

Primary care-based interventions for secondary prevention of opioid dependence in chronic non-cancer pain patients on pharmaceutical opioids: Systematic review

SUPPLEMENTARY MATERIAL

Box S1. Medline (Ovid) search strategy

Note: Intervention studies selected for inclusion in this review, from an initial, broad (population-only), search of the Cochrane Library, were analysed to help identify key search terms, for the different types of intervention used in the secondary prevention of pharmaceutical opioid dependence. These search terms were then used to help increase the specificity of the remaining database searches. An example (Ovid MEDLINE) search strategy is provided here.

Ovid MEDLINE(R) ALL <1946 to November 14, 2022>

[Search structure: Population + Intervention + Study Design Filter]

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1      ((chronic opioid? adj2 (therap* or treat*)) and pain).mp.512
2      (((longterm or long* term) adj2 opioid?) and pain).mp. 1240
3      (COT or LTOT).tw,kf. and pain.mp.      225
4      (chronic opioid? or ((longterm or long* term) adj2 opioid?)).ti. 990
5      or/1-4 2151
6      ((chronic or longterm or long* term) adj2 pain).mp.      74450
7      ((chronic noncancer adj2 pain) or (chronic non-cancer adj2 pain) or CNCP).tw,kf. 1678
8      pain clinic?.mp. 3857
9      *Pain/ and drug therapy.fs.      23652
10     pain.ti. 216565
11     or/6-10 254193
12     ((opioid? or opiate?) adj2 (analgesi* or medicat* or painkiller? or pain killer? or
13     pharmacotherap* or therap* or treat*)).tw,kf. 26600
14     ((prescrip* or prescrib*) and (opiate? or opioid?)).mp. 19222
15     ((prescrip* or prescrib*) and (Alfentanil* or Buprenorphin* or Butorphanol* or Codein* or
16     Co-codamol* or Codamol* or Codydramol* or Co-dydramol* or Coproxamol* or Co-
17     proxamol* or Dextropropoxyphen* or Dezocin* or Dihydrocodein* or Dihydromorphin* or
18     Diamorphin* or Dipipanon* or Pipadon* or Ethylmorphin* or Fentanyl* or Fentanil* or
19     Hydrocodon* or Hydromorphon* or Ketobemidon* or Levorphanol* or Meperidin* or
20     Meptazinol* or Morphin* or Methadon* or Nalbuphin* or Oxycodon* or Oxycontin* or
21     Oxymorphon* or Papaveretum* or Pentazocin* or Pethidin* or Meperidin* or
22     Propoxyphen* or Dextropropoxyphen* or Remifentanil* or Sufentanil* or Tapentadol* or
23     Tramadol* or Percocet* or Vicodin*)).mp.      9221
24     ((prescrip* or prescrib*) and (analgesi* or medication? or pharma* or painkiller? or pain
25     killer?)).tw,kf. 95481
26     ((opioid? or opiate?) adj5 (aberran* use* or (aberran* adj3 behavi*) or abus* or addict* or
27     misus* or dependenc* or dependent or noncomplian* or non-complian* or overus* or over-
28     us* or problem* or violat*)).tw,kf.      19152
29     or/12-16      134655
30     (11 and 17)      15401
31     (5 or 18)      16225
32     education.mp. 1026648
33     academic detailing.tw,kf.      613
34     (drug? adj3 screening).tw,kf. 17535
35     Risk Assessment/      302457
36     Risk Management/      19320
37     (monitoring or surveillance).tw,kf.      807137
38     (((drug or urine) adj2 (tests or testing or screens or screening)) or urinalysis).mp. 82323
39     chronic care model*.tw,kf.      1043
40     ((opioid? or opiate?) adj management).tw,kf.      212
41     ((opioid? or opiate?) adj2 (agreement? or contract? or plan?)).tw,kf.      174
42     (patient? adj3 (provider? or prescriber?) adj3 (contract? or agreement?)).tw,kf. 92

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31 ((therap* or treatment*) adj (agreement? or contract?)).tw,kf. 422
 32 (risk? adj1 (assess* or manag*)).tw,kf. 117646
 33 (safe* adj3 (opioid? or opiate?) adj3 manag*).tw,kf. 43
 34 Prescription Drug Monitoring Programs/ 399
 35 pharmaceutical care.mp. 2949
 36 Counseling/ 39082
 37 Motivational Interviewing/ 2474
 38 Biofeedback, Psychology/ 7671
 39 exp behavior therapy/ or exp cognitive behavioral therapy/ 86879
 40 psychotherapy.mp. 91338
 41 (behavi* adj (intervention or motivat* or support or therap*)).tw,kf. 36013
 42 (CBT or cognitive behavi*).tw,kf. 37907
 43 (counsel* or coach*).tw,kf. 149308
 44 (psycho* adj (intervention or motivat* or support or therap*)).tw,kf. 25483
 45 (feedback or feed* back).tw,kf. 168669
 46 motivat* interview*.tw,kf. 5373
 47 Patient Care Planning/ 39456
 48 treatment plan*.tw,kf. 71780
 49 intersectoral collaboration/ 2566
 50 collaborative care.tw,kf. 3013
 51 ((interdisciplinary or inter-disciplinary or inter-profession* or interprofession* or
 intersector* or inter-sector* or cross-sector* or joint-profession* or jointprofession* or
 jointsector* or joint sector* or multi-agenc* or multiagenc* or multidisciplinary or multi-
 disciplinary or multi-organi?ation* or multiorgani?ation* or multi-profession* or
 multiprofession* or multisector* or multi-sector*) adj3 (collaborat* or coordinat* or co-
 ordinat* or cooperat* or co-operat* or care or delivery or healthcare or intergrat* or
 model* or network* or partners* or pathway? or practice* or program* or service? or
 strateg* or resources or teams or working)).tw,kf. 54386
 52 nurse care manage*.tw,kf. 184
 53 (patient? adj1 (cent* or focus* or tailor*)).mp. 60004
 54 ((speciali* or tailor*) adj prescri*).tw,kf. 173
 55 practice guideline/ 30119
 56 guideline adherence/ 34873
 57 ((guideline? or protocol) adj5 (adopt* or adher* or comply or complian* or
 concordan*)).tw,kf. 32138
 58 Decision Support Systems, Clinical/ 9246
 59 decision support.tw,kf. 20966
 60 (multicomponent* or multi-component or multidimension* or multi* dimension* or
 multifactor* or multi* factor* or multifacet* or multi* facet* or multilevel* or multi* level*
 or multimodal* or multi* mod* or multiparamet* or multi* paramet*).tw,kf. 383064
 61 intervention.ti. or (intervention and control*).ab,kf. 315837
 62 or/20-61 3424959
 63 (19 and 62) 4925
 64 (aberran* or aberan* or abus* or addict* or dependenc* or dependent or diversion or
 divergent or iatrogenic or inappropriate or in-appropriate or misus* or noncomplan* or
 non-complan* or overdos* or over-dos* or overus* or over-us* or problem* or risk* or
 violat* or harm* or safe*).mp. 7316116
 65 (63 and 64) 3382
 66 controlled clinical trial.pt. 95098
 67 randomized controlled trial.pt. 580762
 68 clinical trials as topic/ 200559
 69 (randomi#ed or randomi#ation or randomi#ing).tw,kf. 772855

70 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster
or crossover or cross-over or control* or determine* or divide* or division or distribut* or
expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or
substitut* or treat*))).tw,kf. 688569

71 placebo.tw,kf. 239907

72 trial.ti. 273844

73 (control* adj3 group*).ab. 636565

74 groups.ab. 2434274

75 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).tw,kf. 193955

76 double-blind method/ or random allocation/ or single-blind method/ 301295

77 (control* and (trial or study or group*) and ((treatment or care) adj2 usual)).tw,kf,hw.
23966

78 (nonrandom* or non-random* or nonRCT).tw,kf. 46364

79 (nonblind* or non-blind* or unblind* or un-blind*).tw,kf. 7287

80 comparative study.pt. 1911772

81 ((intervention or control* or compar*) adj3 group?).ab. 921486

82 (control* adj4 study).tw,kf. 276548

83 controlled before-after studies/ 706

84 "controlled before and after".tw,kf. 1283

85 (CBA or (before adj5 after)).tw,kf. 444534

86 (pre-post or (pre adj5 post) or ("pre test*" or pretest*) and (posttest* or "post
test*")).tw,kf. 133475

87 (pre-intervention? or preintervention? or "pre intervention?" or post-intervention? or
postintervention? or "post intervention?").tw,kf. 35077

88 (((pre-study or pre-program* or pre-project or pre-campaign or pre-initiative? or pre-
strateg* or prestudy or preprogram* or preproject or preinitiative? or prestrateg*) and
(post-study or post-program* or post-project or post-campaign or post-initiative? or post-
strateg* or poststudy or postprogram* or postproject or postinitiative? or poststrateg*)) or
(before and after and (pilot or program* or project or campaign or initiative? or
strateg*))).ab. 89720

89 (control* and (before adj10 (after or during))).ab. 156152

90 Interrupted Time Series Analysis/ 1715

91 (time series or time point? or repeated measur*).tw,kf. 233392

92 (quasiexperiment* or quasi experiment* or pseudo experiment* or
pseudoexperiment*).tw,kf. 19736

93 pragmatic clinical trial/ 2159

94 (multicentre or multicenter or multi centre or multi center).ti. 72220

95 (intervention? and (controlled or control?) and (effect? or effectiveness or evaluat* or
impact?)).mp. 344535

96 or/66-95 5942760

97 65 and 96 1206

98 ((acute adj2 pain) not chronic).ti. 6234

99 (((perioperative or peri-operative) adj2 pain) not chronic).ti. 452

100 (advanc* cancer or "in cancer" or "with cancer" or cancer surgery or oncolog* or life
limiting).ti. 138975

101 ((p?ediatric* or infant* or child or children or adolescen* or teen* or youth?) not adult?).ti.
1227532

102 ((prevalence or incidence) not (intervention? or trial)).ti.267629

103 cross-sectional stud*.ti. 51224

104 (survey.pt. or survey.ti.) not (intervention or trial).mp. 151309

105 (review.pt. and review.ti,ab.) not (intervention or trial or study).mp. 991405

106 ((systematic or scoping or literature or narrative or realist) adj review).ti. 272916

107 ((qualitative adj (analys* or evaluation? or study or review)) not (quant* or intervention or trial)).ti. 33811
108 "cochrane database of systematic reviews".jn. 16063
109 1469-493X.is. 16063
110 systematic reviews.jn. 2434
111 2046-4053.is. 2434
112 editorial.pt. 626048
113 or/98-112 3543230
114 97 not 113 898

Figure S1. PRISMA flow chart

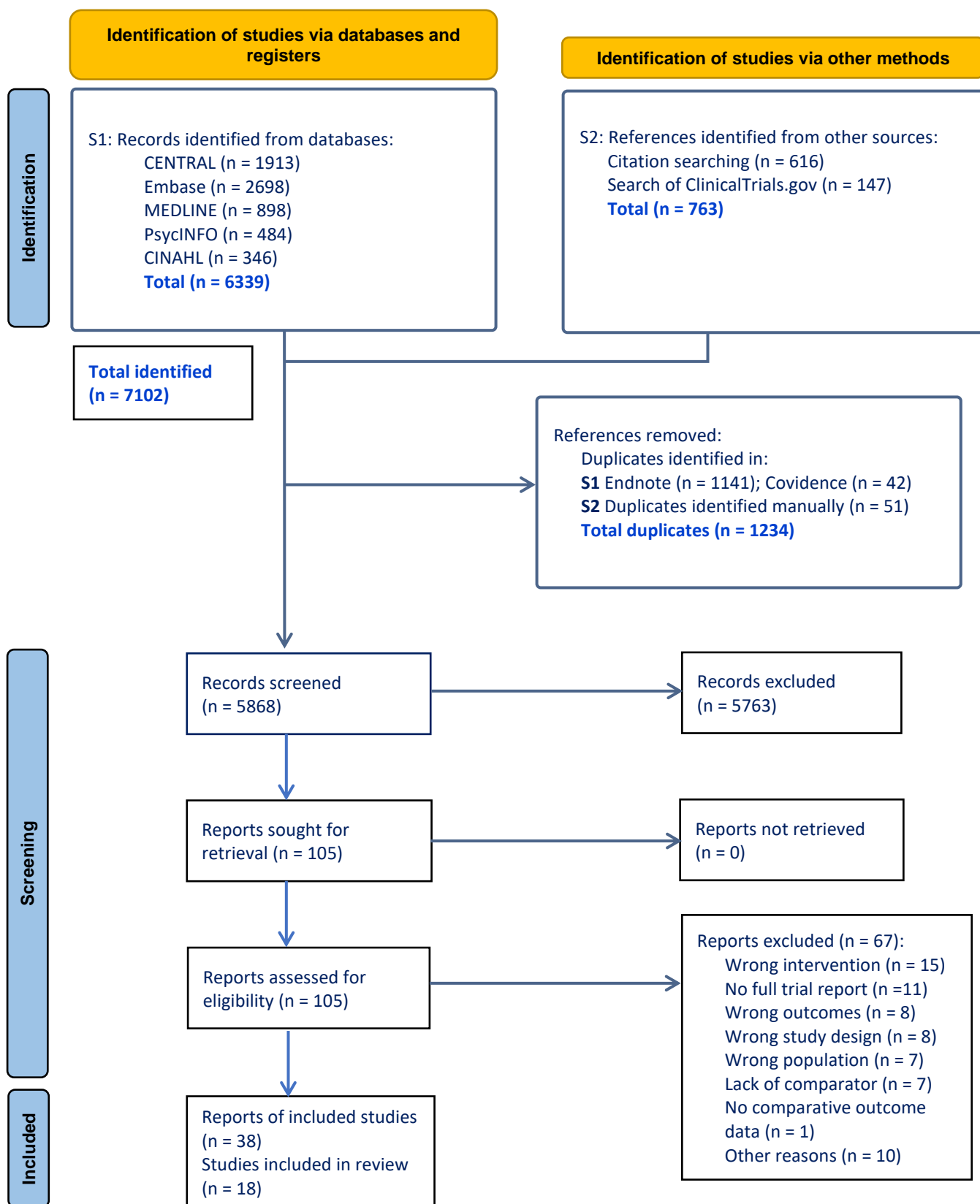


Table S1. Study characteristics

Author, year	Study design	Setting	Sample size	Participant characteristics			Intervention type
				Mean age (SD)	% female	% white ethnicity	
Randomized controlled trials							
Bushey, 2022	RCT	A primary care clinic in the Roudebush Veterans Administration Medical Center and 2 community-based outpatient clinics in Indiana	261	57.9 (9.5)	8%	73%	Nurse care manager-delivered medication optimization
Cedillo, 2022	cRCT	HIV primary care clinics	40	61 (7.3)	55%	5%	Multicomponent
Hurtado, 2019	RCT	Remote (intervention was an app). Patients were recruited from a pain clinic, deployment health clinic, other primary care or a navy medical centre pharmacy	80	NR	38%	50%	Multicomponent
Jamison, 2010	RCT	Hospital pain management clinic	62	47.7 (7.14)	44%	76%	Multicomponent
Kroenke, 2014	RCT	Five primary care clinics in a Veterans Affairs health care system	250	55.1 (NR)	17%	77%	Multicomponent
Liebschutz, 2017	cRCT	Four urban safety-net primary care practices	985	54.7 (11.5)	47%	52%	Multicomponent
Morasco, 2022	cRCT	Primary care clinics in a Veterans Affairs health care system	292	60.7 (11.2)	13%	81%	Multicomponent
Samet, 2021	cRCT	Two safety-net hospital-affiliated HIV clinics	187	53.9 (8.7)	28%	28%	Multicomponent
Non-randomized studies							
Boren, 2019	Controlled before and after study (retrospective chart review)	Outpatient physical medicine and rehabilitation clinic in a tertiary hospital	383	52.7 (12.5)*	55%	NR	Pharmacist-based support
Jamison, 2016	Controlled before and after study	Ten primary care centers (five 'specialist' (intervention) centers and five 'generalist' (control) centers. All were in the greater Boston Metropolitan area	253	53.7 (11.3)	60%	73%	Multicomponent
Marszalek, 2020	A within-subjects comparison of outcomes	Primary care clinic	50	62 [range: 35-87]	19%	81%	Multicomponent
Parchman, 2019	Quasi-experimental interrupted time series	Clinics of six rural serving health care organizations providing care at 20 clinic locations across eastern Washington and central Idaho	3862	[18-44 years: 21.3%; 45-64 years: 50.4%; >64 years: 28.2%]	63%	NR	Multicomponent

Author, year	Study design	Setting	Sample size	Participant characteristics			Intervention type
				Mean age (SD)	% female	% white ethnicity	
Perry, 2023	Controlled before and after study	Community pain clinic	78	Intervention: 65.5 (SD:9.8); Control: 59.9 (SD:13.2)	58%	NR	Multicomponent
Rowe, 2022	Interrupted time series	2 safety-net primary care clinics	273	51.4 (8.5)	28%	35%	Multicomponent
Seal, 2020	Prospective matched cohort	Veterans healthcare system including the San Francisco VA Medical Center, an urban campus, and six affiliated outpatient campuses across Northern California	294	63 (12)	10%	65%	Multicomponent
Soin, 2022	Prospective observational study	Pain clinic	60	Intervention: 59.4 (SD: NR); Control: 60.6 (SD: NR)	Intervention: 63%; Control: 56%	NR	Patient navigator
VonKorff, 2019	Retrospective interrupted time series study	Group practice clinics and care practices	31,142	NR	NR	NR	Multicomponent
Zgierska, 2020	Non-randomized stepped-wedge study	Primary care clinics	3148	53.3 (13.8)	58%	NR	Multicomponent

NR - Not Reported; RCT – Randomized Controlled Trial; cRCT – Cluster Randomized Controlled Trial; SD – Standard Deviation

*SD only reported for patients for the intervention arm

Notes:

1. The design of observational studies is as stated by the study authors, or, if not stated as determined by the review team.
2. In most studies all or most participants were on prescription opioids. Exceptions were Kroenke *et al* 2014(1) in which only a third of participants were, and Hurtado *et al* 2019(2) where the study inclusion criterion was 'patients currently taking a prescription medication with the potential for misuse' with no further information provided on opioid use (but the primary outcome for the study was Current Opioid Misuse Measure (COMM))

Table S2. Summary of intervention components

Author, year	Intervention component																			
	Nurse care manager	Clinical pharmacist	Other specialist support ±	Urine Drug tests	Patient education / training	Provider education / training	Use of diaries	Assessment of risk of opioid misuse	Feedback on risk of opioid misuse	Motivational (compliance) counselling / interviewing	Academic detailing	Patient smartphone app	Decision support tools / skills	Automated symptom monitoring	Electronic patient registries	Developing / reviewing / updating clinic policies, procedures or guidelines	Patient navigator	Shared medical appointments	Medical record review / patient evaluation / patient reports	Provider feedback, performance tracking and/or incentives
Randomised controlled trials																				
Bushey, 2022	✓	✓	✓																	✓
Cedillo, 2022*					✓	✓						✓								✓
Hurtado, 2019					✓			✓	✓			✓	✓							
Jamison, 2010**			✓	✓	✓		✓	✓		✓										
Kroenke, 2014	✓		✓											✓						
Liebschutz, 2017***	✓										✓		✓			✓				
Morasco, 2022****	✓		✓			✓										✓			✓	
Samet, 2021	✓		✓			✓					✓				✓	✓				✓
Non-randomised studies																				
Boren, 2019		✓																		
Jamison, 2016			✓			✓		✓							✓				✓	
Marszalek, 2020					✓			✓									✓		✓	
Parchman, 2019			✓			✓									✓	✓				
Perry, 2023		✓													✓					
Rowe, 2022			✓	✓												✓				
Seal, 2020			✓							✓										
Soin, 2022																	✓			
VonKorff, 2019			✓		✓	✓														✓
Zgierska, 2020						✓					✓					✓				

*Both intervention and control arm patients were provided with the app but control PCPs received no training, no decision support materials, and no access to patients opioid management app data

**Both intervention and control arms used the electronic diaries

***Both intervention and control arms used electronic decision support tools

****Both intervention and control arms received some provider education

±E.g. psychologist, physician with pain management / prescription opioid expertise, addiction specialist

Table S3. Intervention details

Author, year	Intervention details	Comparator details
Randomized Controlled Trials		
Bushey, 2022	<p>Collaborative care with a nurse care manager (NCM)–delivered medication management and analgesic optimization. NCMs assessed past and current treatments for chronic low back pain and delivered algorithm-based analgesic treatment along with guideline-concordant opioid management. NCMs assessed pain severity, treatment response, analgesic adherence, adverse effects, and desire to change treatment. NCMs regularly reviewed cases and treatment plans with physician and pharmacist investigators. Analgesic prescription adjustments were made by the study team with communication to primary care clinicians through the electronic health record as appropriate. A stepped-care analgesic algorithm was used. Medication adjustments were guided by treatment response, adverse effects, and patient preference. Risk of opioid misuse and possible diversion was assessed using clinical and medication history. Urine drug tests were collected at least twice during the study: at baseline, at 6 months, and randomly if concern for diversion arose. Opioid tapering was not an explicit goal of medication adjustments.</p>	<p>Psychologist-Led cognitive behavioural therapy (CBT). Patients were scheduled to receive 8 individual treatment sessions delivered by clinical psychologists during 6 months. The sessions were delivered by telephone or face to face depending on patient preferences. The manualized CBT intervention was augmented by a psychologist-led, one-on-one skills training program designed to increase self-efficacy in managing chronic lower back pain..</p>
Cedillo, 2022	<p>An opioid management app (OM-App) and progress note template (OM-Note). OM-App collected data (directly from the patient) which are not usually in the EHR and/or data that are likely to change over time using a short messaging system-based mobile health technology that delivered a daily text message to the patient containing a link to a rotating survey of 2–3 questions each day. Opioid-specific communication strategies were delivered to patients based on recommendations from people living with HIV.</p>	<p>Control Primary Care Practices (PCPs) received no training, no decision support materials, and no access to patient's OM-App data.</p>

Hurtado, 2019	<p>Prescription drug-abuse education smartphone application in addition to treatment as usual. As a patient-centred prevention effort, this brief intervention in a mobile phone app format focuses on helping military members reduce their risk for prescription drug misuse. It contains modules to: (1) assess risk for misuse and related behavioural health concerns; (2) provide individualized feedback on risk level; (3) store information on current medications and look up drug interaction and related information; (4) enhance communication and decision-making skills within healthcare and other interpersonal contexts by providing interactive scenarios; (5) teach about the risks of prescription drug misuse; and (6) provide resources for help with prescription drug misuse.</p>	<p>Treatment as usual plus provided with a list of resources for help with prescription drug and other substance abuse issues.</p>
Jamison, 2010	<p>Five components: 1) completion of monthly electronic diaries; 2) monthly urine screens for 6 months; 3) monthly completion of the Opioid Compliance Checklist (OCC); 4) monthly group education sessions (led by a psychiatrist trained in pain and addiction medicine) with worksheet handouts on topics related to substance misuse; and 5) participation in individual motivational compliance counselling (led by a clinical psychologist trained in pain and behavioural medicine). Those assigned to the High-Risk Experimental Group were asked to participate in monthly individual counselling and at least one monthly group session designed to offer knowledge and training for substance misuse awareness and recovery.</p>	<p>Monthly electronic diaries only.</p>
Kroenke, 2013	<p>Telecare intervention consisting of automated symptom monitoring and optimized analgesic management by a NCM/physician pain specialist team. These components are carried out in collaboration with the primary care physician in accordance with the principles of the Three-Component Model, which comprises a partnership between the primary physician, the care manager, and the physician specialist in caring for the patient's target condition.</p>	<p>Patients randomized to usual care continue to receive care for chronic pain from their primary care physician.</p>

Liebschutz, 2017	<p>(1) NCM (who performs initial and ongoing patient assessments for pain, addiction, and opioid misuse risk) prepares prescriptions for the primary care clinician (PCC) to sign or reminds the PCC to print prescriptions; collects UDTs; conducts pill counts (i.e., counts pills between refills to monitor medication use); checks prescription drug monitoring programs on behalf of PCCs; and assesses for concerning patient issues (e.g., unexpected UDT results) and collaborates with the PCC to develop appropriate clinical responses to these issues); (2) web-based electronic registry to facilitate population management by importing data from the electronic health record (EHR) (e.g., refill dates, UDT results) and producing reports used to direct work flow (e.g., lists of patients with opioid prescriptions due on a certain day or week) and to support academic detailing (e.g., provide feedback on PCC panel characteristics such as percentage of patients with an agreement); (3) single 1-on-1 academic detailing session between an opioid-prescribing expert and the PCC; (4) orientation about and access to electronic decision tools through an online platform (http://mytopcare.org/) that includes evidence-based tools for assessment of patient opioid misuse risk (e.g., the Opioid Risk Tool (ORT)) and interactive tools to assist with UDT ordering and interpretation.</p>	<p>Orientation about and access to electronic decision tools through an online platform (http://mytopcare.org/) that includes evidence-based tools for assessment of patient opioid misuse risk (e.g., the ORT) and interactive tools to assist with UDT ordering and interpretation (same as intervention group).</p>
Morasco, 2022	<p>2-hour clinician educational session, plus clinicians and patients received support from the Improving the Safety of Opioid Therapy intervention team which included a nurse care manager (NCM), internal medicine physician with expertise in chronic pain treatment in primary care, and psychologist with expertise in treating comorbid pain and substance use disorder. Following comprehensive medical record review, the NCM met with patients for a one-time visit to provide rationale for prescription opioid adherence screening, discuss ways that opioid-related adverse effects could be mitigated, and review methods for preventing opioid misuse. Meetings were individually tailored to the patient. The NCM then provided tailored recommendations to the primary care providers about strategies for improving opioid safety. Ongoing record review by the NCM was conducted biweekly for 1 year and as-needed recommendations were made to the</p>	<p>Clinician 2-hour educational session. Other than that they provided care as usual.</p>

patient's care team. A registry of enrolled patients was maintained by the NCM tracking urine drug test (UDT) administrations and results, queries of prescription drug monitoring databases, contraindicated co-prescriptions, and monitoring aberrant behaviours. If evidence of potential hazardous opioid use was identified, the NCM could collaborate with the consulting physician or psychologist to provide decision support for primary care providers.

Samet, 2021	(TEACH) was modelled on the TOPCARE (Transforming Opioid Prescribing in primary CARE) intervention]. Three components: (1) a NCM with an interactive electronic registry to manage patients; (2) opioid education and academic detailing; and (3) facilitated access to addiction specialists [Targeting Effective Analgesia in Clinics for Human immunodeficiency virus (HIV).	Providers in the control group received an informational brochure summarizing guidelines for Chronic Opioid Therapy (COT) and listing a web resource with electronic tools.
Non-randomized studies		
Boren, 2019	Addition of a clinical pharmacist to the physical medicine and rehabilitation clinic.	Outcomes were assessed before and after the addition of a clinical pharmacist to the physical medicine and rehabilitation clinic.
Jamison, 2016	Practitioners in the intervention group (Specialist centres) received monthly patient summary reports that consisted of pain, mood, activity levels, healthcare utilization, and results of the OCC. Practitioners were given the name and contact information of the nurse practitioner at the Brigham and Women's Hospital (BWH) Pain Management Center, available to all the Specialist centers, and were encouraged to contact her through clinical messaging or email to help facilitate a referral to the BWH Pain Management Center. The PCPs were informed of the intent to manage the patients using a team approach with the pain management specialists, and that patients at lower risk could be treated as usual by the PCP whilst those at moderate or high risk would be offered to be evaluated further at the BWH Pain Management Center by a pain specialist. Whether patients were evaluated or treated at the BWH Pain Management Center was up to the discretion of the PCP. Each center was offered informational sessions on risk assessment, opioid management, urine toxicology screening, and alternative treatments for pain. All participating PCPs were informed that individual	In the Generalist condition, all patients were managed by the practitioner alone and these centers represented the "treatment as usual" condition. Centers did not have access to the electronic medical record system utilized by the Specialists centers, even though they may have had their own system of electronic record keeping. The practitioners were not offered educational sessions on pain management and did not receive the monthly patient evaluations.

support regarding any particular patient could be offered if needed. The Specialist centers were also offered practitioner education on the management of chronic pain patients. Handouts about opioid risk statistics, risk factors for opioid abuse, the use of risk assessment tools in clinical practice, universal precautions, components, and benefits of an opioid protocol, role of urine drug testing, and information on interpreting urine screen results were made available.

Marszalek, 2020

Patients enrolled in the program attend a shared medical appointment every six months or until discontinuation of opioid therapy. The shared medical appointments last ~60 minutes each and are offered twice a week to facilitate scheduling and compliance. Class enrolment is capped at 40 patients per class. Patients are asked to complete several tasks during and after each shared medical appointment. The programme comprised five essential elements: Medical record review, education, evaluation (of anxiety, depression, physical functioning, drug use/abuse, quality of life), prescription of Naloxone nasal spray and polyethylene glycol and a treatment plan.

Patients with chronic non-cancer pain receiving opioid therapy for more than three months in primary care who did not participate in the Whole Health Primary Care Pain Education and Opioid Monitoring program either because they declined or their PCP opted them out.

Parchman, 2019

Six Building Blocks' for team-based redesign of opioid medication management within smaller primary care practice settings: (1) provide leadership support, (2) revise and align clinic policies, use of patient agreements, and defined workflows, (3) track the patient population, (4) implement planned, patient-centered visits, (5) identify resources for complex patients, and (6) measure success.

Patients in the comparison group were members of a large regional health plan and resided in the same primary care service areas as the clinics where the Six Building Blocks were implemented. The study sites did not accept patients on this health plan, so none of the patients in the comparison group were exposed to the intervention.

Perry, 2023	<p>Pharmacist-assisted initiative - including a letter informing patients of the provider's intent, pharmacist outreach to intervention patients, and pharmacist development of a patient registry, updated regularly with clinical data, recommendations, and outcomes for the provider to reference throughout the project. The intervention provider engaged patients in care plans that included tapering of opioids, initiation or changes in non-opioid medications, and referrals for further evaluation and/or treatment of chronic non-cancer pain. Provider referrals included physical therapy and complementary care, interventional pain procedures, specialty referral for evaluation and treatment of pain, and referral to a community pain clinic for comprehensive pain management. It is important to note the community pain clinic assumed opioid prescribing after referral but co-managed the care plans of these patients with the intervention provider. The intervention provider reviewed, discussed, and supported these care plans with the referred patients as needed.</p>	<p>The control group consisted of all patients being prescribed long term opioid therapy for chronic, non-malignant pain by the remaining 6 providers at the primary care clinic.</p>
Rowe, 2022	<p>Policies establishing standard protocols for dispensing opioid refills and conducting urine toxicology testing, and a new committee facilitating opioid treatment decisions for complex patient cases. The opioid refill policy established uniform procedures for refilling opioid medications. Specifically, the policy outlined procedures for refilling opioid medications when patients request early or late refills or report lost or stolen opioid medications or prescriptions. The policy established a limit of one early or late refill in a 12-month period and outlined requirements for increased monitoring and a detailed treatment plan assessment (including possible dose modification) in the case of multiple early or late refill requests or for patients who have exhibited yellow flag behaviour. The urine toxicology policy established uniform procedures for requesting urine samples from patients for toxicological testing, interpreting results, and taking action based on results. The policy required that all patients prescribed chronic opioids be asked to submit a urine sample for toxicology testing prior to initiating therapy and at least once per 12 months while continuing therapy. More frequent testing was performed as clinically indicated. The policy outlined procedures for</p>	<p>The control clinic is unique among the network's clinics in that, during a time of both national and local reductions in opioid prescribing, it did not implement formal policies to reduce prescribing, whereas other clinics in the network did. In addition, the control clinic is partially managed by a local university and not subject to the same oversight as other clinics in the network.</p>

	<p>when urine toxicology results were inconsistent with prescribing (e.g., negative for the prescribed opioid, or positive for cocaine, methamphetamine, or non-prescribed controlled substances), including a detailed assessment of the patient’s treatment plan and possible opioid discontinuation with a taper. The “yellow flag” committee was designed to discuss treatment plans for the following types of patients: those on opioids whose use has become problematic for the patient, provider, or staff; those with three or more “yellow flag” behaviours; those with a behavioural agreement for disruptive or violent behaviour related to opioids; and those on opioids who are at higher risk for overdose or death.</p>	
Seal, 2020	<p>Integrated Pain Team (IPT) clinic - an interdisciplinary, colocated team of primary care providers with training in pain management and motivational interviewing and shared decision-making; pain pharmacists; and pain psychologists. IPT members are based at the San Francisco Veteran Affairs Medical Center (SFVAMC), embedded in primary care, where visits are conducted in-person and via video telehealth for veterans living in rural areas. IPT’s main goals are to improve pain and decrease opioid risk through opioid dose reduction and other opioid risk mitigation strategies. IPT engages patients in multimodal pain care planning based on patients’ values and goals, emphasizing self-management strategies. IPT specifically encourages behavioural health strategies (e.g., cognitive behavioural therapy for chronic pain and mindfulness), physical modalities (e.g., acupuncture, chiropractic care, heat, and ice), and exercise (e.g., physical therapy, yoga, Tai Chi).</p>	Usual primary care
Soin, 2022	<p>Patients in the navigator group had access to a non-physician, non-advanced practice provider staff member who acted as a health coach. The patient navigator initiated frequent contact with patients via phone, telemedicine, or in-clinic visits to discuss the patient’s health goals.</p>	Monthly physician visits as part of their follow-up.

VonKorff, 2019	The group practice employed: patient education materials; a care plan template; an online calculator for estimating Morphine Equivalent Dose; performance measures tracking the development of COT care plans in the electronic health record; medical staff leader advocacy; expert consultation for physicians in each primary care clinic; and financial incentives for completing COT care plans. Medical staff leadership mandated a 90-minute online continuing medical education course about chronic pain management and opioids.	The contracted care clinicians in the control clinics were exposed only to the statewide guideline and legislation, but not the augmented implementation of the guidelines that took place in the intervention (group practice) clinics. Patients on COT in the contracted care clinics served as controls for evaluating the incremental effects of the more extensive efforts to change opioid prescribing practices implemented in the group practice setting.
Zgierska, 2020	The quality improvement (QI) intervention at each clinic consisted of: a) one 1-h academic detailing session, delivered by the project physicians, outlining the project, the national guidelines, and the health system's opioid policy recommendations; b) two 20–21 question online educational modules: one on shared decision-making in the context of opioid therapy for chronic pain, and another on the guideline and health system policy recommendations for opioid therapy management; and c) six 1-hour practice facilitation sessions delivered at each clinic over 4–6 months by the project's trained facilitators. The practice facilitation sessions focused on optimizing clinical workflows to promote clinician adherence to the guideline and health system policy recommendations with measurable outcomes ("QI targets").	Details not provided.

COT: Chronic Opioid Therapy; NCM: Nurse Care Manager; PCP: Primary Care Practice; PCC: Primary Care Clinician; UDT = Urine Drug Test; EHR = Electronic Health Record; IPT = Integrated Pain Team; SFVAMC = San Francisco Veteran Affairs Medical Center; ORT = Opioid Risk Tool; OCC = Opioid Compliance Checklist; Cognitive Behavioural Therapy (CBT); Opioid Management App (OM-App); Brigham and Women's Hospital (BWH); QI = Quality Improvement.

Table S4. Supporting statements for risk of bias assessments - Randomized Controlled Trials

Author Year	Outcome	D1	D2	D3	D4	D5	Overall judgement	Supporting text
Bushey, 2022	COMM	Low	Low	Some concerns	Low	Low	Some concerns	COMM data available for <90% of participants at follow up (82.4% in the intervention group and 80.8% in the comparator group). Missingness could potentially depend on the true outcome.
	MME	Low	Low	Some concerns	Low	Low	Some concerns	MME data available for <90% of participants at follow up (82.4% in the intervention group and 80.8% in the comparator group). Missingness could potentially depend on the true outcome.
Hurtado, 2019	COMM	High	Low	Low	Some concerns	Low	High risk of bias	Principle investigator who randomized was also involved in the study and the analyses. COMM appears to have been scored by averaging 17 individual items (scale 0-4) across participants instead of adding them together and averaging the result (scale 0-68) as per COMM guidance.
Jamison, 2010	UDT	Some concerns	Low	Low	Low	Some concerns	Some concerns	Lack of information on allocation concealment and lack of a protocol / pre-specified analysis plan.
	DMI	Some concerns	Low	Low	Low	Some concerns	Some concerns	Lack of information on allocation concealment and lack of a protocol / pre-specified analysis plan.
Kroenke, 2014	MEDD	Low	Low	Low	Low	Low	Low risk of bias	No particular concerns – the study appears to have been well conducted.

UDT = Urine Drug Test; DMI = Drug Misuse Index; COMM = Current Opioid Misuse Measure; MEDD = Morphine-Equivalent Daily Dose; MME = Mean Morphine Equivalent.

D1 Randomization process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

Table S5. Supporting statements for risk of bias assessments - Cluster Randomized Controlled Trials

Author Year	Outcome	D1a	D1b	D2	D3	D4	D5	Overall judgement	Supporting text
Cedillo, 2022	MME	Low	Low	Low	Low	Low	Low	Low risk of bias	No particular concerns – the study appears to have been well conducted.
Liebschutz, 2017	COMM	Low	Low	Low	Low	Low	Low	Low risk of bias	No particular concerns – the study appears to have been well conducted.
	MEDD	Low	Low	Low	Low	Low	Low	Low risk of bias	No particular concerns – the study appears to have been well conducted.
Morasco, 2022	COMM	Some concerns	Low	Low	Low	Low	Low	Some concerns	Concerns regarding allocation concealment since each clinician received an email from the principal investigator informing them of allocations.
	UDT	Some concerns	Low	Low	Low	Low	Low	Some concerns	Concerns regarding allocation concealment since each clinician received an email from the principal investigator informing them of allocations.
Samet, 2021	OC	Low	Low	Low	Low	Low	Low	Low risk of bias	No particular concerns – the study appears to have been well conducted.
	COMM	Low	Low	Low	Low	Low	Low	Low risk of bias	No particular concerns – the study appears to have been well conducted.

UDT = Urine Drug Test; COMM = Current Opioid Misuse Measure; MEDD = Morphine-Equivalent Daily Dose; MME = Mean Morphine Equivalent; OC = Opioid Cessation.

D1a Randomization process

D1b Timing of identification or recruitment of participants

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

Table S6. Intervention effects – Randomized controlled trials

Author, year	Outcome	Follow-up timepoint	Follow-up measurement - intervention group	Follow-up measurement - comparator group	Difference between groups (intervention vs. control) in follow-up measurements	Difference between groups (intervention vs. control) - change in measurement from baseline to follow-up	Factors adjusted for (if applicable)
Bushey, 2023	Mean COMM score	12 months	7.60 (SD: 6.96)	8.96 (SD: 7.94)		-1.37 (95% CI: -3.38-0.65), p=0.12	P-value calculated for score change from multivariable mixed-effects models accounting for within-participant correlation for repeated measures and adjusted for baseline outcome measure score
	Health-related quality of life 36-item Short Form Health Survey (SF-36) General Health component - mean score (SD)	12 months	42.70 (SD: 23.03)	42.44 (SD: 20.17)	0.26 (95% CI: -5.60 to 6.11)	Calculated for score change from multivariable mixed-effects models: p=0.44	Accounts for within-participant correlation for repeated measures and adjusted for baseline outcome measure score
Cedillo, 2022	Mean COMM score	9 months	6.0 (SD: 4.8)	2.9 (SD: 3.1)		Difference between groups in change in COMM score from baseline to follow-up: 1.9 [Authors state "No statistically significant difference"]	
	Median morphine equivalents (IQR)	9 months	75 mg (IQR: 40-160)	24.8 mg (9.4, 101.3)		p-value adjusted for multiple testing: 0.26*	Multiple testing (using the Benjamini and Hochberg method)
Hurtado, 2019	Mean COMM score	1 month	0.62 (SD: 0.47)	0.63 (SD: 0.40)		p-value for the group by time (group: intervention/control, by time: baseline/1 month) interaction): p=0.72	
	Pain Medication Questionnaire (PMQ) Shortened Scale - mean score	1 month	1.37 (SD: 0.43)	1.41 (SD: 0.49)		p-value for the group by time (group: intervention/control, by time: baseline/1 month) interaction): p=0.598	
Jamison, 2010	Positive score on Drug Misuse Index (DMI)	6 months	Proportion with positive DMI score: 26.3%	Proportion with positive DMI score: 73.7%	47.4%^		
	Abnormal Urine Drug Test (UDT) result	6 months	Proportion with abnormal UDT	Proportion with abnormal UDT result at 6 months: 11.8%	Authors state "Not Significant"		

Author, year	Outcome	Follow-up timepoint	Follow-up measurement - intervention group	Follow-up measurement - comparator group	Difference between groups (intervention vs. control) in follow-up measurements	Difference between groups (intervention vs. control) - change in measurement from baseline to follow-up	Factors adjusted for (if applicable)
			result at 6 months: 35.3%				
	Mean (SD) MEDD in mg	12 months	12.8 mg (SD: 36.7 mg)	8.1 mg (SD: 32.0 mg)	Difference between groups in MEDD at 12 month follow-up: 4.7 (p=0.16).	Difference between groups in change in MEDD from baseline to follow-up: 0.8	
Kroenke, 2014	Health-related quality of life 36-item Short Form Health Survey (SF-36)	12 months	Social Functioning mean score: 72.6 (SD: 26.6); Vitality: 44.8 (24.4); Mental Health: 72.2 (20.5)	Social Functioning mean score: 67.3 (SD: 27.4); Vitality: 42.6 (23.1); Mental Health: 70.3 (21.9)	Social Functioning: 5.3 (95% CI -1.6 to 12.2) p = 0.03; Vitality: 2.2 (-3.9 to 8.2) p = 0.09; Mental Health: 1.9 (-3.5 to 7.3) p=0.26	Social Functioning: 4.7 (0.2); Vitality: 2.4 (1.6); Mental Health: 0.1 (1.1)	Time effect & baseline value of outcome variable
	Mean MEDD (mg)	12 months	60.8 mg (SD: 93.7 mg)	67.3 mg (SD: 80.4 mg)	Adjusted difference: -6.8 (SE: 1.6) mg lower in intervention vs. control patients (P≤0.01)		Drug use diagnosis, mental health problems, English-speaking, and baseline levels of outcome measures
Liebschutz, 2017**	Discontinuation of opioid prescription	12 months	21.3% (125/586)	16.8% (67/399)	4.5 percentage points. Adjusted odds ratio: 1.5 (1.0-2.1)		Drug use diagnosis, mental health problems, English-speaking, and baseline levels of outcome measures
	Mean COMM score	12 months	8.6 (SD: 5.7)	9.3 (SD: 6.5)		Predicted difference in change (after adjustment): -1.12 (-2.45, 0.20), p=0.097	Age, gender, depression severity, pain intensity, provider type (NP vs physician), and provider proportion of panel with opioid prescription
Morasco, 2022	Any aberrant Urine Drug Test (UDT) result	12 months	10.2%	16.2%		Predicted difference in change in proportion with the outcome (after adjustment): -0.04 (-0.15, 0.06), p=0.401	Age, gender, depression severity, pain intensity, provider type (nurse practitioner vs physician), and provider proportion of panel with opioid prescription
	Discontinuation of prescription opioids	6 months	20.0%	8.1%	11.9% [^] , p=0.007	NA	

Author, year	Outcome	Follow-up timepoint	Follow-up measurement - intervention group	Follow-up measurement - comparator group	Difference between groups (intervention vs. control) in follow-up measurements	Difference between groups (intervention vs. control) - change in measurement from baseline to follow-up	Factors adjusted for (if applicable)
	Mean MEDD (mg)	12 months	34.4 mg (SD: 34.8 mg)	33.6 mg (SD: 42.2 mg)		-8.7 mg***	
	Proportion with COMM score of 9+	12 months	38.7%	39.9%	Adjusted odds ratio: 0.78 (0.33–1.88)		Stratification variables were site (Boston vs Atlanta) and patient volume (1–2, 3–6, 7–11, and ≥12 patients)
Samet, 2021	Discontinuation of opioid prescriptions	12 months	30.3%	25.6%	4.7 percentage points. Adjusted odds ratio: 1.62 (0.82–3.22), p=0.17		Analyses adjusted for drug use diagnosis, mental health problems, English-speaking, and baseline levels of outcome measures

NA: Not Applicable; SD: Standard Deviation; MEDD: Morphine Equivalent Daily Dose; COMM: Current Opioid Misuse Measure; MME: (daily) Morphine Milligram Equivalents; DMI: Drug Misuse Index; UDT: Urine Drug Test; PMQ: Pain Medication Questionnaire.

^Calculated by review team using data presented in the manuscript and/or obtained from study authors. This was only done where 'Difference between groups (intervention vs. control) - change in measurement from baseline to follow-up' (the most meaningful measure of intervention effectiveness) was not available but 'Difference between groups (intervention vs. control) in follow-up measurements' could instead be calculated.

*Authors state: "p-value for change from baseline to follow-up between intervention and control patients using a mixed effects model with a random intercept. Generalized estimating equations with a logit link function (in an effort to account for repeated measures) were applied, while adjusting p-values for multiple testing using the Benjamini and Hochberg method'.

**Study also reports on 10% opioid dose reduction - data not reported here as this overlaps with the outcome measure 'MEDD, mean'.

***Note that baseline MEDD was higher in the intervention compared to control group (mean: 46.8mg (SD: 51.0) vs 37.3mg (SD: 65.3)).

Table S7. Intervention effects – Non-randomized studies

Author, year	Outcome	Follow-up timepoint	Follow-up measurement - intervention group	Follow-up measurement - comparator group	Difference between groups (intervention vs. control) in follow-up measurements	Difference between groups (intervention vs. control) - change in measurement from baseline to follow-up	Factors adjusted for (if applicable)
Boren, 2019	MEDD, mean (SD)	NR	140mg (151mg)	152mg (194mg)	12mg [^] (p-value for difference between groups: 0.25)		
Jamison, 2016	Opioid Compliance Checklist (8-item compliance checklist, modified from the original 12-item scale)	6 months	0.6 +/- 0.9	0.6 +/- 0.8	No difference	No difference	
Marszalek, 2020	Morphine equivalent daily dose (MEDD), mean	6 months	40.2mg (SD: 52.7 mg)	25.1 mg (SD:41.0 mg)	15.1 mg [^]		
	Proportion of patients on high-dose opioids (≥ 100 MED)	15 months	9.60%	12.70%		The rate of decrease in the proportion of patients on high-dose opioids was significantly greater in the study group compared with the control group (coefficient: 0.242, SE: 0.094, P=0.018)	
Parchman, 2019	Number of patients on long-term opioid therapy	15 months	NR	NR	NR	There was a 14.0% decrease in the intervention group and a 4.7% decrease in the control group. The rate of decrease in the total number of patients receiving an opioid prescription was greater during the intervention period compared with the pre-intervention period (coefficient for the change in slope: -75.8, P<.001).	
Perry, 2023	Daily MME, mean	18 months	7.0 mg (SD: 13.2 mg)	14.5 mg (SD: 14.5 mg)		16.2 mg [^] (p<0.001)	

Author, year	Outcome	Follow-up timepoint	Follow-up measurement - intervention group	Follow-up measurement - comparator group	Difference between groups (intervention vs. control) in follow-up measurements	Difference between groups (intervention vs. control) - change in measurement from baseline to follow-up	Factors adjusted for (if applicable)
	Discontinuation of opioid prescription	18 months	n=18	n=6		<0.001	
Rowe, 2022	Mean opioid dose (MME)	4 years	NR	NR		Year 1 conditional difference-in-differences estimate: -52.0 MME [95% confidence interval: -109.9, -10.6]; year 2: -106.2 MME [-195.0, -34.6]; year 3: -98.6 MME [-198.7, -23.9]; year 4: -72.6 MME [-160.4, 3.6]	
Seal, 2020	MEDD, mean (SD)	6 months	68.4 mg (SD:166.1 mg)	107.1 gm (SD: 223.4 mg)		Odds of reducing opioid dose (MEDD in mg) ≥50% from baseline (in intervention grp vs. comparator) at 6 months: OR: 2.53 (95% CI:1.44–4.43), p<0.01; Adjusted odds: 2.03 (95% CI:1.04–3.95), p=0.04	Adjusted for race, baseline opioid dose (MEDD in mg), persistent moderate-to-severe pain, and opioid use disorder
Soin, 2022	Morphine milligram equivalents (MMEs) per day	At least 90 days	16.0 mg	28.4 mg		8.3 mg [^]	
VonKorff, 2019	Average daily morphine equivalent dose in milligrams	8.25 years	40.0 mg	64.6 mg		8.3 mg [^]	
Zgierska, 2020	Morphine-equivalent dose (MED; milligrams/day)	2 years	64.1 mg [^]	46.0 mg [^]		Mean (SE) -1.7 mg (4.0) 95% CI (- 9.6, 6.2) p=0.937 Cohen's d = 0.2*	

NR: Not reported; NA: not applicable; SD: standard deviation; MEDD: Morphine Equivalent Daily Dose; COMM: Current Opioid Misuse Measure; MME: (daily) Morphine Milligram Equivalents; DMI: Drug Misuse Index; UDT: Urine Drug Test.

[^]Calculated by review team using data presented in the manuscript and/or obtained from study authors. This was only done where 'Difference between groups (intervention vs. control) - change in measurement from baseline to follow-up' (the most meaningful measure of intervention effectiveness) was not available but 'Difference between groups (intervention vs. control) in follow-up measurements' could instead be calculated.

*Note that baseline MED was much higher in intervention vs. control clinics 75.7 mg (SD: 29.7 mg) vs. 55.9 mg (SD: 19.4 mg).