadone Surgical and emergent conditions	Cases: 67 patients on MMT, aged 18+, without a chronic pain condition Controls: 67 non-MMT patients matched by medical/surgical condition, gender, age, and without chronic pain or opioid use prior to admission
McCormick, 2013[4] N = 1	Case study Emergency Department 2 months	Buprenorphine/naltrexone Emergent conditions, then surgical	Case: 50-year-old man with history of McArdle's disease presented at ED with severe bilateral anterior thigh pain (rated as 10 out of 10), taking buprenorphine/naloxone for chronic pain and opioid dependence No comparator
Sartain, 2002[5] N = 1	Case study Hospital 34 days	Methadone then slow-release morphine Emergent conditions, then surgical	Case: 25-year-old man presented with fractures to his face, left femur, and upper limbs; had history of IV opioid, diazepam, and cannabis use; on a methadone treatment program until 7 weeks before hospital admission and switched to slow-release morphine 100mg twice a day No comparator
Tucker, 1990[6] N = 3	Case study Hospital	Methadone Emergent conditions, then	2 of the 3 cases were not on MAT. Case: 52-year-old man admitted for lower abdominal pain, cramping, nausea,

Author, Year N	Study design Setting Duration	Type of MAT Type of condition	Population and comparator
		surgical	and fever for 5 days; received surgery on his appendix; had history of IV heroin abuse; on a methadone maintenance program
Kornfeld, 2010[7] N = 5	Case series Private practice patients receiving surgery in a hospital 2-9 days	Buprenorphine Surgical	All patients were stabilized on sublingual buprenorphine for chronic musculoskeletal pain for >1 yr before major surgery. 1 patient (not specified) had nephrolithiasis. Several had remote histories of opioid dependence. Case 1: 60-year-old man with hepatic flexure carcinoma, underwent right colectomy and cholecystectomy Cases 2 and 3: 43-year-old man underwent a right total knee replacement and 2 yrs later underwent a left total knee replacement Case 4: 60-year-old man admitted for surgery with a small bowel stricture with peritoneal mass Cases 5 and 6: 42-year-old woman with ductal carcinoma in situ of the breast underwent bilateral subcutaneous mastectomy with reconstruction and implantation of tissue expanders. 8 months later, this patient underwent removal of bilateral tissue expanders with subsequent placement of implants. Case 7: 58-year-old man with history of back pain and chronic pain syndrome underwent surgical removal of 2 X-stop spacer devices from his lumbar spine and lumbar decompression
MacIntyre, 2013[8] N = 51	Retrospective cohort study Postsurgical patients seen by acute pain service of tertiary hospital 24 hours post-surgery	Buprenorphine opioid substitution therapy, methadone opioid substitution therapy Surgical	Patients who required IV patient-controlled analgesia without concurrent continuous regional or epidural analgesia or local anesthetic wound infusions. 29 (57%) were taking methadone, and 22 (43%) were taking buprenorphine. Similar ages in both groups, but more male patients on BOST. 17 patients across both groups underwent orthopedic surgery, 14 abdominal surgery, 8 orofacial surgery, 7 thoracic surgery, 5 other surgeries. 13 MOST and 6 BOST patients used benzodiazepines preoperatively, which were continued after surgery in all but one patient in each group.

Abbreviations: BMI = Body Mass Index; BOST = buprenorphine opioid substitution therapy; IV = intravenous; mg = milligram; MMT = methadone maintenance therapy; MOST = methadone opioid substitution therapy; yrs = years

Intervention Characteristics

Author, Year N	Intervention	Outcomes
Hansen, 2016[1] N = 51	Perioperative pain management was similar between cases and controls in terms of: · Regional block with 48 hrs of postoperative infusion (35% vs 50%) · Preoperative anesthesia adjunct medications (24% vs 18%) · Pain regimen (35% vs 15% IV patient-controlled anesthesia; 65% vs 76% intermittent IV analgesia; 0% vs 9% no IV analgesia) Pain management was different between cases and controls in terms of: · Mean morphine-equivalent dose of oral narcotics prescribed at time of discharge in mg [SD]: (793.5 [577.2] vs 109.2 [36]; *P* < .001) · Mean change in morphine-equivalent dose of oral narcotics prescribed at time of discharge in mg [SD]: (-203.5 [804] vs 84.3 [53]; *P* = .044) Referrals to pain service for intractable pain were also significantly higher in case vs control: · 9 patients in case vs 1 in control (*P* < .05)	6 weeks post-surgery, cases and controls were similar in terms of: · Length of hospital stay (days to discharge) (3.4 days vs 3.6 days) · Mean Knee Society Score pain (66.5 vs 74) · Knee Society Score function (49.4 vs 60.8) · Mean knee range of motion (98.1 vs 98.3) · Harris Hip Score (68.4 vs 77.1) · Mental Component Score-12 (47.6 vs 51.4) · Physical Component Score-12 (35.0 vs 33.2) · Mean pain score (3.9 vs 3.25) No significant differences in same measures between cases and controls at 1 year, except for knee ROM which was significantly worse (77.5 vs 109.4, *P* = .032) in MAT vs no MAT group. · Mean Knee Society Score pain (87.6 vs 84.4) · Knee Society Score function (61 vs 80.9) · Harris Hip Score (89.2 vs 85.3) · Mental Component Score -12 (47.1 vs 52.9) · Physical Component Score -12 (35.4 vs 38.5) · Mean pain score (2.8 vs 2.1) Postoperative complications were not statistically different between groups.
Harrington, 2010[2] N = 1	Patient agitation was initially managed with haloperidol and lorazepam. Pain was treated with high dose full agonist opiates, which were decreased on postinjury Day 4. Subsequent tapering of narcotics not successful, and patient received 50mg of morphine, 37mg of haloperidol, 8mg of lorazepam, and 17mg of midazolam on postinjury Day 6. Patient likely had delirium due to TBI and psychoactive medications. Mental status and agitation improved after discontinuing buprenorphine.	Patient discharged with 120mg/d of oxycodone.

Hines, 2008[3] N = 134	MMT patients and others did not differ in relation to median morphine dose received (5.07 vs 6.67mg); around 40% of both groups were administered a non-opioid analgesic. A small proportion of both groups received some non-drug pain relief (8% vs 5%). The MMT group received a higher median dosage of benzodiazepines (5.00 vs 2.67mg). MMT patients were on an average of 82.4mg (range 22.5-200mg) of methadone at admission. 12% had methadone increased.	Significant differences between MMT patients and controls: · MMT had higher median number of days in hospital (7 vs 4, *P* < .01) although this was not significant once obstetric cases were excluded (6 vs 5). · Behavioral problems reported was higher in MMT: 39 vs 5. · MMT less likely to receive a hospital discharge (79% vs 97%, *P* < .01) · MMT more likely to be discharged against advice (14% vs 2%, *P* < .01) · MMT more likely to be transferred to another hospital (8% vs 2%, *P* < .01) MMT patients and controls were similar in terms of: · Average number of pain reports per day (1 vs 1) · Drug-seeking behaviors (10% vs 6%).
McCormick, 2013[4] N = 1	Patient was given a total of 12mg IV hydromorphone over 8 hrs (minimal relief), then PCA with hydromorphone at 0.5mg as needed with 15-min lock-out. After patient was taken for emergent bilateral fasciotomies, the hydromorphone PCA increased to 0.8mg as needed with 15-min lock-out and a basal rate of 0.5mg/hr 2 days after surgery, he was transitioned to oxycodone and hydrocodone/acetaminophen.	Reported a 3/10 pain intensity 2 days after surgery. He was discharged with a prescription for hydrocodone/acetaminophen. 2 months later, he restarted suboxone and a buprenorphine transdermal patch.
Sartain, 2002[5] N = 1	After surgery, patient received IV morphine 115mg over first 8 hrs with paracetamol 4g/d; commenced IV PCA morphine with 2mg boluses, 5-min lock-out, and 2mg/hr as a background infusion. On Day 2, naproxen 500mg bd with MS Contin 100mg bd + 310 mg morphine by PCA was added in the next 24 hrs due to severe pain; received PCA mixture and ketamine at same dosage as morphine. On Days 4-6, he received reduced morphine 241 mg/d. Further surgery on Days 6 and 9 increased pain and morphine dosage. On Day 10, he received 509mg of IV morphine, 769mg of ketamine, oral paracetamol, naproxen, and 100mg of oral morphine in 24 hrs Morphine and ketamine were stopped, but paracetamol and naproxen + 200mg oral methadone were continued. Methadone continued at 50mg four times a day for 2 days, then reduced to 30mg four times a day.	Patient discharged on Day 20, taking methadone 70mg/d. 2 weeks after discharge, he recommenced slow release morphine to control his opioid addiction.
Tucker, 1990[6] N = 3	Case 2: 24 hrs after surgery, he received morphine every 6 hrs. He then likely received 15mg every 4-6 hours for 3 days. On Day 5, he was switched to acetaminophen with codeine as needed and methadone 20mg/d.	Case 2: Discharged after 2 days after switching to acetaminophen with codeine as needed and methadone 20 mg/d.
Kornfeld, 2010[7] N = 5	Case 1: Epidural morphine with IV PCA morphine starting at 27mg/d, reduced to 6mg/d before discharge; sublingual buprenorphine was increased to 32mg/d during hospitalization. Given oral hydrocodone	Pain assessment at discharge: · Case 1: "Pain free" · Cases 2 and 3: "Excellent pain management" and

10mg for breakthrough pain at discharge. Length of stay: 9 days

Cases 2 and 3: Epidural morphine limited to single dose 0.2 mg in the recovery room; then maintained on bupivacaine for 48 hrs; given IV hydromorphone on POD 1-3 at an average of <1 mg/hr; added oral hydromorphone and oxycodone on POD 2 and 3; sublingual buprenorphine continued during hospital stay. Discharged on buprenorphine 16mg and oral hydromorphone for breakthrough pain. Length of stay: 4 days. In this patient's second surgery 2 years later, he received epidural hydromorphone at an average 7mg/d + epidural bupivacaine + epidural fentanyl as PCA averaging 70 micrograms/d for first 2 days then discontinued. On the day of surgery, he received IV morphine 5mg; after discontinuation, he was given short and long-acting opioids at low dosages; IV ketamine given during surgery, continued orally during POD 1-3 before discharge. Length of stay: 3 days

Case 4: "Full agonist opioids were used without difficulty at conventional doses." Example: fentanyl 150 micrograms given intraoperatively; hydromorphone 1mg used in the recovery room; epidural bupivacaine with hydromorphone 0.2mg/hr until POD 3. PCA IV hydromorphone 5-10mg/d used through POD 4. Discharged on sublingual buprenorphine at preoperative dose. Length of stay: 5 days

Cases 5 and 6: Patient was maintained on 2 mg of sublingual buprenorphine throughout hospitalization. Patient was treated with an Accufuser local anesthetic pump containing bupivacaine as a PCA. Postoperatively, she also had an IV PCA of hydromorphone 26mg/d, discontinued on POD 2. Needed oral hydromorphone (up to 96mg on POD 2) and IV hydromorphone (up to 16mg on POD 2). Pain scores were higher in Case 5, but she responded well to hydromorphone. Discharged on sublingual buprenorphine at the preoperative dose and on oral hydromorphone for breakthrough pain. Length of stay: 4 days. 8 months later, patient had bilateral expanders removed and implants inserted. Intraoperatively received fentanyl 350 micrograms. On day of surgery, received sublingual buprenorphine 4mg, IV hydromorphone 5.4mg, and oral hydromorphone 16mg. Pain was well controlled. Before discharge on POD 1, she received oral hydromorphone 6mg + sublingual buprenorphine 2mg as well as bupivacaine Accufuser. Length of stay: 2 days

Case 7: Intraoperatively received fentanyl 600 micrograms; in the recovery room, received additional IV fentanyl 200 micrograms + IV hydromorphone 4mg. After postoperative transfer and on POD 1, she

"Excellent analgesia"

- Case 4: "Good analgesia"
- Cases 5 and 6: "Pain fluctuates… responds to hydromorphone" & "Good pain control"
- Case 7: "Excellent pain control"

	received PCA IV hydromorphone average 20mg/d + sublingual buprenorphine 3mg/d. On POD 1, she received oral hydromorphone 28mg. Discharged on POD 2 with a reduced need for hydromorphone for breakthrough pain. Pain control was excellent. Length of stay: 3 days	
MacIntyre, 2013[8] N = 51	Use of MAT: Buprenorphine patients received a preoperative mean dose of 13.7mg. 63.6% received a dose on day of surgery and 50% received a dose on the day after surgery. Methadone patients received a preoperative mean dose of 78.9, 79.3% received a dose on day of surgery; and 75.8% on the day after surgery. Intraoperatively: Mean total morphine equivalent dosages given intraoperatively was small: in 21 of the 51 patients, the morphine equivalent dose was <25mg (range 2.5-250mg). 12 received ketamine (range 10-200mg), 6 received clonidine (range 30-165mg). 1 patient on BOST received remifentanil. Postoperatively: All patients received regular paracetamol with varying doses of non-steroidal anti-inflammatory drug or continuous ketamine infusion (4-8mg/hr). 17.2% buprenorphine and 13.6% methadone patients received tramadol.	Patients who were not given MAT on day after surgery required PCA for longer and required longer period of supervision by acute pain service. There were no significant differences in PCA requirements between buprenorphine and methadone patient groups overall or between patients who did or did not receive MAT on the day after surgery. MAT patients who were not given their usual buprenorphine the day after surgery used significantly more PCA opioid (*P* = .02) compared with those who had received their dose. No significant differences in pain scores (rest and movement), incidence of nausea or vomiting requiring treatment, or sedation between buprenorphine and methadone patient groups overall or between those patients within each group who had and had not received methadone/buprenorphine the day after surgery.

Abbreviations: d = day; GT = gastronomic tube; hr = hour; IV = intravenous; mg = milligram; MMT = methadone maintenance therapy; NS = numeric scale; PCA = patient-controlled analgesia; POD = post-operative day; SD = standard deviation

QUESTIONS FOR QUALITY ASSESSMENT OF INCLUDED COHORT STUDIES

Selection bias	· Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? · Do start of follow-up and start of intervention coincide for most participants? · Were adjustment techniques used that are likely to correct for the presence of selection biases?
Bias in classification of interventions	· Were intervention groups clearly defined? · Was the information used to define intervention groups recorded at the start of the intervention? · Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?
Bias due to departures from intended interventions	· Were there deviations from the intended intervention beyond what would be expected in usual practice? · Were important co-interventions balanced across intervention groups? · Was the intervention implemented successfully for most participants? · Did study participants adhere to the assigned intervention regimen?
Bias due to measurement of outcomes	· Could the outcome measure have been influenced by knowledge of the intervention received? · Were outcome assessors aware of the intervention received by study participants? · Were the methods of outcome assessment comparable across intervention groups? · Were any systematic errors in measurement of the outcome related to intervention received?
Bias due to confounding	· Is there potential for confounding of the effect of intervention in this study? · Did the authors use an appropriate analysis method that controlled for all the important confounding domains? · Did the authors control for any post-intervention variables that could have been affected by the intervention?
Bias due to missing data/unreported data	· Were outcome data available for all or nearly all participants? · Were participants excluded due to missing data on intervention status? · Were participants excluded due to missing data on other variables needed for the analysis? · Were results likely to be selected and reported based on results from multiple analyses, multiple outcome measurements or different subgroups?

QUALITY ASSESSMENT OF INCLUDED COHORT STUDIES

Author, Year	Selection bias (low, unclear, high)	Bias in classification of interventions (low, unclear, high)	Bias due to departures from intended interventions (low, unclear, high)	Bias due to measurement of outcomes (low, unclear, high)	Bias due to confounding (low, unclear, high)	Bias due to missing data/unreported data (low, unclear, high)	Overall
Hansen, 2016[1]	Unclear Case selection based on retrospective chart review for patients receiving surgery in a given time period. Matched controls selected 2:1 to be similar to cases on procedure type, sex, diagnosis, age, and BMI, although there were other measures collected that were not controlled for (smoking, other medications).	High Unclear whether authors continued using MAT, what dosage, *etc*, throughout intervention period.	Unclear It is unclear what their intended strategy was, so we cannot assess if it was adhered to.	Unclear No discussion of assessor blinding. Validated measures used in the same way in both groups. Some measures were collected prospectively and some were retrospectively.	High Cases and controls differed in terms of Short Form Health Survey-Mental Health component score, percentage of smokers, and percentage taking antipsychotics.	Low No indication of missing data.	High Most serious issue is that there is no justification for why MAT usage was lowered among cases as well as the potential for confounding.
Hines, 2008[3]	Unclear Cases selected based on retrospective chart review in a given time period. Matched controls matched based on age, gender, medical condition although groups were not equal in terms of age. Also not clear if selection of "first" records for controls were first in terms of alphabet, year, *etc*.	High Authors comment that MAT was increased in some patients, but no explanation for why.	Unclear It is unclear what their intended strategy was, so we cannot assess if it was adhered to.	High Medical record data. Information on drug dosage probably reliable, but "pain reports" were just staff noting how often a patient mentioned that word.	High Methadone pts were younger and heavier smokers.	Low All patients included in outcomes table, although not clear what post-discharge outcomes were.	High Major issues in impact of methadone increase/maintenance/decrease on patient outcomes, poorly measured outcomes including an inability to tell if pain was effectively managed.
MacIntyre, 2013[8]	Unclear Patients selected retrospectively. Likely included all patients on	High Lack of information on why they	Unclear It is unclear what their intended strategy was, so	High No discussion of assessor blinding. Tool for pain scores	High Buprenorphine and methadone pts were different in terms of	Low All patients in outcomes table, analyses were	High Most serious issue is differences between groups at

Author, Year	Selection bias (low, unclear, high)	Bias in classification of interventions (low, unclear, high)	Bias due to departures from intended interventions (low, unclear, high)	Bias due to measurement of outcomes (low, unclear, high)	Bias due to confounding (low, unclear, high)	Bias due to missing data/unreported data (low, unclear, high)	Overall
	methadone or buprenorphine receiving surgery during that time period.	decided to continue MOST or BOST.	we cannot assess if it was adhered to.	not described but presumably this is on a scale.	cannabis and benzodiazepine use (higher in methadone group) and alcohol use (higher in buprenorphine group)	justified.	baseline in terms of use of cannabis, benzodiazepine, and alcohol.

Abbreviations: BMI = Body Mass Index; BOST = buprenorphine opioid substitution therapy; MAT = medication-assisted therapy; MOST = methadone opioid substitution therapy; pts = patients

QUESTIONS FOR ASSESSING QUALITY OF REPORTING FOR INCLUDED CASE SERIES AND STUDIES

Reporting of participant selection	Was the case (*ie*, OUD status, how diagnosed, how long they have had the diagnosis, type and duration of MAT treatment, lifestyle factors, comorbidities) described in sufficient detail?
Reporting of intervention classification	Was the intervention described in sufficient detail (*ie*, drug, dose, duration, any changes, and justification)?
Reporting of outcome measurement	Were outcomes described in sufficient detail, assessed by both patients and clinicians, and measured using a validated tool?
Reporting of confounding	Were potential confounders described in sufficient detail (*ie*, concomitant medications and health issues that could affect outcomes)?
Statistical analyses?	Were statistical analyses used in assessment of outcomes?
No missing data/unreported data	Is there any indication important data is missing or incomplete?

ASSESSMENT OF QUALITY OF REPORTING FOR INCLUDED CASE SERIES AND STUDIES

Author, Year	Reporting of participant selection (total, most, part, none)	Reporting of intervention classification (total, most, part, none)	Reporting of outcome measurement (total, most, part, none)	Reporting of confounding (total, most, part, none)	Statistical analyses? (Yes, no)	No missing or unreported data (total, most, part, none)	Overall
Harrington, 2010[2]	Partly MAT type and dosage were described, but not duration. History of OUD was not described.	Partly Initial "high dosage" opiate treatment and dosage were not described, and when buprenorphine was stopped, it was unclear if this was tapered or done all at once.	Partly Authors note that the patient complained of pain, but no validated measurements were used by physician or patient to assess pain or any other outcomes.	None Agitation managed with haloperidol and lorazepam, but initial dosage not described.	No	Most No information on follow-up after patient was discharged.	Partly reported Not enough information on patient OUD history, details on treatment approach, pain not measured.
McCormick, 2013[4]	Partly MAT type and McArdle's disease complications described, but not MAT dosage or duration of OUD.	Partly Not clear if/when buprenorphine was discontinued and what patient received during surgery.	Partly Case study reports some pain scores on 0-10 scale, but not consistently. No other measured outcomes.	Mostly Complications of McArdle's disease and how it affected treatment were well described.	No	Mostly, although information on post-discharge follow-up was limited.	Partly reported Not enough information on patient OUD history or medication, if/when buprenorphine was discontinued, or how pain was managed during surgery.
Sartain, 2002[5]	Partly MAT type described but not what chronic pain was due to.	Mostly Medication changes, dosages, and changes well described, not clear whether anything changed during surgeries.	Partly Pain described as "severe" on a verbal rating score, but not clear what the scale's potential ratings were.	Partly Medications presumably controlled in inpatient setting, not clear what other health conditions could be causing outcomes	No	Mostly, although limited information after discharge.	Partly reported Not enough information on duration of MAT treatment or what was causing chronic pain condition, as this could have affected outcomes.

Author, Year	Reporting of participant selection (total, most, part, none)	Reporting of intervention classification (total, most, part, none)	Reporting of outcome measurement (total, most, part, none)	Reporting of confounding (total, most, part, none)	Statistical analyses? (Yes, no)	No missing or unreported data (total, most, part, none)	Overall
Tucker, 1990[6]	Partly MAT type described but not duration or dose. Cause of emergent condition described.	Partly Authors give some details on treatment approach for case to including dose and duration of medications, but there are gaps such as what patient received before pain service was called in.	Partly Pain was not measured on a scale for case 2.	Partly Medications presumably controlled in inpatient setting, but it is not clear what other health conditions the patient might have.	No	Partly Not clear if pain was managed at discharge, but presumably it was.	Partly reported For case 2, not enough information was given on duration of MAT treatment and on what pain management the patient received. Outcomes were not measured on a scale.
Kornfeld, 2010[7]	Not reported Patients had been stabilized on sublingual buprenorphine for chronic musculoskeletal pain for at least 1 year and only some had remote history of opioid dependence. No information on OUD diagnosis, duration of diagnosis, dosage of buprenorphine, *etc*	Mostly Medication changes, dosages, and changes were well described.	Partly Pain was not measured on a scale and was provider-assessed.	Partly One patient was diabetic and obese, otherwise these were patients "in generally good health."	No	Mostly Not clear what happened after discharge	Partly reported Major issue is that it is unclear which patients had history of OUD and length of time, dosage of buprenorphine

Abbreviations: OUD = opioid use disorder; MAT = medication-assisted treatment

APPENDIX D. PEER REVIEW COMMENTS

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
001	1	Yes	None.
002	2	Yes	None.
003	3	Yes	None.
004	5	Yes	None.
Is there any indication of bias in our synthesis of the evidence?			
005	1	No	None.
006	2	No	None.
007	3	No	None.
008	5	No	None.
Are there any published or unpublished studies that we may have overlooked?			
009	1	No	None.
010	2	No	None.
011	3	No	None.
012	5	No	None.
Additional suggestions or comments can be provided below.			
013	1	Good executive summary. Good introduction to problem	Thank you.
014	1	Even though there is likely no literature, does type of surgery have implications for management (I think it is considered in the context of VA/DoD guidelines for post-op pain; should these be referenced?). Page 10 (or 5) mentions other guidelines but not VA/DoD post-op guideline. In this context, it might be informative to cite the published taxonomy of acute pain conditions. (Kent ML et al. The ACTTION-APS-AAPM Pain Taxonomy (AAAPT) multidimensional approach to classifying acute pain conditions. Journal of Pain, 2017;18:479-489. (Also published in Pain Medicine, 2017;18:947-958).	Yes, type of surgery has implications for the management of acute pain. We added details to the “findings” section to indicate what types of surgery patients were undergoing in each study, as it is helpful in interpreting findings. Unfortunately, no studies conducted subgroup analyses based on different types of surgery, so we do not know whether certain acute pain management strategies worked better or worse for patients undergoing certain types of surgery. We have also added the ACTTION-APS-AAPM Pain Taxonomy’s definition of acute pain to the “background” section.
015	1	The description of MAT and three medications is excellent; Table 1 is helpful summary	Thank you.
016	1	Good summary of considerations and differences for managing emergent pain versus planned surgeries.	Thank you.
017	1	How important is it to distinguish use of BUP versus BUP/Naloxone and consider their indications and plans for	It was our assumption that patients in these studies were taking buprenorphine or buprenorphine/naloxone as

Comment #	Reviewer #	Comment	Author Response
		acute pain management separately?	prescribed, which would mean the medications would act in the same way (i.e., the naloxone component was not activated for patients taking buprenorphine/naloxone). We clarified this in our report by adding the following statement in the findings: "for studies of buprenorphine, we first report whether the study evaluated buprenorphine alone or in co-formulation with naloxone, then subsequently refer to both medications as "buprenorphine," as it is our assumption that these drugs were taken as prescribed and thus act like buprenorphine alone."
018	1	At least a brief qualifying discussion of the presumed role of opioids for the management of acute pain would likely be helpful. Increasingly, prescribers are reevaluating the analgesic requirements for management of many acute pain conditions, such as dental procedures, factures other than long-bone fractures, and ambulatory and other surgeries.	We added a sentence to the first paragraph of the background indicating: "While professional societies are reconsidering the use of opioids to manage certain acute pain conditions – such as dental procedures and ambulatory surgeries – opioids remain a common treatment for many acute pain conditions."
019	1	How important is it to be clear that most acute pain conditions don't require any medical or other healthcare interventions? Most acute pain conditions resolve on their own (e.g., acute low back pain).	We added a sentence to the first paragraph of the background indicating: "Many cases of acute pain resolve on their own without any medical or other healthcare interventions, while others require use of pharmacological and/or nonpharmacological pain management interventions."
020	1	I'm not sure that listing some "ideal studies" on page 11 (or 6) is indicated before considering the review. This suggests some potential bias of the reviewers that could have influenced their search and review of the findings.	We disagree that pre-specifying which studies are most relevant to our study questions would introduce bias. We have, however, changed the terminology in this section from "ideal studies" to "most informative studies," to make it clear that these types of studies would theoretically offer the most relevant information to address our questions.
021	1	Some more explicit background on the evidence of effectiveness of non-opioid analgesics and co-analgesics and non-pharmacological approaches would also likely be informative and provide important context for the focus of this review. (Page 11 [or 6], line 21).	We have added a section describing the potential use of non-opioid and non-pharmacological management strategies to manage acute pain in patients on MAT to the "background" section: "Given the potential challenges of using opioids for acute pain in patients on MAT, clinicians may prefer to optimize non-opioid management strategies (e.g. non-steroidal anti-inflammatory drugs, benzodiazepines) or non-pharmacologic options (mindfulness and relaxation techniques, acupuncture, use of heating pads and ice packs). However, opioids may still be considered the best option in cases of severe acute pain."
022	1	What is the domain of "acute pain management strategies" being considered? The eligibility criteria are not clear	We added our definition of acute pain to the inclusion criteria. We also replaced "non-opioid adjunctive" with "non-opioid and

Comment #	Reviewer #	Comment	Author Response
		regarding these issues; the use of "etc" is concerning. Why the term "adjuvant" therapies in this context?	non-pharmacological therapies."
023	1	Although there is reference to an interest in non-opioid and nonpharmacological approaches, it did not appear that the search strategy included this focus. If not, why not? And, if not, references to this broader interest should be deleted and it should be clear that the aims were limited to examining use of opioid therapy and "adjuvant medications" for the management of acute pain.	We were interested in any type of acute pain management strategy. Our search strategy was based on our population of interest (patients with opioid use disorder, taking some form of MAT, with acute pain) and therefore would have captured any type of acute pain management. Our description of our search erroneously included *opioids* as a search term, which we have corrected to *opioid use disorder* instead.
024	1	Outcomes: "Pain relief" is recommended as a primary or secondary outcome in acute pain trials. Why wasn't this outcome included in the search and evaluation of the findings? (Cooper SA et al , Research design considerations for single-dose analgesic clinical trials in acute pain: IMMPACT recommendations. Pain, 2016;157:288-301)	We agree that pain relief is important and did include it as an outcome of interest. However, it is not our standard approach to limit by outcome in our search, as it can result in results that are overly exclusive.
025	1	What about other "patient characteristics" beyond the nature of acute pain and type of MAT, including comorbidities, history of SUD, overdose, suicide, and so forth?	We specifically mention MAT medication and type of acute pain as examples of relevant patient subgroups, but we would have included analyses of any patient subgroups that study authors conducted. Unfortunately, we did not identify any studies that conducted these types of analyses.
026	1	Overall, the approach is appropriate, other than the question about non-opioid strategies.	None.
027	1	How is "opioid requirements" defined, and what does it mean to say that an intervention "reduced opioid requirements?" The authors are encouraged to reconsider this kind of terminology, since it suggests a bias in favor of sole reliance on opioids in the acute pain management setting and a sense of a reliable, objective approach to measuring pain and pain relief.	Here and throughout the report, we changed the reference to "high opioid requirements" to "high doses of opioids" so we do not inadvertently suggest opioids are the only viable option to achieve pain relief.
028	2	Page 6, line 58: What does multiple MAT types mean?	This means we identified studies that examined more than 1 type of MAT (for ex, in MacIntyre 2013, some patients were taking methadone and some were taking buprenorphine). We added language to clarify that MAT types includes "buprenorphine/naloxone alone, methadone alone, and studies that looked at multiple MAT medications."
029	2	Page 7, line 12: ["than those that"] Who	Changed "that" to "who."
030	2	Page 7, line 15: ["receive 8-fold the dosage of opioids at discharge with similar outcomes"] Compared to?	Clarified that this is compared to those not taking MAT.
031	2	Page 7, line 18: ["non-MAT patients, MAT patients"] Would use person first language e.g. patients on MAT.	Changed "MAT patients" to "patients taking MAT" as appropriate.

Comment #	Reviewer #	Comment	Author Response
032	2	Page 7, line 25: [“cohort studies - especially emergent conditions – and“] These look like hyphens but should be dashes. Same on next page.	Changed to dashes.
033	2	Page 8, line 54/55: [“the naloxone component is not activated”] The naloxone component is eliminated by the first pass of the liver.	Clarified “the naloxone component is eliminated by the liver and therefore not activated.”
034	2	Page 8, line 58: [”with opioid receptors”] I.e. receptor affinity.	Added “ie, receptor affinity.”
035	2	Page 8, line 59/60: [“it may be difficult to achieve adequate pain control”] I’m struggling with this clause – “it may be difficult to achieve adequate pain control…” Reality may be a little more nuanced. It may be that being on BUP means higher dose IV opioids are needed in patients for whom anesthesiologists are trying to make unconscious and also have total analgesia. However, in the post-operative period, in my experience, buprenorphine is a great long acting opioid for many patients and they can still use short acting opioids on top of buprenorphine with good effect. As written, this sentence seems to imply that stopping buprenorphine may be the best way to go (b/c otherwise it may be difficult to achieve adequate analgesia…) when in fact, the data, as weak as they are, seems to suggest the opposite.	We re-wrote the section on how MAT medications work. We now say: “while it is an effective pain medication for many patients, there is at least a theoretical risk that use of buprenorphine will make pain control more challenging in cases of severe acute pain because higher doses of full agonist opioids may be required to displace buprenorphine from opioid receptors. However, it is unclear whether this theoretical risk is relevant to clinical practice.”
036	2	Page 9, line 4/5: [“patients can experience withdrawal symptoms”] Would say ‘typically experience withdrawal symptoms’ rather than can experience.	We re-wrote the section on how MAT medications work. This now says: “Methadone and buprenorphine help patients manage OUD by reducing opioid cravings and preventing withdrawal, which are both potent drivers of ongoing opioid use.”
037	2	Page 9, line 10/11: [“patients who do not want to use any form of an opioid”] Or are court ordered.	We re-wrote the section on how MAT medications work. This now says: “Extended-release naltrexone is the preferred MAT option for patients who would like to avoid taking any form of opioid or for whom methadone and buprenorphine are contraindicated.”
038	2	Page 9, line 14: [“over time may help prevent opioid cravings”] It doesn’t prevent cravings.	We re-wrote the section on how MAT medications work. The relevant sections now say: “Methadone and buprenorphine help patients manage OUD by reducing opioid cravings and preventing withdrawal, which are both potent drivers of ongoing opioid use.” And “Naltrexone works differently than methadone and buprenorphine to treat OUD – by blocking the effects of opioids, it helps reduce cravings and increase opioid abstinence.” .

Comment #	Reviewer #	Comment	Author Response
039	3	Thanks for the opportunity to review the VA review of acute pain management in persons with OUD on MAT. I was kind of surprised how little and how poor the available data is. Given the very limited lack of evidence and the timeliness of something our group here has accepted for publication (Dale et al., in press) I wanted to share it with you as it seems to provide some data that the authors may wish to consider. We are correcting the author questions this week.	We reviewed this article for potential inclusion. Unfortunately, because it looks at patients with untreated OUD, it does not meet our inclusion criteria.
040	5	Page 6, line 8: ["The ESP Coordinating Center (ESP CC) is responding to a request from VA's Health Services Research"] Possible make this past tense, and more clear that the evidence brief was what the request was for.	Here and in the introduction, we rephrased to say, "The ESP Coordinating Center (ESP CC) developed this evidence brief on acute pain management in patients with opioid use disorder (OUD) who are on medication-assisted treatment (MAT) in response to a request from VA's Health Services Research and Development Service (HSR&D)."
041	5	Page 6, line 13: ["recent guidelines that:"] that recommend:	Changed to "suggest that" since guidelines did not provide strong recommendations on treatment.
042	5	Page 6, line 27: ["We identified no studies of naltrexone. Studies of methadone and buprenorphine"] I think that this is unclear, should note that the naltrexone, etc is the MAT therapy in the background, and the rest of this paragraph is referring to acute pain management techniques, doses, etc.	We revised this to say, "We did not identify any studies conducted in VHA settings, or among Veterans or non-Veterans taking naltrexone for OUD."
043	5	Page 6, line 34: ["Cochrane Central Register of Controlled Trials (CCRT)."] I'm pretty sure that Cochrane change this to 'CENTRAL' several years ago.	Changed to CENTRAL.
044	5	Page 6, line 38/39: ["for opioid use disorder (OUD)."] Suggest adding the list of 3 meds used for this here.	Added "including methadone, buprenorphine/naloxone, and naltrexone" here.
045	5	Page 6, line 42: ["Clinicians may also have a tendency to under-treat pain in patients with OUD"] Do you have a citation for this statement?	We do not typically include citations in the executive summary. Citations supporting this statement are available in the full report, under "background."
046	5	Page 6, line 48: ["these 3 medications work to treat OUD,"] Manage? I don't think that we are ally treating OUD, just trying to contain it.	Changed to "manage."
047	5	Page 6, line 56/57: ["and MAT types"] As a pharmacist, I guess I would object to using the word 'types' – can you just say drugs or medications? Drug treatments	Here and throughout the report, changed "MAT types" to "MAT medications."
048	5	Page 7, line 9: ["rationale for different medications was lacking"] As in the summary above, I find it unclear whether you are referring to the MAT meds or acute pain meds here.	Changed to "rationale for administering different medications (including MAT, opioids, and non-opioid analgesia) was lacking."
049	5	Page 7, line 15: ["outcomes on pain"] Does this mean pain at	Clarified that both pain and hip/knee functionality was

Comment #	Reviewer #	Comment	Author Response
		one year, or just function at one year? This finding also makes me wonder if they were able to taper off these large doses of opioids?	measured at 1 year. Unfortunately, study authors do not report what the average dosage of opioids was like at 1 year, so we do not know if patients were tapered off these or not. We added a sentence to the "findings" section indicating "It was also unclear whether these high opioid doses were titrated down over time."
050	5	Page 7, line 37: ["the ideal use"] Appropriate? Best?	Changed to "best."
051	5	Page 7, line 39/40: ["outcomes such as risk of relapse and overdose"] Did any of these mention other forms of therapy, psychosocial interventions?	None of these studies addressed psychosocial or other types of therapeutic interventions.
052	5	Page 8, line 11: ["is responding to"] As above, the report represents the finished work so seems like this sentence should be re-framed.	Revised so this is in past tense.
053	5	Page 8, line 34: ["Because of the different ways these 3 medications work to treat OUD, patients taking these medications may require different management strategies to effectively treat acute pain. (Table 1)."] This sentence is just slightly awkward, maybe just simplify it.	Changed to "Patients taking these medications may require different management strategies to effectively treat acute pain, as these medications work in different ways to manage OUD."
054	5	Page 8, line 42/43: ["effects"] I don't think that effects is the right word. It can have unpredictable pharmacokinetics, which may affect the effects by building up in the body. But it doesn't have unpredictable effects on the Mu receptors.	Changed to "Methadone is a long-acting opioid medication whose use can result in serious adverse events."
055	5	Page 8, line 42/43: ["with"] after	Changed to "after."
056	5	Page 8, line 42/43: ["It can build up quickly and unexpectedly with dose adjustments and increase the risk of respiratory depression and overdose, particularly when it is used at the same time as other opioids."] This sentence too is a bit awkward and might be better to simplify or break it up.	Revised so this is now 2 sentences: "It can build up quickly and unexpectedly after dose adjustments. It can also increase the risk of respiratory depression and overdose, particularly when it is used at the same time as other opioids."
057	5	Page 8, line 42/43: ["Like other opioids, it can cause withdrawal symptoms if stopped abruptly"] Yes, but with a long half-life, it is probably less of a risk than with other opioids that are shorter acting.	Added "although this risk is lower with methadone than with shorter-acting opioids."
058	5	Page 8, line 47-57: ["Buprenorphine/naloxone is different than methadone and other opioids because it only partially activates the opioid receptor ("partial agonists"). For this reason, buprenorphine/naloxone is useful in treating OUD because it prevents opioid withdrawal symptoms and has a lower risk of overdose. Buprenorphine is co-formulated with naloxone in order to prevent abuse. Naloxone blocks opioid receptor activity	We re-wrote the section on how MAT medications work. We now start with a description of buprenorphine as a partial opioid agonist and its properties, then later discuss how it is typically formulated with naloxone

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		("opioid antagonist"). When buprenorphine/naloxone is taken as prescribed in a sublingual form (under the tongue), the naloxone component is not activated. However, if the medication is crushed and injected or snorted, naloxone is activated to block the effect of opioids and can therefore cause immediate withdrawal symptoms."] I suggest reversing the order of this – starting with the explanation that it is a combination product. Maybe start with buprenorphine is used to treat OUD, and that naloxone is added to the product to prevent abuse. Later on in this section it may be confusing to a reader that it partially activates but binds very tightly with the receptors.	
059	5	Page 8-9, line 57-6: ["Another important feature of buprenorphine/naloxone is how strongly the buprenorphine component bonds with opioid receptors. It has a stronger bond with the receptor than other opioids, so it may be difficult to achieve adequate pain control in patients taking buprenorphine/naloxone because the addition of other opioids (such as morphine or oxycodone) may not be as effective. Like opioids, patients can experience withdrawal symptoms if buprenorphine/naloxone is stopped abruptly."] I suggest simplifying by combining these sentences.	See comment above, this section has been re-ordered for clarity.
060	5	Page 8, line 59/60: ["achieve adequate pain control"] Might be good to add in acute, or some way to more clearly indicate that you mean treating pain on top of treating OUD.	Added "acute."
061	5	Page 9, line 4/5: ["experience withdrawal symptoms"] Above, you noed that this combo drug prevents withdrawal symptoms.	We re-wrote the section on how MAT medications work. We now discuss in the text that MAT medications can help prevent withdrawal symptoms from opioids but note in table 1 there is a risk that patients may experience these symptoms when their MAT is discontinued.
062	5	Page 9, line 14: ["The challenge with acute pain management in patients taking naltrexone is that is also blocks the analgesic effects of opioids. Therefore, until enough time has elapsed that naltrexone is no longer active in the body, opioid pain medications will not be effective. Using higher doses of opioids may be a way to overcome the effects of naltrexone, but there is a risk of overdose once naltrexone starts wearing off."] Alternative forms of treating pain may need to be used? Both drug and non-drug forms are potentials.	In the following paragraph, we discuss that non-opioid and non-pharmacological treatments are possible approaches towards managing acute pain.
063	5	Page 9, line 56/57: ["typical approach"] For both of these	We clarified that these are "possible approaches." We also

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		sentences it seem like a citation is needed. Where do these statements come from?	discuss the American Society of Addiction Medicine's 2015 guidelines in the next paragraph to clarify what guidelines suggest when managing acute pain in patients on MAT.
064	5	Page 10, line 7-9: ["For patients taking naltrexone, a typical approach is to stop naltrexone and use non-opioid pain treatments or higher doses of opioids until naltrexone effects wear off."] It seems like the use of non-pharm or non-opioid treatments is left out in these scenarios. I hear that IV Tylenol is quite effective, for example.	We have added examples of non-opioid (e.g., ketamine, benzodiazepines, non-steroidal anti-inflammatory drugs) and non-pharmacological (e.g., relaxation techniques, heating pads, aromatherapy) treatments for managing acute pain to the beginning of this paragraph, as these approaches are being considered for all patients on MAT.
065	5	Page 10, line 17: ["leading to disengagement from care (such as leaving a hospital or clinic against medical advice);"] Was this potential harm specifically identified a priori? It just seems a bit unusual to have this be exactly what the findings of some studies showed too. Might re-word this to say stopping OUD treatment? I'd think leaving AMA is a bit different, affects the current acute pain episode but potentially not the OUD treatment.	Deleted the clause that uncontrolled pain can lead to disengagement from care as this was indeed informed by our findings.
066	5	Page 10, line 22/23: In cases of ~~unexpected~~ acute pain	Changed to "unplanned." We believe it's important to leave this word in as it distinguishes between unplanned (i.e., emergency) acute pain and planned (i.e., surgical) acute pain, which may require different management strategies.
067	5	Page 11, line 5/6: ["emergent"] I'm sure the definition of this word includes emergency as it is unfolding, but it seems a bit odd here, and elsewhere in tis report. Can you just use emergency?	Replaced "emergent" with "emergency" here and throughout to report.
068	5	Page 11, line 48/49: ["with acute pain"] I see that acute was not pre-defined. Cancer pain, reported below, seems like it may not always be acute, or rarely is. It may be new pain, but less likely to only be expected to have a short duration.	We added our definition of acute pain to the inclusion criteria. We also agree that the Manfredi 2011 article does not meet inclusion criteria, because they did not exclusively examine patients with acute pain (some had acute pain and cancer-related pain, others just had cancer-related pain.) We have removed it from the report.
069	5	Page 11, line 53: ["non-opioid adjunctive therapies"] Did you search for these explicitly? Or was that not necessary as the search was based on the population only?	Our search was based on the population only.
070	5	Page 13, line 9: ["(CCRT)"] As above, the correct term is now CENTRAL.	Changed this to CENTRAL.
071	5	Page 15, line 13: ["1 examined those with cancer pain"] As above, is this really acute pain? The study report may have only covered an acute period, but is the pain expected to really resolve?	See comment #68 above. We have removed this study from the report.

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072	5	Page 15, line 38: ["MAT patients received 8 times the dose of opioids at discharge, which reflected a decrease from baseline for MAT patients and an increase from baseline for non-MAT patients."] I don't understand the second half of this sentence. Obviously, comparing OUD to non-OUD patients is not very useful, but still I'd rather understand what is going on here.	Revised to say: "MAT patients received 8 times the dose of opioids at discharge as non-MAT patients. This difference reflected a decrease in opioid dosage from baseline for MAT patients and an increase in dosage from baseline for non-MAT patients."
073	5	Page 15, line 48: ["discharge against medical advice."] Might note here that they did not report on follow-up, e.g. whether the patient went back to OUD treatment as an outpatient.	Added: "Authors also did not report any follow-up information on these patients, for example, whether they continued OUD treatment in outpatient settings."
074	5	Page 22, line 13: ["such as patients physical and mental health status"] Does this cover the comparison of OUD patients with non-OUD patients? Seems like maybe not quite clear – that is a huge limitation as the findings are apples and oranges.	Added: "This was especially problematic when the two groups being compared were so different (i.e., MAT vs non-MAT patients) that you would not expect to manage pain the same way, making it difficult to interpret data on the effects of different pain management strategies for each."
075	5	Page 22, line 22: ["underwent surgery."] Similarly the criteria used did no defined 'acute'.	We selected studies of sudden onset, time-limited pain and have clarified this definition in the eligibility criteria.
076	5	Page 22, line 33/34: Add that non-drug and non-opioid interventions need to be studied.	We added additional detail under gap #1 that more detailed information is needed on the "specific medication type (including MAT medications, other opioids, and non-opioid medications) …" to address this. Non-drug pain management strategies were outside the scope of this review.
077	5	Page 23, line 17: This review confirmed ~~there is~~ a lack of rigorous evidence	Deleted "there is."

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