Evidence Brief: Benefits and Harms of Long-term Opioid Dose Reduction or Discontinuation in Patients with Chronic Pain

Supplementary Materials

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Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service
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SEARCH STRATEGIES

1. Search for current systematic reviews **Date Searched: 3/15/19**	
Sources:	**Evidence:**
AHRQ	Search: opioid; opiate
CADTH	Search: opioid; opiate
NICE (NHS Evidence)	Search: long-term opioid; opioid tapering
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 March 13, 2019> Search Strategy: --- 1 ((opioid* or opiate* or codeine or clonidine or morphine or hydrocodone or oxycodone) adj3 (taper* or wean* or dose reduc* or reduc* dose or detox* or withdraw* or discontinuat* or cessation or tolerance or conversion or substitution or long-term)).mp. (101) 2 pain.mp. (4539) 3 1 and 2 (75) 4 limit 3 to yr="2017 -Current" (30) **********

2. Systematic reviews currently under development (forthcoming reviews & protocols) **Date Searched: 3/15/19**	
Sources:	**Evidence:**
PROSPERO (SR registry)	Search: long-term opioid; opioid tapering Relevant Results: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=50613 https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=43844
DoPHER (SR Protocols)	Search: opioid

3. Current Guidelines **Date Searched: 3/15/19**	
Sources:	**Evidence:**
VA/DoD Clinical Practice Guidelines	Search: N/A
Guideline Central	Search: opioid
PubMed: Guideline Search	(Guideline[Publication Type] OR (Clinical[All Fields] AND Guideline[Publication Type]) OR Practice Guideline[Publication Type]) AND (long-term[All Fields] AND ("analgesics, opioid"[Pharmacological Action] OR "analgesics, opioid"[MeSH

	Terms] OR ("analgesics"[All Fields] AND "opioid"[All Fields]) OR "opioid analgesics"[All Fields] OR "opioid"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]))

4. Current primary literature **Date Searched: 3/15/19**	
Sources:	**Search Strategy/ Evidence:**
MEDLINE	Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to March 14, 2019> Search Strategy: ---------- 1 ((opioid* or opiate* or codeine or clonidine or morphine or hydrocodone or oxycodone) adj3 (taper* or wean* or dose reduc* or reduc* dose or detox* or withdraw* or discontinuat* or cessation or tolerance or conversion or substitution or long-term)).mp. (13076) 2 exp Pain/ (370985) 3 pain.mp. (654023) 4 2 or 3 (730906) 5 1 and 4 (3778) 6 limit 5 to english language (3590) 7 limit 6 to yr="2017 -Current" (678) **********
PsycINFO	Database: PsycINFO <1806 to March Week 2 2019> Search Strategy: ---------- 1 ((opioid* or opiate* or codeine or clonidine or morphine or hydrocodone or oxycodone) adj3 (taper* or wean* or dose reduc* or reduc* dose or detox* or withdraw* or discontinuat* or cessation or tolerance or conversion or substitution or long-term)).mp. (4840) 2 exp Pain/ (54124) 3 pain.mp. (93334) 4 2 or 3 (103569) 5 1 and 4 (1152) 6 limit 5 to english language (1126) 7 limit 6 to yr="2017 -Current" (121) **********
CCRCT	Database: EBM Reviews - Cochrane Central Register of Controlled Trials <February 2019> Search Strategy: ---------- 1 ((opioid* or opiate* or codeine or clonidine or morphine or hydrocodone or oxycodone) adj3 (taper* or wean* or dose reduc* or reduc* dose or detox* or withdraw* or discontinuat* or cessation or tolerance or conversion or substitution or long-term)).mp. (1815) 2 exp Pain/ (44709) 3 pain.mp. (126301) 4 2 or 3 (133576) 5 1 and 4 (597) 6 limit 5 to english language (422) 7 limit 6 to yr="2017 -Current" (78) **********

EMBASE	Database: Embase <1974 to 2019 March 14> Search Strategy: --- 1 ((opioid* or opiate* or codeine or clonidine or morphine or hydrocodone or oxycodone) adj3 (taper* or wean* or dose reduc* or reduc* dose or detox* or withdraw* or discontinuat* or cessation or tolerance or conversion or substitution or long-term)).mp. (16162) 2 exp Pain/ (1192179) 3 pain.mp. (1142363) 4 2 or 3 (1443230) 5 1 and 4 (5497) 6 limit 5 to english language (5196) 7 limit 6 to yr="2017 -Current" (1062) **********

5. Primary literature currently under development (forthcoming studies & protocols) **Date Searched: 3/15/19**	
Sources:	**Search Strategy/ Evidence:**
Clinicaltrials.gov	Search: Opioid Cessation Relevant Results: *https://clinicaltrials.gov/ct2/results?cond=Opioid+Cessation&term=opioid&cntry=&state=&city=&dist=&Search=Search*

TABLE OF INCLUSION AND EXCLUSION CRITERIA

PICOS	Inclusion/exclusion criteria	Exclusion code
Population	**Include:** Adults prescribed long-term opioids (≥3 months) for chronic pain **Exclude:** patients receiving palliative care or treatment for cancer-related pain	E1
Intervention	**Include:** Dose reduction or discontinuation, voluntary or mandated **Exclude:** Pain intervention with no explicit opioid dose reduction or discontinuation component	E2
Comparator	**Include:** Any	E3
Outcome	**Include:** Pain severity, pain-related function, quality of life, opioid withdrawal symptoms, patient satisfaction, retention in primary care, healthcare utilization, substance use, opioid overdose, suicidal ideation and suicidal self-directed violence **Exclude:** studies that only report MEDD changes without other patient-level outcomes	E4
Setting	**Include:** Any	E5
Study Design	**Include:** Longitudinal comparative studies including pre-post or case-control design **Exclude:** Cross-sectional survey, case reports	E6
Publication type	**Include:** Studies **Exclude:** Commentary, abstract, narrative reviews, etc.	E7
Outdated or Non-prioritized SR	Older or non-prioritized systematic reviews	E8
Language	**Include:** English **Exclude:** Any other language	E9

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	Aboussouan A, Huffman K, Jimenez X. Sustained benefits of an interdisciplinary chronic pain rehabilitation program in women with chronic pelvic pain. Pain Medicine. 2018;19(4):894-895.	E7
2	Barrett D, Zaski A, Edlund MJ, Brintz C. Dialectical pain management skills group for adults on long-term opioid therapy: Feasibility and preliminary outcomes. Global Advances in Health and Medicine. 2018;7:246.	E2
3	Belkin M, Reinheimer HS, Levy J, Johnson B. Ameliorative response to detoxification, psychotherapy, and medical management in patients maintained on opioids for pain. American Journal on Addictions. 2017;26(7):738-743.	E1
4	Buckley FP, Sizemore WA, Charlton JE. Medication management in patients with chronic non-malignant pain. A review of the use of a drug withdrawal protocol. Pain. 1986;26(2):153-165.	E4
5	Buonora M, Perez HR, Heo M, Cunningham CO, Starrels JL. Race and Gender Are Associated with Opioid Dose Reduction Among Patients on Chronic Opioid Therapy. Pain Medicine. 2018;18:18.	E4
6	Buonora MJ, Starrels JL, Ning Y, Perez HR. Race and opioid dose are associated with tapering among patients on chronic opioid therapy. Journal of General Internal Medicine. 2017;32(2 Suppl 1):S296-S297.	E7
7	Burkenroad AD, Roth SL, Khalid L, Starrels JL. Opioid dose reduction outcomes in a resident teaching practice for patients with chronic pain. Journal of General Internal Medicine. 2018;33(2 Suppl 1):s271.	E7
8	Caraway D, Walker V, Becker L, Hinnenthal J. Successful Discontinuation of Systemic Opioids After Implantation of an Intrathecal Drug Delivery System. Neuromodulation. 2015;18(6):508-515; discussion 515-506.	E2
9	Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG. A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Medicine. 2003;4(4):340-351.	E2/E4
10	Crawley A, Murphy L, Regier L, McKee N. Tapering opioids using motivational interviewing. Canadian Family Physician. 2018;64(8):584-587.	E7
11	Darnall BD, Juurlink D, Kerns RD, et al. International Stakeholder Community of Pain Experts and Leaders Call for an Urgent Action on Forced Opioid Tapering. Pain Medicine. 2018;29:29.	E7
12	Darnall BD, Ziadni MS, Stieg RL. Voluntary Opioid Tapering-Reply. JAMA Internal Medicine. 2018;178(6):875.	E7
13	DiBenedetto DJ, Porter R, Estrada-Lyder MJ, et al. Opioid dose reduction does not worsen pain scores, perceived functional abilities or aberrant drug behaviors in patients on high-dose opioids. Pain Medicine. 2014;15(3):511, A165.	E7
14	Dowell D, Haegerich TM. Changing the Conversation About Opioid Tapering. Annals Of Internal Medicine. 2017;167(3):208-209.	E7
15	Dublin S, Von Korff M, Saunders K, et al. Impact of risk reduction initiatives on rates of opioid overdose. Pharmacoepidemiology and Drug Safety. 2017;26(Suppl 2):213.	E7

#	Citation	Exclude reason
16	Eccleston C, Fisher E, Thomas KH, et al. Interventions for the reduction of prescribed opioid use in chronic non-cancer pain. Cochrane Database of Systematic Reviews. 2017(11).	E8
17	Fishbain DA, Pulikal A. Does Opioid Tapering in Chronic Pain Patients Result in Improved Pain or Same Pain vs Increased Pain at Taper Completion? A Structured Evidence-Based Systematic Review. Pain Medicine. 2018;28.	E8
18	Garland EL, Manusov EG, Froeliger B, Kelly A, Williams JM, Howard MO. Mindfulness-oriented recovery enhancement for chronic pain and prescription opioid misuse: results from an early-stage randomized controlled trial. J Consult Clin Psychol. 2014;82(3):448-459.	E2
19	Gee L, Smith H, Ghulam-Jelani Z, et al. Spinal cord stimulation reduces opiate use in patients with chronic pain. Journal of Neurosurgery. 2018;128(4):9.	E2
20	Geller AS. Patient and public safety maximized by rapid opioid taper. JAMA Internal Medicine. 2017;177(6):895-896.	E7
21	Goodman MW, Guck TP, Teply RM. Dialing back opioids for chronic pain one conversation at a time. Journal of Family Practice. 2018;67(12):753-757.	E4
22	Gudin JA, Brennan MJ, Harris ED, Hurwitz PL, Dietze DT, Strader JD. Reduction of opioid use and improvement in chronic pain in opioid-experienced patients after topical analgesic treatment: an exploratory analysis. Postgraduate Medicine. 2018;130(1):42-51.	E2
23	Guildford BJ, Daly-Eichenhardt A, Hill B, Sanderson K, McCracken LM. Analgesic reduction during an interdisciplinary pain management programme: treatment effects and processes of change. British Journal of Pain. 2018;12(2):72-86.	E2
24	Hanson KA, Loftus EV, Jr., Harmsen WS, Diehl NN, Zinsmeister AR, Sandborn WJ. Clinical features and outcome of patients with inflammatory bowel disease who use narcotics: a case-control study. Inflammatory Bowel Diseases. 2009;15(5):772-777.	E2
25	Haroutounian S, Ratz Y, Ginosar Y, et al. The Effect of Medicinal Cannabis on Pain and Quality-of-Life Outcomes in Chronic Pain: A Prospective Open-label Study. Clinical Journal of Pain. 2016;32(12):1036-1043.	E1
26	Hassamal S, Haglund M, Wittnebel K, Danovitch I. A preoperative interdisciplinary biopsychosocial opioid reduction program in patients on chronic opioid analgesia prior to spine surgery: A preliminary report and case series. Scandinavian Journal of Pain. 2016;13:27-31.	E1
27	Henry SG, Paterniti DA, Feng B, et al. Patients' Experience With Opioid Tapering: A Conceptual Model With Recommendations for Clinicians. Journal of pain. 2019;20(2):181-191.	E4
28	Henry SG, Verba S, Feng B, Kravitz RL, Iosif AM, Paterniti D. A conceptual model of patients' experiences with opioid tapering. Journal of General Internal Medicine. 2018;33(2 Suppl 1):s89.	E7
29	Hooten WM, Mantilla CB, Sandroni P, Townsend CO. Associations between heat pain perception and opioid dose among patients with chronic pain undergoing opioid tapering. Pain Medicine. 2010;11(11):1587-1598.	E4
30	Huffman KL, Sweis GW, Gase A, Scheman J, Covington EC. Opioid use 12 months following interdisciplinary pain rehabilitation with weaning. Pain Medicine. 2013;14(12):1908-1917.	E1

#	Citation	Exclude reason
31	Husain JM, Larochelle M, Keosaian J, et al. Effects of discontinuing long-term opioid therapy in patients with chronic pain. Journal of General Internal Medicine. 2017;Conference: 40th annual meeting of the society of general internal medicine, SGIM. 2017. United states 32(2 Supplement 1):S175.	E7
32	Husain JM, LaRochelle M, Keosaian J, Xuan Z, Lasser KE, Liebschutz JM. Reasons for opioid discontinuation and unintended consequences following opioid discontinuation within the topcare trial. Pain Medicine. 2018.	E2
33	Jamison RN, Ross EL, Michna E, Chen LQ, Holcomb C, Wasan AD. Substance misuse treatment for high-risk chronic pain patients on opioid therapy: A randomized trial. Pain. 2010;150(3):390-400.	E2
34	Johnson N, Shields C, Alexander SC, et al. Opioid tapering in patients with chronic pain: A qualitative study of patient and provider experiences. Journal of General Internal Medicine. 2017;32(2 Suppl 1):S257-S258.	E4
35	Kapural L, Kapural M, Bensitel T, Sessler DI. Opioid-sparing effect of intravenous outpatient ketamine infusions appears short-lived in chronic-pain patients with high opioid requirements. Pain Physician. 2010;13(4):389-394.	E2
36	Kennedy LC, Binswanger IA, Mueller S, et al. Barriers and strategies for tapering long-term opioid medications: A qualitative study of primary care provider experiences. Journal of General Internal Medicine. 2017;32(2 Suppl 1):S129.	E4
37	Kennedy LC, Binswanger IA, Mueller SR, et al. "Those Conversations in My Experience Don't Go Well": A Qualitative Study of Primary Care Provider Experiences Tapering Long-term Opioid Medications. Pain Medicine. 2018;19(11):2201-2211.	E7
38	Kroening RJ, Oleson TD. Rapid narcotic detoxification in chronic pain patients treated with auricular electroacupuncture and naloxone. International Journal of the Addictions. 1985;20(9):1347-1360.	E4
39	Kumthekar A, Shull S, Lovejoy TI, Morasco BJ, Chang M, Barton J. Impact of hepatitis C treatment on pain intensity, prescription opioid use and arthritis. International Journal of Rheumatic Diseases. 2019.	E2
40	Lake AE, 3rd, Saper JR, Hamel RL. Comprehensive inpatient treatment of refractory chronic daily headache. Headache. 2009;49(4):555-562.	E4
41	Levine AB, Steven DA, Parrent AG, MacDougall KW. Successful Long-term Nerve Root Stimulation for Chronic Neuropathic Pain: A Real World, Single Center Canadian Experience. Pain Physician. 2017;20(2):95-106.	E4
42	Li H, Yang L, Guo Z, et al. Successful treatment of refractory cancer pain with morphine and ropivacaine: A case report. Medicine. 2017;96(22):e7052.	E6
43	Lovejoy T, Demidenko M, Morasco B, Meath T, Dobscha S. Suicidal ideation and behaviors following clinician-initiated prescription opioid discontinuation among long-term opioid users. Journal of pain. 2017;18(4 Suppl 1):S36.	E7
44	Lovejoy TI, Morasco BJ, Demidenko MI, Meath THA, Dobscha SK. Clinician Referrals for Non-opioid Pain Care Following Discontinuation of Long-term Opioid Therapy Differ Based on Reasons for Discontinuation. Journal of General Internal Medicine. 2018;33(Suppl 1):24-30.	E4
45	Lovejoy TI, Morasco BJ, Demidenko MI, Meath THA, Frank JW, Dobscha SK. Reasons for discontinuation of long-term opioid therapy in patients with and without substance use disorders. Pain. 2017;158(3):526-534.	E4

#	Citation	Exclude reason
46	Maani CV, DeSocio PA, Jansen RK, et al. Use of ultra rapid opioid detoxification in the treatment of US military burn casualties. Journal of Trauma. 2011;71(1 Suppl):S114-119.	E4
47	Maclaren JE, Gross RT, Sperry JA, Boggess JT. Impact of opioid use on outcomes of functional restoration. Clinical Journal of Pain. 2006;22(4):392-398.	E2
48	Manhapra A, Arias AJ, Ballantyne JC. The conundrum of opioid tapering in long-term opioid therapy for chronic pain: A commentary. Substance Abuse. 2017:1-10.	E7
49	Marchetti F, Coutaux A, Bellanger A, Magneux C, Bourgeois P, Mion G. Efficacy and safety of oral ketamine for the relief of intractable chronic pain: A retrospective 5-year study of 51 patients. European Journal of Pain. 2015;19(7):984-993.	E4
50	Matthias MS, Johnson NL, Shields CG, et al. "I'm Not Gonna Pull the Rug out From Under You": Patient-Provider Communication About Opioid Tapering. Journal of pain. 2017;18(11):1365-1373.	E4
51	McAnally H. Rationale for and approach to preoperative opioid weaning: a preoperative optimization protocol. Perioperative Medicine. 2017;6:19.	E7
52	Mehl-Madrona L, Mainguy B, Plummer J. Integration of Complementary and Alternative Medicine Therapies into Primary-Care Pain Management for Opiate Reduction in a Rural Setting. Journal of alternative and complementary medicine. 2016;22(8):621-626.	E2
53	Miller NS, Swiney T, Barkin RL. Effects of opioid prescription medication dependence and detoxification on pain perceptions and self-reports. American Journal of Therapeutics. 2006;13(5):436-444.	E1
54	Minegishi T, Frakt A. Reducing Long-term Opioid Use in the Veterans Health Administration. Journal of General Internal Medicine. 2018;33(6):781-782.	E7
55	Moss C, Bossano C, Patel S, Powell A, Chan Seay R, Borahay MA. Weaning From Long-term Opioid Therapy. Clinical Obstetrics & Gynecology. 2019;62(1):98-109.	E7
56	Murphy JL, Phillips KM, Rafie S. Sex differences between Veterans participating in interdisciplinary chronic pain rehabilitation. Journal of Rehabilitation Research and Development. 2016;53(1):83-94.	E2
57	Murphy L, Babaei-Rad R, Buna D, et al. Guidance on opioid tapering in the context of chronic pain: Evidence, practical advice and frequently asked questions. Canadian Pharmacists Journal. 2018;151(2):114-120.	E7
58	Naylor MR, Naud S, Keefe FJ, Helzer JE. Therapeutic Interactive Voice Response (TIVR) to reduce analgesic medication use for chronic pain management. Journal of pain. 2010;11(12):1410-1419.	E4
59	Nissen LM, Tett SE, Cramond T, Williams B, Smith MT. Opioid analgesic prescribing and use - an audit of analgesic prescribing by general practitioners and The Multidisciplinary Pain Centre at Royal Brisbane Hospital. British Journal of Clinical Pharmacology. 2001;52(6):693-698.	E4
60	Oldfield B, Edmond S, Cervone D, et al. Expanded taper options, including rotation to buprenorphine, within a multi-disciplinary pain clinic for patients on high-risk opioid regimens. Journal of General Internal Medicine. 2018;33(2 Suppl 1):784-785.	E4

#	Citation	Exclude reason
61	Oldfield BJ, Edens EL, Agnoli A, et al. Multimodal Treatment Options, Including Rotating to Buprenorphine, Within a Multidisciplinary Pain Clinic for Patients on Risky Opioid Regimens: A Quality Improvement Study. Pain Medicine. 2018;19(suppl_1):S38-S45.	E4
62	Opperman CP, Butler MM, Stroud AK, Sun MR. The effects on patient retention after opioid weaning in an internal medicine residency clinic. Journal of Opioid Management. 2018;14(2):117-123.	E4
63	Page J, Traver R, Patel S, Saliba C. Implementation of a Proactive Pilot Health Plan-Driven Opioid Tapering Program to Decrease Chronic Opioid Use for Conditions of the Back and Spine in a Medicaid Population. Journal Of Managed Care & Specialty Pharmacy. 2018;24(3):191-196.	E4
64	Pergolizzi J, Rosenblatt M, Mariano D, Colucci R. Clinical tips for managing withdrawal in opioid patients. Postgraduate Medicine. 2018;130(Suppl 1):40-41.	E7
65	Pergolizzi J, Rosenblatt M, Mariano D, LeQuang JA. Tapering opioids: Clinical strategies in light of CDC guidelines. Postgraduate Medicine. 2018;130(Suppl 1):39-40.	E7
66	Pergolizzi JV, Jr., Rosenblatt M, Mariano DJ, Bisney J. Tapering opioid therapy: clinical strategies. Pain Management. 2018;8(6):409-413.	E7
67	Philpot LM, Ramar P, Elrashidi MY, Mwangi R, North F, Ebbert JO. Controlled Substance Agreements for Opioids in a Primary Care Practice. Journal of Pharmaceutical Policy & Practice. 2017;10:29.	E2
68	Philpot LM, Ramar P, Elrashidi MY, Sinclair TA, Ebbert JO. A Before and After Analysis of Health Care Utilization by Patients Enrolled in Opioid Controlled Substance Agreements for Chronic Noncancer Pain. Mayo Clinic Proceedings. 2018;93(10):1431-1439.	E4
69	Pullen S. Chronic Pain Mitigation and Opioid Weaning at a Multidisciplinary AIDS Clinic: A Case Report. Rehabilitation Oncology. 2019;37(1):37-42.	E6
70	Quinlan J. The use of a subanesthetic infusion of intravenous ketamine to allow withdrawal of medically prescribed opioids in people with chronic pain, opioid tolerance and hyperalgesia: outcome at 6 months. Pain Medicine. 2012;13(11):1524-1525.	E4
71	Raj BN, Manamohan N, Hegde D, Huded CB, Pradeep J. A Rare Case of Complicated Opioid Withdrawal in Delirium Without Convulsions. Indian Journal of Psychological Medicine. 2017;39(2):191-193.	E6
72	Ralphs JA, Williams AC, Richardson PH, Pither CE, Nicholas MK. Opiate reduction in chronic pain patients: a comparison of patient-controlled reduction and staff controlled cocktail methods. Pain. 1994;56(3):279-288.	E4
73	Reinke T. Opioids, Part 2: Novel Therapies Could Help Wean Americans Off Opioids. Managed Care. 2017;26(12):26-27.	E7
74	Rivich J, McCauliff J, Schroeder A. Impact of multidisciplinary chart reviews on opioid dose reduction and monitoring practices. Addictive Behaviors. 2018;86:40-43.	E2
75	Robinson M, Wittmer V, George S, Beneciuk J, Fillingim R. Opioids for chronic pain: To wean or not to wean. Journal of Pain. 2008;9(4):51.	E7
76	Rosenberg JM, Bilka BM, Wilson SM, Spevak C. Opioid Therapy for Chronic Pain: Overview of the 2017 US Department of Veterans Affairs and US Department of Defense Clinical Practice Guideline. Pain Medicine. 2018;19(5):928-941.	E7

#	Citation	Exclude reason
77	Sandberg C, Massey M, Hiemenz J, Graham J. Patient case series: Rapid and comfortable ambulatory transitions to buccal buprenorphine. Pain Medicine. 2018;19(4):891.	E4
78	Sandhu H, Underwood M, Furlan AD, Noyes J, Eldabe S. What interventions are effective to taper opioids in patients with chronic pain? BMJ. 2018;362:k2990.	E7
79	Schatman ME, DiBenedetto DJ, Kulich RJ. Voluntary Opioid Tapering-Barriers to Delivering Care. JAMA Internal Medicine. 2018;178(6):874-875.	E7
80	Schneider JP, Kirsh KL. Defining clinical issues around tolerance, hyperalgesia, and addiction: a quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. Journal of Opioid Management. 2010;6(6):385-395.	E4
81	Shaw J, King R, Cooper N. A multi-disciplinary team (MDT) approach to opioid reduction in patients prescribed long term opioid medication for chronic pain (CP): A service evaluation. British Journal of Pain. 2017;11(2 Suppl 1):74.	E4
82	Sloan P, DeVito R. Perceived barriers to implementation of current guidelines on long-term opioid therapy: Results of an opioid post-course survey. Pain Medicine. 2017;18(3):606-607.	E4
83	Sloan P. Perceived barriers to implementation of current guidelines on long-term opioid therapy: Results of an opioid post-course survey. Supportive Care in Cancer. 2017;25(2 Suppl 1):S109-S110.	E4
84	Smith DH, Kuntz J, Dickerson JF, et al. Predictors of opioid tapering success. Pharmacoepidemiology and Drug Safety. 2018;27(Suppl 2):183.	E4
85	Streltzer J, Davidson R, Goebert D. An observational study of buprenorphine treatment of the prescription opioid dependent pain patient. American Journal on Addictions. 2015;24(4):357-361.	E4
86	Strickler EM, Schwenk ES, Cohen MJ, Viscusi ER. Use of Ketamine in a Multimodal Analgesia Setting for Rapid Opioid Tapering in a Profoundly Opioid-Tolerant Patient: A Case Report. A&A Practice. 2018;10(7):179-181.	E6
87	Tennant FS, Jr., Rawson RA. Outpatient treatment of prescription opioid dependence: comparison of two methods. Archives of Internal Medicine. 1982;142(10):1845-1847.	E4
88	Thakral M, Walker RL, Saunders K, et al. Impact of Opioid Dose Reduction and Risk Mitigation Initiatives on Chronic Opioid Therapy Patients at Higher Risk for Opioid-Related Adverse Outcomes. Pain Medicine. 2018;19(12):2450-2458.	E4
89	Thieme K, Gromnica-Ihle E, Flor H. Operant behavioral treatment of fibromyalgia: a controlled study. Arthritis and rheumatism. 2003;49(3):314-320.	E1
90	Townsend CO, Kerkvliet JL, Bruce BK, et al. A longitudinal study of the efficacy of a comprehensive pain rehabilitation program with opioid withdrawal: comparison of treatment outcomes based on opioid use status at admission. Pain. 2008;140(1):177-189.	E6
91	Twillman RK, Hemmenway N, Passik SD, Thompson CA, Shrum M, DeGeorge MK. Impact of opioid dose reduction on individuals with chronic pain: results of an online survey. Journal of Pain Research. 2018;11:2769-2779.	E6
92	Vines SW, Cox A, Nicoll L, Garrett S. Effects of a multimodal pain rehabilitation program: a pilot study. Rehabilitation Nursing. 1996;21(1):25-30, 40.	E2

#	Citation	Exclude reason
93	Weinstein ZM, Gryczynski G, Cheng DM, et al. Tapering off and returning to buprenorphine maintenance in a primary care Office Based Addiction Treatment (OBAT) program. Drug & Alcohol Dependence. 2018;189:166-171.	E1
94	Wenger S, Drott J, Fillipo R, et al. Reducing Opioid Use for Patients With Chronic Pain: An Evidence-Based Perspective. Physical Therapy. 2018;98(5):424-433.	E7
95	Whitten SK, Stanik-Hutt J. Group cognitive behavioral therapy to improve the quality of care to opioid-treated patients with chronic noncancer pain: a practice improvement project. J Am Assoc Nurse Pract. 2013;25(7):368-376.	E2
96	Williams AC, Richardson PH, Nicholas MK, et al. Inpatient vs outpatient pain management: results of a randomised controlled trial. Pain. 1996;66(1):13-22.	E4
97	Williams DR, Stark RJ. Intravenous lignocaine (lidocaine) infusion for the treatment of chronic daily headache with substantial medication overuse. Cephalalgia. 2003;23(10):963-971.	E4
98	Wyse JJ, Morasco BJ, Dobscha SK, Demidenko MI, Meath THA, Lovejoy TI. Provider reasons for discontinuing long-term opioid therapy following aberrant urine drug tests differ based on the type of substance identified. Journal of Opioid Management. 2018;14(4):295-303.	E2
99	Zekry O, Gibson SB, Aggarwal A. Subanesthetic, Subcutaneous Ketamine Infusion Therapy in the Treatment of Chronic Nonmalignant Pain. Journal of Pain & Palliative Care Pharmacotherapy. 2016;30(2):91-98.	E2
100	Zgierska AE, Burzinski CA, Cox J, et al. Mindfulness Meditation and Cognitive Behavioral Therapy Intervention Reduces Pain Severity and Sensitivity in Opioid-Treated Chronic Low Back Pain: Pilot Findings from a Randomized Controlled Trial. Pain Medicine. 2016;17(10):1865-1881.	E2
101	Zgierska AE, Burzinski CA, Cox J, et al. Mindfulness Meditation-Based Intervention Is Feasible, Acceptable, and Safe for Chronic Low Back Pain Requiring Long-Term Daily Opioid Therapy. Journal of alternative and complementary medicine. 2016;22(8):610-620.	E4
102	Zheng Z, Guo RJ, Helme RD, Muir A, Da Costa C, Xue CC. The effect of electroacupuncture on opioid-like medication consumption by chronic pain patients: a pilot randomized controlled clinical trial. European Journal of Pain. 2008;12(5):671-676.	E2
103	Zhou K, Jia P, Bhargava S, et al. Opioid tapering in patients with prescription opioid use disorder: A retrospective study. Scandinavian Journal of Pain. 2017;17:167-173.	E4
104	Ziadni M, Stieg R, Mackey I, et al. Patient-centered prescription opioid tapering in community outpatients with chronic pain. Pain Medicine. 2018;19(4):860-861.	E7

EVIDENCE TABLES

DATA ABSTRACTION OF INCLUDED PRIMARY STUDIES

Study and Patient Characteristics

Author Year N	Study Design Follow-up	Setting	Patient Characteristics Mean age % male % white	Type of chronic pain	Co-morbid substance use or mental health disorder	MEDD at baseline
Baron, 2006[1] 23	Pre-post Range 14-180 days	Inpatient psychiatric facility with outpatient follow-up	50.7 yrs. 70% male Race NR	Musculoskeletal pain	None	MED: mean 556 mg Extended-release oxycodone (22%); fentanyl (26%); hydrocodone (8%); methadone (8%); and morphine (8%) Duration NR
Berland, 2013[2] 76	Pre-post Up to 25 months	2 in patient hospitals	48 yrs. 42% male Race NR	Musculoskeletal (33%); Fibromyalgia (30%); Abdomen (12%); Other (25%)	Psychiatric comorbidity (including generalized anxiety, depression, borderline personality disorder, PTSD) (70%); evidence for addiction (24%); benzodiazepine treated (39%)	MED: median 400 mg Type NR Duration: "all patients had been treated for many years"
Bienek, 2019[3] 195	Retrospective cohort 6 weeks	One hospital (Department of Pain Medicine of the University Hospital Bergmannsheil, Germany)	23 yrs. 57.4% male NR	Neuropathic (34%); musculoskeletal (26%); back (25%), chronic regional pain syndrome (5%), other (10%)	NR	MED: mean 229 mg/d (253 mg/d for ISD group; 185 mg/d for FSD group) Most used opioid types: Morphine (14.9%); Hydromorphone (21%); Oxycodone (21%); Oxycodone/ naloxone (11.3%); Fentanyl (14.9%) Duration: at least 1 year

Author Year N	Study Design Follow-up	Setting	Patient Characteristics Mean age % male % white	Type of chronic pain	Co-morbid substance use or mental health disorder	MEDD at baseline
Blondell, 2010[4] 12	RCT 6 months	Multidisciplinary outpatient pain management program	45 yrs. 50% male 91.5% white	NR ("Well documented chronic non-cancer pain")	"Self-identified addiction to prescription opioids"	MED dose NR Hydrocodone (), Oxycodone (), Methadone (), Morphine (), Fentanyl () Duration NR
Cowan, 2005[5] 10	RCT 120 hours	Outpatient pain clinic	56 yrs. 60% male Race NR	Degenerative diseases 80%	NR	MED: mean 40 mg/day of morphine for ≥ 2 years
Crisostomo, 2008[6] 383	Pre-post 3 weeks	Outpatient multidisciplinary pain rehab center	47 yrs. 38% male 93.3% white	Low-back pain	NR	58% on opioids at baseline MED: mean 61mg Type and duration NR
Cunningham, 2016[7] 131	Pre-post 3 weeks	Outpatient multidisciplinary pain rehab center	46 yrs. 19% male 61.6% white	NR	NR	42% on opioids MED: mean 99 mg Type: hydrocodone (29%); oxycodone/acetaminophen (13%); oxycodone extended release (20%); oxycodone (15%); fentanyl patches (9%); methadone (11%); morphine (15%) Duration: mean 4.5 yrs.
Daitch, 2012[8] 104	Pre-post Mean treatment duration 10.3 months (range 2-42)	Interventional pain management practice	49 yrs. 58% male Race NR	NR	NR	MED: mean 180 mg Type: oxycodone (45.19%), fentanyl (14.42%), hydrocodone (13.46%), methadone (10.58%), oxymorphone (9.62%), morphine (6.73%) Duration NR

Author Year N	Study Design Follow-up	Setting	Patient Characteristics Mean age % male % white	Type of chronic pain	Co-morbid substance use or mental health disorder	MEDD at baseline
Daitch, 2014[9] 35	Pre-post Mean treatment duration 6 months	Interventional pain management practice	46 yrs. 60% male Race NR	NR	NR	MED: mean 550 mg Type: oxycodone (34%), hydromorphone (11%), oxymorphone (6%), fentanyl (17%), methadone (14%), morphine (17%) Duration NR
Darchuk, 2010[10] 292	Pre-post 6 months	Interventional pain management practice	46 yrs. 21% male 95.3% white	Primary pain diagnosis: low back (24.5%); fibromyalgia (20.9%); headache (10%); generalized (6.9%); abdominal (7.1%); neck (6.9%); other (23.6%)	NR	56% on opioids MED: mean 112 mg Type and duration NR
Darnall, 2018[11] 82	Pre-post 4 months	Community pain clinic	51 yrs. 40% male NR	"Non-cancer-related chronic pain"	Patients with substance use disorder excluded; comorbidities included fatigue, anxiety, depression, sleep disturbance	MED: mean 288 (IQR 153-587) Type NR Duration: median 6 years (IQR 3-9)
Demidenko, 2017[12] 509	Case-control 12 months	VHA	55 yrs. 94.3% male 70.7% white	Musculoskeletal (85.1%); neuropathy (5.5%); migraine headache (10.4%)	Substance use disorder (~50% had at least one); depressive disorder (24.4%); bipolar disorder (8.1%); PTSD (30.6%), other anxiety disorder (25.3%); psychotic disorder (8.1%)	MED: mean 75.7 $\pm$ 89.6 Type and duration NR
Dersh, 2008[13] 1323	Pre-post 1 year	Outpatient interdisciplinary functional restoration program	42 yrs. 62% male 70.8% white	Chronic disabling spinal disorders	Opioid use disorder (15%) Other major disorders: major depressive disorder (56.2%); paranoid PD (30.7%); borderline PD (25.8%)	NR

Author Year N	Study Design Follow-up	Setting	Patient Characteristics Mean age % male % white	Type of chronic pain	Co-morbid substance use or mental health disorder	MEDD at baseline
Drossman, 2012[14] 39	Pre-post 3 months	Inpatient gastroenterology consult service; outpatient gastroenterology clinic	40 yrs. 8% male Race NR	IBS (21%); inflammatory bowel disease (37%); fibromyalgia, other functional, somatic or orthopedic (29%); and postoperative or other (13)%	Using antidepressants (76.92%); using benzodiazepines (46.15%); using atypical antipsychotics (33.33%)	MED: mean 75 mg Type: oxycodone (61.54%); fentanyl (23.08%); hydromorphone (20.51%); other (25.64%) Duration: mean 5 yrs.
Harden, 2015[15] 50	Pre-post 1 year	VHA	54 yrs. 88% male 60% white	Back (35%); osteoarthritis (14%); cervical (10%); neuropathies (10%); muscle (8%); foot/limb (3%); abdominal (2%); headache (2%); amputee (1%)	NR	MED: NR 64% with MED dose ≥ 200 mg 56% of patients on combination of long-acting and short-acting opioids
Heiwe, 2011[16] 29	Pre-post Mean 2.1 yrs.	Inpatient and outpatient academic dependency center	44 yrs. 14% male Race NR	"mostly musculoskeletal"	NR	MED: NR 10% taking "strong" opioids Duration: mean 8 years analgesic consumption
Hooten, 2007[17] 159	Pre-post 3 weeks	Outpatient multidisciplinary pain rehab center	45 yrs. 14% male Race NR	Fibromyalgia	4 patients with chemical dependency dismissed to substance abuse program	38% on opioids MED, type and duration NR
Hooten, 2007b[18] 66	Pre-post 3 weeks	Outpatient multidisciplinary pain rehab center	47 yrs. 50% male 90.5% white	Fibromyalgia	Program not recommended for patients with substance abuse or dependence disorders, severe mood disorders, psychotic disorders or dementia	32% on opioids MED: mean 64 mg men, mean 39 mg women Type and duration NR
Hooten, 2009[19] 1241	Pre-post 3 weeks	Outpatient multidisciplinary pain rehab center	46 yrs. 25% male 94.7% white	Primary pain site included: low back, fibromyalgia, headache, generalized	Program not recommended for patients with substance abuse or dependence disorders, severe mood	50% on opioids MED: mean 118 mg Type and duration NR

Author Year N	Study Design Follow-up	Setting	Patient Characteristics Mean age % male % white	Type of chronic pain	Co-morbid substance use or mental health disorder	MEDD at baseline
					disorders, psychotic disorders or dementia	
Hooten, 2015[20] 21	Pre-post 3 weeks	Outpatient multidisciplinary pain rehab center	49 yrs. 72% male 100% white	Pain sites included: fibromyalgia, low back pain, generalized pain, pelvic pain	Program not recommended for patients with substance abuse or dependence disorders, severe mood disorders, psychotic disorders or dementia	MED: mean 98 mg Type and duration NR
Huffman, 2017[21] 1457	Pre-post 12 months	Outpatient interdisciplinary chronic pain rehabilitation program	46.3 yrs. 38% male Race NR	NR	Moderate levels of depression and anxiety at admission.	MED: mean 177 mg 28% on high dose, 36% on low dose
Hundley, 2018[22] 43	Pre-post 5 years (Jan. 1, 2012 – Jan. 1, 2017)	VHA (North Florida/South Georgia Veterans Health System)	61 yrs. 95.3% male 83.7% White	NR	Alcohol use (30.2%); substance abuse treatment program referral (16.3%)	MED: mean 330 mg 83.7% methadone; 16.2% other opioid Long-acting + short-acting: 79.1% Long-acting only: 20.9% (n = 9) Duration: 7.8 years
Kidner, 2009[23] 1226	Pre-post 12 months	Outpatient interdisciplinary functional restoration program	44.1 yrs. 48% male 58% white	Injured regions: cervical (5.5%); thoracic/lumbar (46.3%); upper extremity (10.4%); lower extremity (4.8%); multiple musculoskeletal (33%)	NR	48.6% on opioids MED: ≤ 30 mg (23%) 31-60 mg (10%) > 60 mg (12%) Type and duration NR
Krumova, 2013[24] 102	Pre-post 12 months	Inpatient pain management service	51 yrs. 54% male Race NR	Diagnoses: Neuropathic pain syndrome (36.3%); non-neuropathic pain	NR	MED: mean 367 mg Type: morphine (93.1%); fentanyl (28.4%); hydromorphone (17.6%);

Author Year N	Study Design Follow-up	Setting	Patient Characteristics Mean age % male % white	Type of chronic pain	Co-morbid substance use or mental health disorder	MEDD at baseline
				syndromes (52.9%); others (10.8%)		oxycodone (13.7%); buprenorphine (6.9%) Duration: mean 43.3 months
Kurita, 2018[25] 35	RCT 6 months	Outpatient multidisciplinary pain center	53 yrs. 40% male Race NR	Neuropathic (14.3%); Nociceptive somatic (34.3%); Neuropathic + nociceptive somatic (47.6%); Neuropathic + nociceptive visceral (2.8%)	NR	MED: mean 280.3 mg Types: Sustained released opioids (fentanyl, hydromorphone, morphine, oxycodone, tramadol or methadone) Duration: mean 8.0 yrs.
Malinoff, 2005[26] 95	Pre-post Mean 8.8 months	Outpatient	51.3 yrs. 52% male Race NR	NR	8.42% opiate dependent	MED and type NR Duration: mean 8.8 years
Mark, 2019[27] 494	Uncontrolled cohort 90 days	Medicaid	47 yrs. 51% male Race NR	NR	60% SUD 27% mood disorder 25% anxiety disorder	MEDD: mean >=120 mg for 613 days
McPherson, 2018[28] 551	Pre-post 24 months	VHA	54.6 yrs. 95% male 71% white	Chronic musculoskeletal (87%); Neuropathic (6%); Headache (11%)	Substance use disorder (51%); Depressive disorder (25%); Bipolar disorder (7%); PTSD (32%); Other anxiety (25%); Psychotic disorder (8%)	MEDD: mean 75.76 mg Type and duration NR
Murphy, 2013[29] 705	Pre-post 3 weeks	Inpatient chronic pain rehabilitation program	50.1 yrs. 79.8% male 66.1% white	Primary pain site: back (60.2%); extremity (15.4%); neck (10%); head (6.3%); other (8.1%)	NR	37% of program completers on opioids MED: mean 61 mg
Nilsen, 2010[30] 11	Pre-post 3 months	Outpatient multidisciplinary pain clinic	43 yrs. 18.2% male	NR	All patients had "problematic opioid use" with 3/5 criteria (Chabal et al.)	MED: mean 36 mg Type: Codeine

Author Year N	Study Design Follow-up	Setting	Patient Characteristics Mean age % male % white	Type of chronic pain	Co-morbid substance use or mental health disorder	MEDD at baseline
						Duration: range 1 to >10 years
Rome, 2004[31] 356	Pre-post 3 weeks	Outpatient multidisciplinary pain rehab center	44.3 yrs. 25.8% male 96% white	Primary pain diagnosis: fibromyalgia (23.9%); low back (21.6%); headache (10.7%); generalized (9%); abdominal (7.65); neck (6.7%); other (20.5%)	NR	38% on opioids MED: mean 78 mg Type: most frequently oxycodone (immediate and sustained release), hydrocodone, fentanyl, and propoxyphene Duration NR
Rosenblum, 2012[32] 12	Pre-post	Outpatient pain management center	50 yrs. 58% male 67% white	NR	Chronic illness (83%); 25% Taking medication for a psychiatric disorder (25%); Past history of substance use disorder (33%)	MED: mean 142 mg Type: codeine, oxycodone, morphine, methadone, fentanyl Duration NR
Roux, 2013[33] 43	Pre-post 7 weeks	Inpatient psychiatric clinic	48 yrs. 64% male 32% white	NR	All patients met DSM-IV criteria for opioid dependence. Exclusions included current major Axis I psychopathology other than opioid dependence	MED: median 60 mg Type: oxycodone, hydrocodone, hydromorphone, and tramadol Duration: median 5 years
Schwarzer, 2015[34] 32	Retrospective cohort 3 weeks	Inpatient pain management program	23 yrs. 50% male Race NR	Pain diagnoses: Neuropathic (44%); nociceptive (50%); headache (6%)	Opioid-related disorders (23%), Depressive and adjustment disorder (56%), Cardiac comorbidity (55%), COPD (17%)	56% on opioids MED: mean 175 mg Type: NR Duration: at least 6 months
Sharp, 2018[35] 2492	Retrospective cohort	Health system (Kaiser Permanente	54.5% < 65 yrs., 45.6% ≥ 65 yrs.	NR	NR	NR

Author Year N	Study Design Follow-up	Setting	Patient Characteristics Mean age % male % white	Type of chronic pain	Co-morbid substance use or mental health disorder	MEDD at baseline
	≥ 30 days	Southern California)	38.6% male 73.9% White			
Sullivan, 2017[36] 35	RCT 22 weeks	Outpatient multidisciplinary pain center	54 yrs. 29% male 85.7% white	NR	57% scored 10 or more on PHQ-9 (moderate or greater depressive symptom severity) at baseline	MED: mean 226 mg Type: NR Duration: <1 year (12%); 1 to 10 years (38%); 10 to <15 years (21%); 15+ years (29%)
Thakral, 2018[37] 1588	Interrupted time series 8 years (2006 – 2014)	Health System (Group Health)	49.9% 45 - 64 yrs. 41.9% ≥65 yrs. 36.5% male 85.8% White	NR	Nonopioid drug use disorder (7.7%); Mental disorders (65.9); Comorbidity score: 0 (46.2%), 1 to 2 (25.1%), 3 or more (28.7%)	MED: mean 58 mg Type NR Duration: >1 year
Taylor, 1980[38] 7	Pre-post 6 months	Inpatient pain management program	49 yrs. 43% male Race NR	Abdominal (86%); headache (14%)	NR	MED, type, duration NR
Townsend, 2008[39] 373	Pre-post 6 months	Outpatient multidisciplinary pain rehab center	44.5 yrs. 20.9% male 95.7% white	Low back (24.4%); fibromyalgia (19.8%); headache (11.5%); generalized (8.8%); abdominal (7.2%); other (21.9%)	Taking tricyclic antidepressant (22.5%); Taking SSRIs (29.8%), Taking other antidepressants (43.4%)	57.1% on opioids MED: mean 99 mg Type: NR Duration: mean 3.9 years
Twillman, 2018[40] 362	Cross-sectional 6 months	Online survey for members of the US Pain Foundation	NR	NR	NR	MED NR Immediate-release opioid use (76.9%) Duration of treatment with an extended-release (ER)/long-acting (LA) opioid: >1 year (91.0%); 7mo.-1yr. (9.0%)
Von Korff, 2019[41] 31142	Interrupted time series	Health System (Group Health)	NR	NR	NR	NR

Author Year N	Study Design Follow-up	Setting	Patient Characteristics Mean age % male % white	Type of chronic pain	Co-morbid substance use or mental health disorder	MEDD at baseline
	8 years (2006-2014)					
Wang, 2011[42] 63	Pre-post 6 months	Outpatient orthopedic surgery clinic	49.3 yrs. 60% male Race NR	Chronic low back pain	Depression (45.5%)	35.7% on opioids MED: mean 107 mg Duration: mean 17 months
Webster, 2016[43] 39	RCT 24 hours	Inpatient clinical trial	42.3 yrs. 46% male 74.3% white	NR	All patients opioid dependent by naloxone challenge	MED: 80-160 mg (85%) 161-220 mg (15%) Type: morphine or oxycodone Duration: ≥ 6 months
Weimer, 2016[44] 516	Pre-post 28 months	Academic primary care practice	59 yrs. 37% male 92.6% white	Rheumatoid arthritis (36.6%); osteoarthritis (36.2%); neuropathic pain (23.1%); headache (17.1%); back pain (66.5%)	Schizophrenia or bipolar disorder (5.8%); depression (59.7%); anxiety (27.7%); substance use disorder (35.5%)	22% in high dose (> 120 mg) with mean MED 263 mg
Younger, 2008[45] 12	Pre-post 7-14 days	Inpatient pain rehabilitation program (Stanford Comprehensive Interdisciplinary Pain Program)	47.9 yrs. 58.3% male Race NR	Low back pain (42%); CRPS (25%); Failed back syndrome (8%); Migraine (8%); Cervicalgia (17%)	NR	MED: mean 33 mg; median 194 mg Type and duration NR
Ziadni, 2018[46] 51	Pre-post 4 months	Outpatient	NR	NR	NR	MED: median 288 mg

Abbreviations: COPD = chronic obstructive pulmonary disease; IBS = irritable bowel syndrome; ISD = individualized starting dosage; FSD = fixed starting dosage; MED = morphine equivalent dose; mo. = month; NR = not reported; PD = personality disorder; VHA = Veterans Health Administration; yr. = years

Intervention Characteristics

Author Year N	Intervention Type	Intervention	Comparator	Voluntary or Mandated	Intent of Taper (dose reduction or discontinuation)
Baron, 2006[1] 23	Pharmacologic	Ibuprofen + buprenorphine	Ibuprofen only	Voluntary	Discontinuation
Berland, 2013[2] 76	Pharmacologic	Inpatient opioid discontinuation with buprenorphine	None	Voluntary	Discontinuation
Bienek, 2019[3] 195	Multimodal care team	Inpatient opioid withdrawal with contract between physician and patient and collection of opioids	Individualized starting dose (ISD) vs low fixed starting dosage (FSD)	Voluntary	Discontinuation
Blondell, 2010[4] 12	Pharmacologic	Inpatient opioid discontinuation with steady doses of buprenorphine/ naloxone for opioid replacement with outpatient follow-up	Inpatient opioid discontinuation with tapering doses of buprenorphine/ naloxone for opioid weaning with outpatient follow-up	Voluntary	Both
Cowan, 2005[5] 10	Pharmacologic	Cessation of opioids during 60-hour period	Continuation of morphine during 60-hour period	Voluntary	Discontinuation
Crisostomo, 2008[6] 383	Multimodal care team	Multidisciplinary pain rehab with secondary treatment goal of reduction in analgesics, including opioids	None	Voluntary	Both
Cunningham, 2016[7] 131	Multimodal care team	Multidisciplinary pain rehab incorporating pain medication discontinuation	None	Voluntary	Discontinuation
Daitch, 2012[8] 104	Pharmacologic	Outpatient conversion to sublingual buprenorphine	None	Voluntary	Discontinuation
Daitch, 2014[9] 35	Pharmacologic	Outpatient conversion to sublingual buprenorphine	None	Voluntary	Discontinuation
Darchuk, 2010[10] 292	Multimodal care team	3-week intensive multidisciplinary pain rehab incorporating opioid discontinuation	None	Voluntary	Discontinuation
Darnall, 2018[11] 82	Primary-care based	Self-help book with a slow, individually designed taper	None	Voluntary	Dose reduction
Demidenko, 2017[12] 509	Primary-care based	Clinician initiated taper/ discontinuation (no specific intervention)	None	Mandated taper (clinician initiated)	Discontinuation

Author Year N	Intervention Type	Intervention	Comparator	Voluntary or Mandated	Intent of Taper (dose reduction or discontinuation)
Dersh, 2008[13] 1323	Non-pharm	Intensive physical reactivation and pain/disability management with mandatory opioid discontinuation	None	Voluntary	Discontinuation
Drossman, 2012[14] 39	Multimodal care team	Inpatient opioid discontinuation with consult service or outpatient discontinuation; guided by multimodal protocol	None	Voluntary	Discontinuation
Harden, 2015[15] 50	Primary-care based	Opioid safety initiative care, dose reduction implemented by primary care, pain service, or pharmacist run pain clinic	None	Mandated (opioid safety initiative)	Dose reduction
Heiwe, 2011[16] 29	Non-pharm	Opioid discontinuation with counseling and optional auricular acupuncture and PT	None	Voluntary	Discontinuation
Hooten, 2007[17] 159	Multimodal care team	Intensive multidisciplinary pain rehab incorporating opioid discontinuation	None	Voluntary	Discontinuation
Hooten, 2007b[18] 66	Multimodal care team	Intensive multidisciplinary pain rehab incorporating opioid discontinuation	None	Voluntary	Discontinuation
Hooten, 2009[19] 1241	Multimodal care team	Intensive multidisciplinary pain rehab incorporating opioid discontinuation	None	Voluntary	Discontinuation
Hooten, 2015[20] 21	Pharmacologic	Varenicline within intensive multidisciplinary pain rehab incorporating opioid discontinuation	Placebo	Voluntary	Discontinuation
Huffman, 2017[21] 1457	Multimodal care team	3-4-week interdisciplinary chronic pain rehab program incorporating opioid discontinuation	None	Voluntary	Both
Hundley, 2018[22] 43	Primary-care based	Opioid safety initiative prompted opioid discontinuation agreements	None	Mandated (clinician driven by opioid safety initiative)	Discontinuation

Author Year N	Intervention Type	Intervention	Comparator	Voluntary or Mandated	Intent of Taper (dose reduction or discontinuation)
Kidner, 2009[23] 1226	Multimodal care team	Outpatient interdisciplinary restoration program incorporating opioid discontinuation	None	Voluntary	Discontinuation
Krumova, 2013[24] 102	Pharmacologic	Inpatient opioid tapering with pharm management of withdrawal symptoms and outpatient multidisciplinary follow-up	None	Voluntary	Both
Kurita, 2018[25] 35	Multimodal care team	Scheduled opioid taper	Stable treatment (usual care)	Voluntary	Discontinuation
Malinoff, 2005[26] 95	Pharmacologic	Outpatient conversion to sublingual buprenorphine	None	Voluntary	Discontinuation
Mark, 2019[27] 494	Not specified	NR	None	NR	Discontinuation
McPherson, 2018[28] 551	Primary-care based	NR	None	Voluntary (15%), Mandated (85%)	Discontinuation
Murphy, 2013[29] 705	Multimodal care team	3 wk. interdisciplinary pain program incorporating pain medication discontinuation	None	Voluntary	Discontinuation
Nilsen, 2010[30] 11	Non-pharm	6 one-hour physician-led CBT sessions during 8-week period with gradual tapering	None	Voluntary	Discontinuation
Rome, 2004[31] 356	Multimodal care team	3-week intensive multidisciplinary pain rehab program incorporating opioid discontinuation	None	Voluntary	Discontinuation
Rosenblum, 2012[32] 12	Pharmacologic	Outpatient conversion to sublingual buprenorphine/ naloxone	None	Voluntary	Discontinuation
Roux, 2013[33] 43	Pharmacologic	7-week inpatient conversion to buprenorphine/ naloxone at 3 doses		Voluntary	Discontinuation

Author Year N	Intervention Type	Intervention	Comparator	Voluntary or Mandated	Intent of Taper (dose reduction or discontinuation)
Schwarzer, 2015[34] 32	Pharmacologic	3-week inpatient opioid tapering with pharmacologic management of withdrawal symptoms and outpatient multidisciplinary follow-up		Voluntary	Discontinuation
Sharp, 2018[35] 2492	Primary-care based	NR	Patients with no opioid dose reduction	NR	Dose reduction
Sullivan, 2017[36] 35	Multimodal care team	22-week outpatient tapering support with psychiatric consult, motivational interviewing and pain self-management	Usual care	Voluntary	Both
Thakral, 2018[37] 1588	Non-pharm	Inpatient detoxification from analgesic medications with education on relaxation and supportive therapy	None	Voluntary	Discontinuation
Taylor, 1980[38] 7	Primary-care based	Risk reduction initiatives among chronic opioid therapy patients within a health system	Patients in contracted-care settings without dose reduction initiatives	Mandated (health system policy driven)	Dose reduction
Townsend, 2008[39] 373	Multimodal care team	3-week intensive multidisciplinary pain rehab program incorporating opioid discontinuation	None	Voluntary	Discontinuation
Twillman, 2018[40] 362	NR	NR	Respondents whose opioid dosage was increased or stayed the same	NR	Dose reduction
Von Korff, 2019[41] 31142	Primary-care based	Risk reduction initiatives among chronic opioid therapy patients within a health system	Patients in contracted-care settings without dose reduction initiatives	Mandated (health system policy driven)	Dose reduction
Wang, 2011[42] 63	Pharmacologic	Outpatient opioid tapering with symptomatic support with doxepin	None	Voluntary	Discontinuation
Webster, 2016[43] 39	Pharmacologic	24-hour periods of bucca buprenorphine at 50% baseline opioid dose	24-hour periods of full opioid agonist at 50% baseline opioid dose	Voluntary	Discontinuation

Author Year N	Intervention Type	Intervention	Comparator	Voluntary or Mandated	Intent of Taper (dose reduction or discontinuation)
Weimer, 2016[44] 516	Primary-care based	Opioid dosing policy and provider education	None	Mandated (health system policy driven)	Dose reduction
Younger, 2008[45] 12	Multimodal care team	Inpatient pain rehab with opioid detox using blinded pain cocktail	None	Voluntary	Both
Ziadni, 2018[46] 51	Primary-care based	Individually-tailored taper with physician	NR	Voluntary	Dose reduction

Outcomes

Author Year N	MEDD Outcomes	Pain Outcomes	Withdrawal Outcomes	Quality of Life/ Patient Satisfaction	Healthcare Utilization	Suicide or Depression	Opioid Overdose or Other Adverse Events
Baron, 2006[1] 23	100% discontinued opioid medications	21/23 reported improved pain severity (P < 0.001) Significant pain reduction compared to baseline (NRS 8 vs 3.3, P < 0.001) NSD in pain reduction between treatment groups	NR	NR	NR	NR	NR
Berland, 2013[2] 76	100% discontinued opioid medications during intervention At follow-up, 54% on buprenorphine, 26% resumed opioids, and 10% not on opioids	Pain improvement: Much better or better 67% Functional improvements: Much better or somewhat better 60%	NR	NR	NR	NR	NR
Bienek, 2019[3] 195	Mean MED at discharge: 46.1 ISD vs 57.3 FSD Complete taper: 85.8% ISD vs 86.8% FSD; Partial taper: 7.9% ISD vs 10.3% FSD	Pain severity	10-day mean daily Subjective Opioid Withdrawal Scale (SOWS): 16.11 ISD vs 14.9 FSD (P < 0.05) # of days with high burden of withdrawal symptoms in first 10 days: 17.6% ISD vs 12.4% ISD (P < 0.01)	NR	NR	NR	2 cases during individualized taper Serious adverse events: 4.6% ISD vs 2.2% FSD (aggravation of psychiatric problems, malignant hypertension, hypoglycemia, pneumonia, stupor-like symptoms,

Author Year N	MEDD Outcomes	Pain Outcomes	Withdrawal Outcomes	Quality of Life/ Patient Satisfaction	Healthcare Utilization	Suicide or Depression	Opioid Overdose or Other Adverse Events
							and hip-joint effusion)
Blondell, 2010[4] 12	100% discontinued opioid medications during intervention At 6 months: 8/10 patients on buprenorphine, 2/10 resumed opioids	6/10 reported improved pain and 8/10 reported improved function vs baseline at 6 months	NR	NR	5 (50%) initiated counseling for addiction disorder; 5 (50%) initiated pain management behavioral therapy; 4 (40%; 2 for each type) continued with therapy beyond intake evaluation	NR	NR
Cowan, 2005[5] 10	100% in intervention group discontinued opioids during intervention	Increased pain an interference at the end of 60 hour abstinence period (P < 0.05)	30% reported withdrawal symptoms	NR	NR	NR	2 patients reported diarrhea, 1 patient reported rhinorrhea
Crisostomo, 2008[6] 383	Proportion of patients using opioid medications decreased 79% at discharge vs admission	Significant improvements in pain severity and physical function among all patients (CSQ-C change scores)	NR	NR	NR	Significant improvement depressive symptomatology in all patients (CES-D change scores)	NR
Cunningham, 2016[7] 131	100% discontinued opioids during program	Patients taking opioids at baseline had significantly improved pain: mean NRS 5.2 vs 7.2 (P < 0.001), and interference: mean MPI 45.0 vs 55.2 (P < 0.001) at follow-up compared to baseline	Withdrawal symptoms (COWS) not different based on opioid dose (P = 0.22) or duration of use (P = 0.8)	Patients taking opioids at baseline had significantly improved QoL (Health Perception SF-36): 42.9 vs 33.3 (P < 0.001), Perceived life control (MPI)	NR	Among patients taking opioids at baseline, depression (CES-D) decreased from baseline to post-treatment (30.4 vs 18.0, P < 0.001)	NR

Author Year N	MEDD Outcomes	Pain Outcomes	Withdrawal Outcomes	Quality of Life/ Patient Satisfaction	Healthcare Utilization	Suicide or Depression	Opioid Overdose or Other Adverse Events
				45.0 vs 55.2 (P < 0.001)			
Daitch, 2012[8] 104	NA (Study excluded patients who continued to use opioid medications or did not continue buprenorphine ≥ 60 days	Significant reduction in pain severity after conversion to buprenorphine (mean NRS 2.3 point reduction, P < 0.001)	NR	Patient Quality of Life scale was not significantly affected by buprenorphine therapy (P = .14).	NR	NR	NR
Daitch, 2014[9] 35	NA (Study excluded patients who continued to use opioid medications or did not continue buprenorphine ≥ 60 days	Significant reduction in pain severity after conversion to buprenorphine (mean NRS 7.2 to 3.5, P < 0.01)	All patients experienced withdrawal symptoms within the first week of buprenorphine, oral clonidine offered	Quality of life scores increased from 6.1 to 7.1 after conversion to buprenorphine	NR	NR	NR
Darchuk, 2010[10] 292	94% discontinued opioid medications as discharge 15% reported opioid use at 6 month follow-up	Significant improvements in pain severity, pain interference, and general activity (MPI) at 6 months vs admission (P < 0.001)	NR	NR	NR	Patients had significantly improved depression (CES-D) (P < 0.001) from admission to discharge and admission to 6 months post-treatment	NR
Darnall, 2018[11] 82	Median MDD was reduced from 288 mg to 150 mg (P = .002)	Baseline vs 4 months: Pain intensity: 5 vs 4.5 (P = 0.29) PCS: 22 vs 15 (P = 0.04) Pain interference (PROMIS): 63 vs 63 (P = 0.44)	NR	NR	NR	NR	NR

Author Year N	MEDD Outcomes	Pain Outcomes	Withdrawal Outcomes	Quality of Life/ Patient Satisfaction	Healthcare Utilization	Suicide or Depression	Opioid Overdose or Other Adverse Events
		Pain behavior (PROMIS): 60 vs 59 (P = 0.47) Physical function (NRS): 39 vs 39 (P = 0.78)					
Demidenko, 2017[12] 509	NR (Cohort was patients who discontinued opioids)	NR	NR	NR	NR	12% (n = 59) had suicidal self-directed violence (SSV) or suicidal ideation (SI) in the 12 months following discontinuation of opioid therapy.	NR
Dersh, 2008[13] 1323	Opioid discontinuation required for program completion, but not specifically reported. Opioid use at 1 yr. follow-up NR	NR	NR	89.7% non-ODD and 80.4% ODD patients returned to work	2.19 non-ODD and 39.9 ODD mean visits to a new provider, 2.7 non-ODD and 5.6 ODD new surgeries within 1 year	NR	NR
Drossman, 2012[14] 39	100% decreased opioid dose, 90% discontinued opioids at program completion 66% resumed opioids at average 97 days post-treatment	51% reported ≥ 30% reduction in pain severity after discontinuation vs baseline Significant improvement in the catastrophizing coping score (19.9 before detox; 16.4 after detox, P = .025).	82% reported withdrawal symptoms	NR	NR	No significant differences were observed between before and after detox for Hospital Anxiety and Depression scale anxiety and depression or for the Symptom Checklist-90 overall psychological distress.	NR
Harden, 2015[15]	Mean opioid dose reduction of 46% at 12	68% of patients experienced no change	NR	NR	NR	NR	NR

Author Year N	MEDD Outcomes	Pain Outcomes	Withdrawal Outcomes	Quality of Life/ Patient Satisfaction	Healthcare Utilization	Suicide or Depression	Opioid Overdose or Other Adverse Events
50	months 94% decreased opioid dose at 12 months 13% discontinued opioid medications	or less pain at 12 months vs baseline					
Heiwe, 2011[16] 29	66% of patients discontinued opioid medications 46% on opioids at follow-up (32% of completers, 78% of non-completers)	Among completers, pain severity improved at follow-up vs baseline (median NRS 4.0 vs 5.0)	Among completers, withdrawal symptoms improved at follow-up vs baseline (S-SOWS 5 vs 21)	NR	NR	No change in depression symptoms among all participants. Drop-outs had significantly higher depression ratings at baseline and follow-up.	NR
Hooten, 2007[17] 159	93% of patients on opioids discontinued at program completion	Among all patients, pain severity (MPI), life interference (MPI), affective distress (MPI), and general activity (MPI) improved significantly at program completion vs admission (P < 0.001)	NR	Among all patients, life control (MPI), social activity (MPI), and activities of daily living (SF-36) improved significantly at program completion vs admission (P < 0.001)	NR	Decrease in depressive scores (CES-D) from admission (mean 25.8) to program completion (mean 13.2)	NR
Hooten, 2007b[18] 66	95% discontinued opioid medications	Among all patients, pain severity and physical function (MPI) improved significantly at program completion vs admission (P < 0.001)	NR	Among all patients, there was significant improvement in SF-36 subscales at program	NR	Mean difference in pre- and post-treatment scores significant within-gender improvements in depressive	NR

Author Year N	MEDD Outcomes	Pain Outcomes	Withdrawal Outcomes	Quality of Life/ Patient Satisfaction	Healthcare Utilization	Suicide or Depression	Opioid Overdose or Other Adverse Events
				completion vs admission. (P < 0.001)		symptomatology (P < .004 in all cases)	
Hooten, 2009[19] 1241	Proportion of patients using opioid medications decreased from 50% at admission to 2% at discharge	Pain severity significantly higher at program completion among patients who continued to use opioids vs those who discontinued opioid medications (mean MPI pain 43.4 vs 37.0, P = 0.01)	NR	NR	NR	NR	NR
Hooten, 2015[20] 21	95% of study completers discontinued opioids	For the treatment group, baseline MPI pain severity decreased from 50.6 at baseline to 34.6 at dismissal. For the placebo group, pain severity decreased from 53.5 to 41.3. (P = .001)	Withdrawal symptoms decreased over time in patients in varenicline group (5/7) and placebo group (4/11)	NR	NR	For the treatment group, CES-D scores decreased from 31.0 at baseline to 10.0 at dismissal. For the placebo group, CES-D scores decreased from 30.0 to 12.0. (P < .001)	No adverse effects among patients in either group
Huffman, 2017[21] 1457	87% discontinued opioids, 4% discharged on buprenorphine, 10% continued full-agonist opioids Among patients who discontinued opioids, 31% resumed opioid use at 12-month follow-up	Improved pain (6.61 baseline vs 3.5 discharge vs 4.45 at 6 months vs 4.65 at 12 months) (P < 0.001), and functional impairment (42.95 baseline vs 18.29 discharge vs 23.7 at 6 and 12 months) (P < 0.001).	NR	NR	NR	Improvements in depression (18.93 baseline vs 6.36 discharge) and anxiety (13.26 baseline vs 6.59 discharge).	NR
Hundley, 2018[22]	65% discontinued completed (of these	NR	NR	NR	Average utilization before vs after	0 suicide attempts	0 overdoses

Author Year N	MEDD Outcomes	Pain Outcomes	Withdrawal Outcomes	Quality of Life/ Patient Satisfaction	Healthcare Utilization	Suicide or Depression	Opioid Overdose or Other Adverse Events
43	71% achieved long-term abstinence) 16% dose reduction 19% did not taper or discontinue				discontinuation: ED visits: 0.96 vs 1.54 (P = 0.184) Primary care visits: 2.43 vs 1.79 9P = 0.059) Hospitalizations: 0.57 vs 0.61 (P = 0.885) Psychiatric hospitalizations: 0.04 vs 0.14 (P = 0.375)		
Kidner, 2009[23] 1226	74% of patients on opioids at baseline discontinued opioid medications	Program completers on opioids at baseline reported improved pain, baseline vs discharge (mean NRS 6.6 vs 4.9) and disability (mean ODI 42 vs 24)	NR	Program completers on opoids at baseline reported improved physical health (SF-36) baseline vs discharge (29.7 vs 34.9) 88.1% of patients on opiods at baseline returned to work and 68.8% were retained at work 1 year post-discharge	Patients on opioids at baseline, 4.4% had a new surgery to the original injiry site, 29.9% were seeking treatment from a new provider,and 5.2% were receiving social security disability or supplemental income.	Patients on opioids at baseline had improved depression score (BDI) baseline vs discharge (16.4 vs 9.7	NR
Krumova, 2013[24] 102	76% discontinued opioids, 24% reduced dose by an average of 82%	Pain severity improved at program completion vs baseline (mean NRS 5.4 vs 7.1, P < 0.001) At 6-12 months pain	"Virtually all patients experienced withdrawal	SF-36 physical health scores from admission to	NR	No change in depression (CES-D) score from admission to follow-up (25.9	NR

Author Year N	MEDD Outcomes	Pain Outcomes	Withdrawal Outcomes	Quality of Life/ Patient Satisfaction	Healthcare Utilization	Suicide or Depression	Opioid Overdose or Other Adverse Events
	42% resumed opioids at follow-up	severity (mean NRS 5.9 vs 7.1, P < 0.001) and pain related disability (mean PDI, 30.4 vs 37.7, P < 0.001) improved vs baseline	symptoms to some degree"	follow-up (26.1 vs 27.8) (P = NR)		vs, 25.6) (P = NR)	
Kurita, 2018[25] 35	Baseline vs follow-up (4th assessment) mean MED increased in control group (220.8 mg vs 300.8 mg) and decreased in intervention group (367.4 mg vs 226.6) No significant difference in dose at follow-up (4th assessment)	No difference in pain at follow-up (4th assessment) (average pain 19 control vs 10 intervention (P = 1.0)	NR	Intervention group felt significantly more rested at the third assessment (35% control vs 80% intervention, P = .0082) No differences in other SF-36 factors.	Control Group had a mean 1.5 contacts/appointments with the pain team, while the intervention group had 4.3	No differences in depression or anxiety between intervention and control at 4th assessment	NR
Malinoff, 2005[26] 95	94% discontinued opioids and initiated buprenorphine, none of these patients returned to opioid medications	86% reported "substantial improvement" in pain severity "Most patients" reported improved functional status	6 patients discontinued treatment during detoxification due to side effects	Patient and family satisfaction was "robust".	NR	NR	No patients died or were hospitalized
Mark, 2019[27] 494	NR (Cohort was patients who discontinued opioids)	NR	NR	NR	ED visit with SUD diagnosis: 91% Hospitalization with SUD diagnosis: 7%	NR	NR
McPherson, 2018[28] 551	NR (Cohort was patients who discontinued opioids)	Baseline pain (NRS) 4.9 Slope of 12-month post-discontinuation pain: -0.07 (P < 0.01) Adjusted for demographic, clinical,	NR	NR	NR	NR	NR

Author Year N	MEDD Outcomes	Pain Outcomes	Withdrawal Outcomes	Quality of Life/ Patient Satisfaction	Healthcare Utilization	Suicide or Depression	Opioid Overdose or Other Adverse Events
		and pain treatment utilization, pain treatment did not significantly change over 12 months post-discontinuation (B = -0.2, P = 0.14)					
Murphy, 2013[29] 705	100% discontinued opioids at program discharge (baseline opioid use significantly more common among non-completers, 55% vs 37%)	Among patients on opioids at baseline, pain severity (NRS 6.5 vs 7.0, P < 0.001) and function (mean POQ-ADL, 13 vs 16, P < 0.001) improved at program completion vs baseline	NR	Overall satisfaction at discharge was M 8.30 among patients on opioids at baseline	NR	NR	NR
Nilsen, 2010[30] 11	55% discontinued opioids, 45% remained off codeine at 3 months Mean opioid dose decreased by 81% posttreatment (P < 0.01)	Pain severity (mean NRS 5.4 vs 6.2, P > 0.05), function (mean SF-36 physical function 65 vs 55, P = 0.07) did not differ at 3 months vs baseline	All patients reported withdrawal symptoms	QoL (mean SF-36 general health 48 vs 34, P = 0.15) did not differ at 3 months vs baseline	NR	NR	NR
Rome, 2004[31] 356	98% of patients discontinued opioids at discharge	Among patients on opioids at admission, significant improvement in pain severity (mean MPI difference 8.4, P < 0.001), interference (mean MPI difference 12.5, P < 0.001) at program completion vs admission	NR	Among patients on opioids at admission, significant improvement in perceived life control (mean MPI difference -9.1, P < 0.001) at program	NR	Among patients on opioids at admission, significant reductions in depression (mean difference 10.2, P < .001)	NR

Author Year N	MEDD Outcomes	Pain Outcomes	Withdrawal Outcomes	Quality of Life/ Patient Satisfaction	Healthcare Utilization	Suicide or Depression	Opioid Overdose or Other Adverse Events
				completion vs admission			
Rosenblum, 2012[32] 12	33% of patients completed transition to buprenorphine	Pain severity (mean BPI 3.4 vs 6.6, P < 0.01) and interference (mean BPI 2.9 vs 6.0, P NR) decreased vs baseline	83% experience an adverse effect, including 7 who stopped treatment as a result, 1 patient hospitalized due to withdrawal symptoms and increased pain	NR	NR	NR	NR
Roux, 2013[33] 43	72% completed the conversion to buprenorphine/naloxone	Pain severity was reduced on buprenorphine/naloxone vs pre-admission (median MPQ 21 vs 38, P < 0.001)	Withdrawal symptoms reported in 83% of study sessions	NR	NR	NR	NR
Schwarzer, 2015[34] 32	100% of patients on opioids at baseline discontinued opioids, 1 patient (5.6%) resumed low-dose opioids	Among patients on opioids at baseline, non-significant decrease in average pain at discharge vs baseline (mean NRS 6.6 vs 7.2, P = 0.22)	NR	NR	NR	No change in depression (9.8 vs 9.3, P = 0.57) or anxiety (8.6 vs 8.1, P - 0.50) (HADS) from baseline to discharge	NR
Sharp, 2018[35] 2492	Among patients with reduction in opioids to below 50 MED: Median decrease of 80 mg (mean decrease: 109 mg)	NR	NR	Favorable satisfaction with (86.4%) or without (89.9%) dose reduction. Dose reduction not associated	NR	NR	NR

Author Year N	MEDD Outcomes	Pain Outcomes	Withdrawal Outcomes	Quality of Life/ Patient Satisfaction	Healthcare Utilization	Suicide or Depression	Opioid Overdose or Other Adverse Events
				with unfavorable scores for visits with an assigned PCP (OR 1.16; 95% CI 0.79-1.70) but were associated with unfavorable scores for unassigned provider (OR 1.50; 95% CI 1.01-2.23)			
Sullivan, 2017[36] 35	37% in intervention and 12% in usual care reduced opioid dose by ≥ 50% at 22 weeks (adjusted mean difference - 42.9 ,g MED, P = 0.09)	Pain severity ratings decreased in both groups at 22 weeks, no significant difference between groups (adjusted mean difference = -0.68; 95% CI -2.01 o 0.64) The treatment group improved significantly more than usual care in self-reported pain interference (adjusted mean difference = −1.39; 95% CI: −2.78, −0.01) and pain self-efficacy (adjusted mean difference = 7.86; 95% CI: 1.22, 14.50)	NR	NR	NR	NR	NR
Thakral, 2018[37]	100% discontinued opioids over an average	Pain severity reduced at 6 months vs baseline	NR	NR	NR	Four patients (57%) exhibited	NR

Author Year N	MEDD Outcomes	Pain Outcomes	Withdrawal Outcomes	Quality of Life/ Patient Satisfaction	Healthcare Utilization	Suicide or Depression	Opioid Overdose or Other Adverse Events
1588	3.7 days 50% of patients reported taking opioids at 6 months	(mean NRS 1.44 vs 2.89, P < 0.001) 50% reported increased activity at 6 months				significantly higher rating in mood between prehospitalization and immediate post-hospitalization; however, this change remained significant for only 2 patients at 6-month follow-up.	
Taylor, 1980[38] 7	NR	Difference between intervention and control (PEG): pain severity (0.17, 95% CI -0.02 to 0.35), pain interference daily activities (-0.12, 95% CI -0.40 to 0.16), pain interference enjoyment in life (-0.18, 95% CI -0.47 to 0.11)	NR	In both care settings, 62.5% reported that opioids were "very or extremely helpful" and 85.7% reported side effects were "not at all or a little bothersome".	NR	Depression (PHQ-8) between intervention vs control: -.64 (95% CI -1.19 to -.08)	NR
Townsend, 2008[39] 373	93% discontinued opioids by program completion 14% were taking opioids at 6 months	Among patients on opioids at baseline, improvement in pain severity (mean MPI 39 vs 49, P = 0.002) and pain interference (mean MPI 36 vs 51, P = 0.002) at 6 months vs baseline	NR	Among patients on opioids at baseline, improvement baseline to posttreatment in (SF-36) emotional factors (36.5	NR	Among patients on opioids at baseline, significant improvements in depression baseline to posttreatment (CES-D 29.3 vs 16.3, P < .001)	NR

Author Year N	MEDD Outcomes	Pain Outcomes	Withdrawal Outcomes	Quality of Life/ Patient Satisfaction	Healthcare Utilization	Suicide or Depression	Opioid Overdose or Other Adverse Events
				vs 46.2), physical factors (29.6 vs 41.3), and social functioning (29.8 vs 43.4) (all P < 0.001)			
Twillman, 2018[40] 362	Tapered dosage of ER/LA opioid in the past 6 months: 32.3%	Respondents reporting decreased dosage significantly more likely (P < .05) to rate their condition as "worse" than those who reported no ER/LA dose change	Respondents reporting decreased dosage were more likely (P ≤ .05) to report increases in the frequency of 7 of the 8 adverse events associated with opioid withdrawal.	Patients who decreased dosage were more likely to report that overall level of function (67.8% vs 31.5%), ability to work (62.9% vs 33.8%), and relationships with family/friends (48.3% vs 25.8%) "got worse."	Patients who decreased dosage were more likely than those whose dosage was unchanged to report that relationships with medical professionals "got worse" (55.0% vs 14.6%)	NR	NR
Von Korff, 2019[41] 31142	Percent of patients receiving ≥ 120 mg MED decreased from 16.8% to 6.3% in the intervention clinics. Average daily MED decreased from 75.8 to 40.0 mg among intervention patients, compared with a decrease of 92.1 to 64.6	NR	NR	NR	NR	NR	311 overdoses; 41 (13.2%) were fatal Reduction in overdose rate during dose reduction period in intervention group (RR

Author Year N	MEDD Outcomes	Pain Outcomes	Withdrawal Outcomes	Quality of Life/ Patient Satisfaction	Healthcare Utilization	Suicide or Depression	Opioid Overdose or Other Adverse Events
	mg among control patients.						0.83, 95% CI 0.70 to 0.99) but not in control group (RR 0.98, 95% CI 0.70 to 1.39)
Wang, 2011[42] 63	91% discontinued opioids by day 21 15% on opioids at 6 month follow-up	Decrease in heat pain thresholds over time, no difference compared to other groups (no opioids, healthy controls)	NR	NR	NR	NR	NR
Webster, 2016[43] 39	92% completed both 24 hour treatments	No change from baseline in mean NRS scores	2/33 patients in 80-161 mg MED group experienced opioid withdrawal No difference in mean COWS total score in buprenorphine and opioid groups during intervention (4.6 to 5.5 bup. vs 5.3 to 6.3 opioid)	NR	NR	NR	In 80-161 mg MED group, 56.3% and 41% experienced an adverse event during buprenorphine and full agonist treatment, respectively
Weimer, 2016[44] 516	37% reduced opioid dose below 120 mg Mean opioid dose decreased from 263 mg to 199 mg	Among patients who reduced opioid dose pain (mean NRS 5.4 vs 5.6) did not change post intervention vs pre intervention	NR	Among patients who reduced opioid dose, QoL (mean NRS 5.1 vs 5.2) did not change	NR	NR	NR

Author Year N	MEDD Outcomes	Pain Outcomes	Withdrawal Outcomes	Quality of Life/ Patient Satisfaction	Healthcare Utilization	Suicide or Depression	Opioid Overdose or Other Adverse Events
				post intervention vs pre intervention.			
Younger, 2008[45] 12	58% discontinued opioid therapy; 17% greatly reduced high-dose therapy	Baseline vs discharge: Pain tolerance: 18.3 vs 12.7 (P = 0.03) VAS pain: 6.9 vs 6.4 (P = 0.57)	Baseline vs discharge: Objective SOWS: 1.1 vs 0.7 (P = 0.17) Subjective SOWS: 22.8 vs 15.8 (P = 0.26)	NR	NR	NR	NR
Ziadni, 2018[46] 51	MEDD at 4-month follow-up: median 150 dose reduced (P=.002), exceeding 50% dose reduction	Pain intensity and pain interference did not increase with opioid reduction (P = 0.29)	NR	NR	NR	NR	NR

Abbreviations: FSD = fixed starting dose; ISD = individualized starting dose; MED = morphine equivalent dose

QUALITY ASSESSMENT OF INCLUDED SYSTEMATIC REVIEWS

Author Year	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Study Appraisal	Synthesis and Findings	Overall Risk of Bias
Frank, 2017[47]	Low The review adhered to pre-defined and appropriate objectives and eligibility criteria.	Low The search strategy was published and included appropriate terms and covered a range of databases/electronic. There were no restrictions on publication date.	Low All relevant study characteristics were collected and reviewed by two authors. Study appraisal was assessed using criteria developed by the U.S. Preventive Services Task Force. Overall quality was assessed using GRADE.	Low All pre-defined analyses were reported. There was not attempted meta-analyses due to heterogeneity across and methodological limitations of included studies.	Low Well conducted review that followed PRISMA guidelines.

QUALITY ASSESSMENT OF INCLUDED PRIMARY STUDIES

Quality Assessment of RCTs

Author Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of participants and personnel?	Blinding of outcome assessors?	Incomplete outcome data?	Selective reporting?	Overall risk of bias?
Kurita, 2014[25]	Unclear Randomization (1:1) was done by the research nurses, not details on sequence generation.	Low Concealment was performed using a sealed envelope system.	Unclear Participants and nurses unable to be blinded due to nature of the intervention. The nurses at the Multidisciplinary Pain Centre who were involved in the treatment reinforced the procedures of each treatment arm and followed-up patients in both groups by telephone appointments according to the clinical routine.	Unclear Outcomes pulled from patient records were performed by the same nurses who treated the patients.	Unclear 86% of those randomized completed 4th assessment 47% of total enrolled randomized	Low Reporting of pre-specified outcomes	Unclear

Quality Assessment of Observational Studies

Author, Year	Selection bias (High, Low, Unclear)	Bias in classification of interventions (High, Low, Unclear)	Bias due to departures from intended interventions (High, Low, Unclear)	Bias due to measurement of outcomes? (High, Low, Unclear)	Bias due to confounding? (High, Low, Unclear)	Bias due to missing data? (High, Low, Unclear)	Bias in the selection of reported results (High, Low, Unclear)	Overall bias (High, Low, Unclear)
Bienek, 2019[3]	Unclear Patients who abandoned the tapering program during the first five days were excluded. Statistically difference in number excluded between groups.	Low Control and experimental groups were clearly defined by time period of opioid withdrawal.	Unclear No information on fidelity to intervention or co-interventions. Patients could request psychotherapy or physiotherapy, but no info on how many did.	Low Methods of assessment were identical between groups. Self-assessment by patients during their time stay, data was gathered retrospectively, so patients didn't know they were a part of a study.	Low Groups similar at baseline, appropriate sub-group analyses were performed to identify and adjust for potential confounders.	Unclear 37% of patients not included in final analysis. Analyzed differences between included and excluded patients. Only difference was in age.	Low Reported based on results from multiple analyses, multiple outcome measurements, and different subgroups.	Unclear

Author, Year	Selection bias (High, Low, Unclear)	Bias in classification of interventions (High, Low, Unclear)	Bias due to departures from intended interventions (High, Low, Unclear)	Bias due to measurement of outcomes? (High, Low, Unclear)	Bias due to confounding? (High, Low, Unclear)	Bias due to missing data? (High, Low, Unclear)	Bias in the selection of reported results (High, Low, Unclear)	Overall bias (High, Low, Unclear)
Sharp, 2018[35]	Low Retrospective groups based on whether or not dose was reduced. Differences between groups adjusted for in analyses.	Low Control and experimental groups were clearly defined.	Unclear No specific details on clinical encounters that led to either dosage reduction or not. No information on potential co-interventions during the dose reduction period.	Unclear Unclear how opioid dose was measured. Other factors self-reported.	Low Mixed effects regression and sub-group analyses performed. Adjusted for patient age, patient gender, Elixhauser score, provider years of experience, assigned primary care provider visit, and provider partner status to account for observable differences between groups.	Unclear Missing data were not mentioned.	Low Reported based on results from multiple analyses, multiple outcome measurements, and different subgroups.	Unclear
Thakral, 2018[37]	Unclear Response rates varied from 39.7% among group practice patients to 27.8% among contracted care patients.	Low Control and experimental groups were clearly defined.	Unclear Fidelity to intervention not described, unclear if outside providers had any sort of opioid tapering interventions or intents.	Unclear Patient reported measures via telephone interviews, interviewers likely knew if patients were a part of the intervention, since it was the location of care.	Unclear Control group patients seen at different clinics, adjusted for patient-level covariates, but may be other potential confounders (*ie*, baseline pain, baseline MED).	Low Analyses were weighted for nonresponse, low level of missing data (<1%)	Low Reported based on results from all predefined analyses.	Unclear

Author, Year	Selection bias (High, Low, Unclear)	Bias in classification of interventions (High, Low, Unclear)	Bias due to departures from intended interventions (High, Low, Unclear)	Bias due to measurement of outcomes? (High, Low, Unclear)	Bias due to confounding? (High, Low, Unclear)	Bias due to missing data? (High, Low, Unclear)	Bias in the selection of reported results (High, Low, Unclear)	Overall bias (High, Low, Unclear)
Von Korff, 2019	Low All patients on chronic opioid therapy within the health plan included.	Low Control and experimental groups were clearly defined.	Unclear Unclear if providers/care differed between groups or if there were any co-interventions.	Low Objective outcome measures which were pre-defined for opioid overdose.	Unclear Control group patients seen at different clinics, adjusted for patient-level covariates, but may be other potential confounders (*ie*, baseline pain, baseline MED).	Unclear Analyses were weighted for nonresponse. Unclear level of missing data.	Low Reported based on results from multiple analyses, multiple outcome measurements, and different subgroups.	Unclear

Abbreviations: MED = morphine equivalent dose; RCT = randomized controlled trial

PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	*None*
2	2	Yes	*None*
3	3	Yes	*None*
4	4	Yes	*None*
5	5	Yes	*None*
Is there any indication of bias in our synthesis of the evidence?			
6	1	No	*None*
7	2	No	*None*
8	3	No	*None*
9	4	No	*None*
10	5	No	*None*
Are there any published or unpublished studies that we may have overlooked?			
11	1	No	*None*
12	2	No	*None*
13	3	No	*None*
14	4	Yes - Mark TL, Parish W. Opioid medication discontinuation and risk of adverse opioid-related health care events. J Subst Abuse Treat. 2019 Aug;103:58-63	We did not identify this study in our literature search because the study was published after our search date. We have now included this study.
15	5	No	*None*
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.			
	1	Overall, this is really well done: strong writing, methodologically sound, nuanced interpretations of a challenging subject.	Thank you.
	1	Clearly identify the potential benefits of tapering (ie - why consider doing it in the first place) and frame the findings in terms of whether or not there is evidence that LTOT achieves those benefits (which is different from saying it does not seem to worsen outcome)	We appreciate this suggestion and have added language to the introduction to more clearly describe the potential risks and benefits of LTOT as well as the risks and benefits of tapering. We also cite the goal of tapering per VHA/DoD guidelines, “the goal of opioid tapering is to “improve the balance of risks and clinically meaningful benefits for patients on LTOT.”
	1	consider changing "very low" to "insufficient" - in my opinion, very low is often interpreted similarly to "low" by	We used the GRADE framework for assessing the quality (certainty) of the body of evidence because

	readers that are not intimately familiar with review terminology (which will be most readers) - if the point is really to convey a lack of enough data to draw any meaningful conclusions, then I think "insufficient" or "inconclusive" is more direct	this is the framework used by Frank et al and we wanted findings to be comparable. GRADE uses the terms low and very low, rather than insufficient. However, we agree that this term will not be meaningful to most readers. We changed language in the Key Findings and Executive Summary and Discussion to emphasize that evidence is inconclusive and that the distinction between low and very low is probably not clinically important. For example, in the Discussion section we now state the following: “The distinction between low and very low quality of evidence has little clinical importance as the bottom-line is the same – despite findings that pain and pain-related function may improve or remain unchanged with LTOT tapers, limitations of the evidence do not allow strong conclusions to be made based on these results and it is possible that future studies may have different findings.”
1	the summary finding that pain is unchanged or improves in most patients following LTOT is not clearly supported by the evidence as presented in the results. I would suggest either modifying the summary statement, or the way the results are presented to better align with the statement.	We agree that the original wording was overly broad. We have revised the language in the Executive Summary, Results, and Discussion as follows in order to convey more nuanced results. For example, in the Executive Summary we now state the following: “Patients on LTOT who voluntarily participate in intensive pain management interventions that incorporate opioid tapering may experience improvements in pain severity and pain-related function, while those who taper opioids with less intensive co-interventions may have unchanged pain and function. However, our confidence in these findings is low and additional evidence is needed before drawing stronger conclusions.” We also highlight the questionable clinical importance of mean changes in pain and function scales.

1	the issues re: intervention, population, voluntary vs involuntary taper etc are mentioned in the report, but they are so critical that the evidence should be more clearly presented in the context of these considerations. For example, a different way of phrasing the summary statement at the beginning of the conclusions would be something like "Among patients who chose to enroll in a complex, multimodal, multi-week intensive pain intervention which included LTOT, pain scores improved or were stable at the end of the intervention period". I think that conveys something pretty different from the current phrasing, even with the qualifier in the second sentence.	We appreciate this point and have made revisions in the Results and Discussion sections to frame our findings more clearly in the context of intervention types. For example, in the Discussion section we now state the following: “The greatest improvements in pain severity and function were among studies of intensive multimodal rehabilitation programs, including an inpatient VHA program. However, it is unlikely that a majority of patients with chronic pain on LTOT would have the means to travel to where such programs are offered or have sufficient motivation to do so. Also, the clinical importance of the changes in mean pain scores is unclear as noted above. Studies were also not designed to evaluate long-term outcomes, which would be particularly important to know given that interventions were limited to several weeks and patients may not have experienced sustained improvements.”
1	consider presenting the results in a "best evidence" framework according to the intensity of the intervention - eg - "The best evidence examining LTOT in the context of intensive pain interventions comes from....", "The best evidence examining LTOT as a stand-alone intervention or an intervention with minimal additional co-intervention comes from...."	Our synthesis focuses entirely on the “best evidence.” Our synthesis is limited only to a subset of studies we identified as the highest priority that are the most applicable and informative for VHA: 1) studies conducted in VHA settings, 2) studies conducted in non-VHA outpatient settings with sufficiently described patient populations and tapering interventions to assess their applicability to VHA, 3) studies that evaluated serious harms of tapering (*ie*, suicide and overdose). In this way, we have used a “best evidence” framework. We made revisions as above to frame our findings more clearly in terms of the types of interventions (high intensity vs low) and used the phrase “best evidence” when results of one study were particularly important to highlight.

		For example, in the Results section we state the following: “The impact of LTOT tapers on new or increased substance use is unclear, as studies have not directly examined this outcome. The best evidence comes from the 2019 study by Mark et al of Medicaid claims data in Vermont among patients who discontinued opioids. Retrospectively, the investigators assembled a cohort of 694 Medicaid recipients who were on ≥ 120mg MEDD…”
1	the graphs are perhaps too nice/digestible given the many questions in the evidence base. Consider simply presenting key data from each study rather than an over-simplified summary of the evidence.	We appreciate this point and removed this stable from the Executive Summary.
2	This evidence synthesis builds on and extends the review by Frank et al. (2017) on patient outcomes following intervention to taper or discontinue long-term opioid therapy by adding 9 new articles and selecting 34 of 40 from the Frank et al. article. The authors should be commended in their decision to include additional patient outcomes (e.g., mental health, including suicide, and substance use outcomes). Perhaps not surprisingly, and possibly why Frank et al. chose not to include them, the number of studies addressing these outcomes is very limited and little can be said about the evidence in these domains, other than additional high-quality studies are needed. One additional point of consideration is the authors' note that poor quality studies were excluded from the review (p. 10, line 25). It is thus surprising that the overall strength of evidence from the included studies is low or very low. This requires some clarification. Overall, this is a nicely conducted evidence synthesis that extends the findings of Frank et al.	Thank you. Although we prioritized synthesis of fair or better quality studies, our confidence in their findings remains low or very low due to limitations of observational study design and sparse and/or inconsistent evidence for several outcomes. We applied the following general algorithm: evidence comprised of multiple mostly uncontrolled studies with consistent findings received a rating of “low”; whereas, the same type of evidence with few studies and/or indirectness and inconsistency would be downgraded to “very low.” For example, we identified very only 2 studies that evaluated healthcare utilization and the results were not consistent, so we considered the quality of evidence “very low.” We updated the language in our paragraph describing how we decided to prioritize studies to clarify our methods as follows: “We prioritized synthesis of evidence that was most likely to be informative and applicable to VHA. Fifteen studies (Table 1) (2 RCTs,[34,66] 2 controlled observational studies,[70,72] and 11 uncontrolled

		observational studies[43,46,48,49,52,56,71,73-76]) met these criteria, which we refer to as prioritized studies. The remaining studies either had low applicability to VHA patients or care settings or included patients or interventions that were not well-described. Also, we abstracted information from but do not discuss in detail studies included in Frank et al that were deemed poor quality, unless they met our prioritization criteria."
3	Page 4, line 23-24: In addition to a lack of access to non-pharmacologic pain treatments, system barriers to adequate social and psychological support and access to mental health and substance use disorder treatment when needed during tapering should be considered.	We agree and have revised this sentence as follows: "Lack of access to non-pharmacologic pain treatments such as physical therapy, psychosocial support services, and mental health and substance use disorder treatment may also contribute to patient concerns about stopping opioids without adding more supports."
3	Page 18, Section: Substance Use, lines 11-27: Clinician-initiated LTOT tapering may have been due to evidence of aberrant behaviors potentially indicating an underlying or pre-existing substance use disorder, including opioid use disorder. Therefore, the specific indication for tapering is an important factor to consider when evaluating the outcome of increased or new substance use disorders. For example, the retrospective VHA study by McPherson et al evaluated mostly (75%) clinician-initiated tapers due to aberrant behaviors. Evaluating a larger and more diverse population of LTOT tapering will be important to determining the true rate of new or increased substance use disorders as an outcome of tapering in the general LTOT population.	We agree and highlighted this point in our discussion of the 2019 Mark et al study in the Results section. Our discussion of this study includes the following language: "This study does not describe the circumstances regarding opioid discontinuation or exclude the potential for reverse causality (i.e. a diagnosis of substance use disorder was the reason prescription opioids were discontinued). This limitation highlights why understanding the indications for LTOT discontinuation is important to interpret the impact of tapering on new or increased substance use." We also highlight in several patients in the report that 2 distinct patient groups are of interest. "Two distinct patient groups with potentially different risks for LTOT tapering harms should be considered, those who voluntarily engage in a tapering plan and

		those who are tapering due to clinician concerns for LTOT safety and/or opioid misuse."
3	Page 18, Section: Opioid Overdose, lines 31-34: As noted with suicide-related events, evaluating the outcome of opioid overdose with the current available evidence may be limited by underreporting and limited documentation as many studies published have been observational and/or retrospective with information gathered via chart review. Patients who disengage with care due to tapering may be even less likely to have the outcomes of overdose or suicide-related events reported, making identification of patients who disengage or seek care elsewhere important to consider.	We agree and added the following sentence to the Opioid Overdose section in Results following the discussion of Hundley et al, "An important limitation of this and other observational studies based on chart review is likely underreporting of total opioid overdoses due to inability to account for patients who disengage in medical care or who seek care elsewhere." To further highlight this point, we also added language to the Results section regarding the study by Demidenko et al, "The study also excluded patients who had no VHA contact in the year following discontinuation, which also could have led to an underestimate of suicidal ideation and suicidal self-directed violence."
	Page 22, Section: Limitations, lines 39-42 / Page 23, Section: Gaps and Future Research, lines 15-17 and line 45: · In addition to fewer patients being prescribed high doses, other changes in opioid prescribing habits may impact tapering outcomes (e.g. long-acting vs short-acting opioids, methadone vs other opioids for chronic pain). · While it may be challenging to accomplish, future comparisons and consideration of the specific opioid regimen may be a factor to investigate given that pharmacologic differences may theoretically influence tapering outcomes.	We agree and added the following language to the limitations section, "Other changes in opioid prescribing practices (eg short-acting vs long-acting or specific opioids such as methadone vs other opioids) may also limit the applicability of studies to current practice." We also revised the language to the Gaps and Future Research section to highlight this gap by stating, "Specific patient and intervention characteristics associated with improved pain and function following opioid tapers, including how outcomes may differ between voluntary/patient-initiated tapers and mandated tapers and by opioid regimen."
	Page 23, Section: Gaps and Future Research: Many studies were in patients tapered within specific programs or pain clinics, which may have an increased level of patient support and monitoring during and after tapering compared to other treatment settings. Further research to inform tapering in other settings (e.g. primary care) and	We agree and added the following statement to the Gaps and Future Research section, "Given that multiple studies to date have been conducted in pain clinics or other specialized settings such as functional rehabilitation programs, further research in primary care settings is needed to evaluate

	appropriate identification of the need for referral to a higher level of care for LTOT tapering is needed.	outcomes with moderate and low-intensity interventions."
4	Page 1-2: The Executive Summary is very well-written, clear & concise.	Thank you.
4	Page 6: Consider presenting bulleted list of pre-specified benefits & harms. In the current presentation, it is not clear that this list was pre-specified. A bulleted list would also align well with presentation of KQ2. Also, recommend removing "(through reduction in opioid-induced hyperalgesia)". This would be appropriate in the Discussion but is unnecessary here.	The outcomes were prespecified and are listed as such in the protocol on PROSPERO, (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42019129110. We have removed the reference to opioid-induced hyperalgesia.
4	Page 10: It is not clear why "Voluntary or Mandated Tapers" is given a separate section here as this presentation does not align with the KQ1/KQ2 organization. Consider one more subheading above such as 'Sample Characteristics'.	Our intent was to break up a long section and agree that the separate subheading for "Voluntary or Mandated Tapers" may have added confusion that was not intended. We added "Sample Characteristics" as another subheading and revised the second subheading to "Taper Characteristics."
4	Page 21-23: Also well-written and clear. The Limitations section appropriately notes several key limitations.	Thank you.
5	There is some potential for confusion with discussion of "physiologic dependence", "complex persistent opioid dependence". and "iatrogenic opioid addiction" on p4 l.45-l. 55. Real clarity is likely not possible because these concepts are actively evolving. Perhaps we just need to state this.	We agree and have removed the sentence pertaining to "iatrogenic opioid addiction" to avoid introducing too many definitions. We also revised the discussion of complex persistent opioid dependence as follows: "The concept of "complex persistent opioid dependence" has been introduced by experts in the field of pain management and addiction medicine to describe a type of opioid dependence that results from long-term treatment with opioids for pain. For some patients, this dependence is not easily reversible and can manifest as protracted withdrawal symptoms including mood and sleep disturbance, rebound of pain symptoms, irritability and decreased ability to focus, and exacerbation of underlying mental health disorders. While the criteria that define "complex persistent opioid

		dependence" are still evolving, the concept may help explain the destabilization that can occur for some patients during opioid tapers, which can present as erratic behaviors and new or increased use of illicit opioids and other substances."
5	On Gaps and Future Research, on p. 23 l. 8-9, the following might be added to the second bullet concerning "rates of newly diagnosed OUD during LTOT tapers": prevalence of "complex persistent opioid dependence", including possibly criteria to distinguish this CPOD from OUD.	We agreed and have revised language in the Gaps and Future Research section, "Rates of newly diagnosed OUD during LTOT tapers, prevalence of "complex persistent opioid dependence" and criteria distinguishing this diagnosis from OUD, and the percentage of patients who are referred to substance use treatment."

REFERENCES

1. Baron MJ, McDonald PW. Significant pain reduction in chronic pain patients after detoxification from high-dose opioids. *Journal of Opioid Management.* 2006;2(5):277-282.
2. Berland DW, Malinoff HL, Weiner MA, Przybylski R. When opioids fail in chronic pain management: The role for buprenorphine and hospitalization. *American Journal of Therapeutics.* 2013;20(4):316-321.
3. Bienek N, Maier C, Kaisler M, Michel-Lauter B, Schwarzer A, Meyer-Friesem CH. Intensity of withdrawal symptoms during opioid taper in patients with chronic pain-individualized or fixed starting dosage? *Pain Medicine.* 2019;26.
4. Blondell RD, Ashrafioun L, Dambra CM, Foschio EM, Zielinski AL, Salcedo DM. A clinical trial comparing tapering doses of buprenorphine with steady doses for chronic pain and co-existent opioid addiction. *Journal of Addiction Medicine.* 2010;4(3):140-146.
5. Cowan DT, Wilson-Barnett J, Griffiths P, Vaughan DJ, Gondhia A, Allan LG. A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. *Pain Medicine.* 2005;6(2):113-121.
6. Crisostomo RA, Schmidt JE, Hooten WM, Kerkvliet JL, Townsend CO, Bruce BK. Withdrawal of analgesic medication for chronic low-back pain patients: Improvement in outcomes of multidisciplinary rehabilitation regardless of surgical history. *American Journal of Physical Medicine & Rehabilitation.* 2008;87(7):527-536.
7. Cunningham JL, Evans MM, King SM, Gehin JM, Loukianova LL. Opioid tapering in fibromyalgia patients: Experience from an interdisciplinary pain rehabilitation program. *Pain Medicine.* 2016;17(9):1676-1685.
8. Daitch J, Frey ME, Silver D, Mitnick C, Daitch D, Pergolizzi J, Jr. Conversion of chronic pain patients from full-opioid agonists to sublingual buprenorphine. *Pain Physician.* 2012;15(3 Suppl):Es59-66.
9. Daitch D, Daitch J, Novinson D, Frey M, Mitnick C, Pergolizzi J, Jr. Conversion from high-dose full-opioid agonists to sublingual buprenorphine reduces pain scores and improves quality of life for chronic pain patients. *Pain Medicine.* 2014;15(12):2087-2094.
10. Darchuk KM, Townsend CO, Rome JD, Bruce BK, Hooten WM. Longitudinal treatment outcomes for geriatric patients with chronic non-cancer pain at an interdisciplinary pain rehabilitation program. *Pain Medicine.* 2010;11(9):1352-1364.
11. Darnall BD, Ziadni MS, Stieg RL, Mackey IG, Kao MC, Flood P. Patient-centered prescription opioid tapering in community outpatients with chronic pain. *JAMA Internal Medicine.* 2018;178(5):707-708.
12. Demidenko MI, Dobscha SK, Morasco BJ, Meath TH, Ilgen MA, Lovejoy TI. Suicidal ideation and suicidal self-directed violence following clinician-initiated prescription opioid discontinuation among long-term opioid users. *General Hospital Psychiatry.* 2017;47:29-35.
13. Dersh J, Mayer TG, Gatchel RJ, Polatin PB, Theodore BR, Mayer EA. Prescription opioid dependence is associated with poorer outcomes in disabling spinal disorders. *Spine.* 2008;33(20):2219-2227.
14. Drossman DA, Morris CB, Edwards H, et al. Diagnosis, characterization, and 3-month outcome after detoxification of 39 patients with narcotic bowel syndrome. *American Journal of Gastroenterology.* 2012;107(9):1426-1440.

15. Harden P, Ahmed S, Ang K, Wiedemer N. Clinical implications of tapering chronic opioids in a veteran population. *Pain Medicine.* 2015;16(10):1975-1981.
16. Heiwe S, Lonnquist I, Kallmen H. Potential risk factors associated with risk for drop-out and relapse during and following withdrawal of opioid prescription medication. *European Journal of Pain.* 2011;15(9):966-970.
17. Hooten WM, Townsend CO, Sletten CD, Bruce BK, Rome JD. Treatment outcomes after multidisciplinary pain rehabilitation with analgesic medication withdrawal for patients with fibromyalgia. *Pain Medicine.* 2007;8(1):8-16.
18. Hooten WM, Townsend CO, Decker PA. Gender differences among patients with fibromyalgia undergoing multidisciplinary pain rehabilitation. *Pain Medicine.* 2007;8(8):624-632.
19. Hooten WM, Townsend CO, Bruce BK, Warner DO. The effects of smoking status on opioid tapering among patients with chronic pain. *Anesthesia and Analgesia.* 2009;108(1):308-315.
20. Hooten WM, Warner DO. Varenicline for opioid withdrawal in patients with chronic pain: A randomized, single-blinded, placebo controlled pilot trial. *Addictive Behaviors.* 2015;42:69-72.
21. Huffman KL, Rush TE, Fan Y, et al. Sustained improvements in pain, mood, function and opioid use post interdisciplinary pain rehabilitation in patients weaned from high and low dose chronic opioid therapy. *Pain.* 2017;158(7):1380-1394.
22. Hundley L, Spradley S, Donelenko S. Assessment of outcomes following high-dose opioid tapering in a veterans healthcare system. *Journal of Opioid Management.* 2018;14(2):89-101.
23. Kidner CL, Mayer TG, Gatchel RJ. Higher opioid doses predict poorer functional outcome in patients with chronic disabling occupational musculoskeletal disorders. *Journal of Bone and Joint Surgery.* 2009;91(4):919-927.
24. Krumova EK, Bennemann P, Kindler D, Schwarzer A, Zenz M, Maier C. Low pain intensity after opioid withdrawal as a first step of a comprehensive pain rehabilitation program predicts long-term nonuse of opioids in chronic noncancer pain. *Clinical Journal of Pain.* 2013;29(9):760-769.
25. Kurita GP, Hojsted J, Sjogren P. Tapering off long-term opioid therapy in chronic non-cancer pain patients: A randomized clinical trial. *European Journal of Pain.* 2018;22(8):1528-1543.
26. Malinoff HL, Barkin RL, Wilson G. Sublingual buprenorphine is effective in the treatment of chronic pain syndrome. *American Journal of Therapeutics.* 2005;12(5):379-384.
27. Mark TL, Parish W. Opioid medication discontinuation and risk of adverse opioid-related health care events. *Journal of Substance Abuse Treatment.* 2019.
28. McPherson S, Lederhos Smith C, Dobscha SK, et al. Changes in pain intensity after discontinuation of long-term opioid therapy for chronic noncancer pain. *Pain.* 2018;159(10):2097-2104.
29. Murphy JL, Clark ME, Banou E. Opioid cessation and multidimensional outcomes after interdisciplinary chronic pain treatment. *Clinical Journal of Pain.* 2013;29(2):109-117.
30. Nilsen HK, Stiles TC, Landro NI, Fors EA, Kaasa S, Borchgrevink PC. Patients with problematic opioid use can be weaned from codeine without pain escalation. *Acta Anaesthesiologica Scandinavica.* 2010;54(5):571-579.

31. Rome JD, Townsend CO, Bruce BK, Sletten CD, Luedtke CA, Hodgson JE. Chronic noncancer pain rehabilitation with opioid withdrawal: Comparison of treatment outcomes based on opioid use status at admission. *Mayo Clinic Proceedings.* 2004;79(6):759-768.
32. Rosenblum A, Cruciani RA, Strain EC, et al. Sublingual buprenorphine/naloxone for chronic pain in at-risk patients: Development and pilot test of a clinical protocol. *Journal of Opioid Management.* 2012;8(6):369-382.
33. Roux P, Sullivan MA, Cohen J, et al. Buprenorphine/naloxone as a promising therapeutic option for opioid abusing patients with chronic pain: Reduction of pain, opioid withdrawal symptoms, and abuse liability of oral oxycodone. *Pain.* 2013;154(8):1442-1448.
34. Schwarzer A, Aichinger-Hinterhofer M, Maier C, Vollert J, Walther JW. Sleep-disordered breathing decreases after opioid withdrawal: Results of a prospective controlled trial. *Pain.* 2015;156(11):2167-2174.
35. Sharp AL, Shen E, Wu YL, et al. Satisfaction with care after reducing opioids for chronic pain. *American Journal of Managed Care.* 2018;24(6):e196-e199.
36. Sullivan MD, Turner JA, DiLodovico C, D'Appollonio A, Stephens K, Chan Y-F. Prescription opioid taper support for outpatients with chronic pain: A randomized controlled trial. *Journal of Pain.* 2017;18(3):308-318.
37. Thakral M, Walker RL, Saunders K, et al. Comparing pain and depressive symptoms of chronic opioid therapy patients receiving dose reduction and risk mitigation initiatives with usual care. *Journal of Pain.* 2018;19(1):111-120.
38. Taylor CB, Zlutnick SI, Corley MJ, Flora J. The effects of detoxification, relaxation, and brief supportive therapy on chronic pain. *Pain.* 1980;8(3):319-329.
39. Townsend CO, Kerkvliet JL, Bruce BK, et al. A longitudinal study of the efficacy of a comprehensive pain rehabilitation program with opioid withdrawal: Comparison of treatment outcomes based on opioid use status at admission. *Pain.* 2008;140(1):177-189.
40. Twillman RK, Hemmenway N, Passik SD, Thompson CA, Shrum M, DeGeorge MK. Impact of opioid dose reduction on individuals with chronic pain: Results of an online survey. *Journal of Pain Research.* 2018;11:2769-2779.
41. Von Korff M, Saunders K, Dublin S, et al. Impact of chronic opioid therapy risk reduction initiatives on opioid overdose. *Journal of Pain.* 2019;20(1):108-117.
42. Wang H, Akbar M, Weinsheimer N, Gantz S, Schiltenwolf M. Longitudinal observation of changes in pain sensitivity during opioid tapering in patients with chronic low-back pain. *Pain Medicine.* 2011;12(12):1720-1726.
43. Webster L, Gruener D, Kirby T, Xiang Q, Tzanis E, Finn A. Evaluation of the tolerability of switching patients on chronic full mu-opioid agonist therapy to buccal buprenorphine. *Pain Medicine.* 2016.
44. Weimer MB, Hartung DM, Ahmed S, Nicolaidis C. A chronic opioid therapy dose reduction policy in primary care. *Substance Abuse.* 2016;37(1):141-147.
45. Younger J, Barelka P, Carroll I, et al. Reduced cold pain tolerance in chronic pain patients following opioid detoxification. *Pain Medicine.* 2008;9(8):1158-1163.
46. Ziadni M, Stieg R, Mackey I, et al. Patient-centered prescription opioid tapering in community outpatients with chronic pain. *Pain Medicine.* 2018;19(4):860-861.
47. Frank JW, Lovejoy TI, Becker WC, et al. Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: A systematic review. *Annals of Internal Medicine.* 2017;167(3):181-191.