

The New England Comparative Effectiveness Public Advisory Council Public Meeting – June 20, 2014

Management of Patients with Opioid Dependence: A Review of Clinical, Delivery System, and Policy Options

Appendices

This document contains only the appendices to a full report, available at: <u>http://cepac.icer-review.org/?page_id=1222</u>

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Appendix A. Literature Search & Synthesis Strategy

<u>Treatment for Opioid Dependence – Literature Search & Synthesis Strategy</u>

• De novo searches will include data published from January, 2003 to current date (i.e., studies published during the Suboxone era)

- Databases included: MEDLINE, Cochrane Central Register of Controlled Trials, PsycINFO
 - 1) Maintenance therapy versus assisted opioid withdrawal (detoxification)

Detoxification will be defined as any type of assisted opioid withdrawal therapy, given up to a maximum of 30 days.

Data source:	De novo search
	Additional source for key studies: • Mattick RP et al. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. <i>Cochrane Database Syst</i> <i>Rev.</i> 2009;3:CD002209.
Included studies:	RCTs, comparative cohorts, case series with ≥100 patients

2) Methadone versus buprenorphine versus naltrexone (*evaluated in context of maintenance treatment only*)

Data source:	 Mattick RP et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. <i>Cochrane Database Syst Rev.</i> 2014;2:CD002207. Updated search required: January, 2013 – present
	Minozzi S et al. Oral naltrexone maintenance treatment for opioid dependence. <i>Cochrane Database Syst Rev</i> . 2011;4:CD001333. • Updated search required: June, 2010 - present
Included studies:	RCTs only

* Data to be sub-grouped by dosage form of buprenorphine

3) Dosing and time limits

Evaluation of treatment approaches will include any strategy extending beyond 30 days (including long-term withdrawal approaches).

Data source:	De novo search
Included studies:	RCTs, comparative cohorts, case series with ≥100 patients

Other treatment requirements

Data source: De novo search Additional sources for key studies: • Amato L et al. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. Cochrane Database Syst Rev. 2011;9:CD005031. • Mattick RP et al. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependency. Cochrane Database Syst Rev. 2009;3:CD002209. Included studies: RCTs, comparative cohorts, case series with ≥100 patients

(evaluated in context of maintenance treatment only)

4) Patient Care models/ Delivery system policies
 (evaluated in context of maintenance treatment only)

Data source:	De novo search
Included studies:	RCTs, comparative cohorts, case series with ≥100 patients

5) Special populations: Adolescents

Data source:	 Minozzi S et al. Detoxification treatments for opiate dependent adolescents. <i>Cochrane Database Syst Rev</i>. 2009;4:CD006749. Minozzi S et al. Maintenance treatments for opiate dependent adolescent. <i>Cochrane Database Syst Rev</i>. 2009;2:CD007210. Updated search required: August, 2008 - present Available sub-group data from RCTs where patient populations include participants ≤18 years
Included studies:	RCTs, comparative cohorts, case series with ≥100 patients

Appendix B. Summary of Federal and State Standards for Substance Abuse Treatment Facilities

Table 1B. Summary of Federal Standards for Opioid Treatment Programs (<u>42 CFR Part 8</u>).

Certification Staff	OTPs must receive certification from SAMHSA by meeting all pertinent federal and state laws, and receiving valid accreditation from an approved accreditation body. Certification is valid for three years with the opportunity for renewal. Programs must allow for inspections by SAMHSA, accreditation bodies, the DEA, and other federal and state employees. Programs must be separately registered with the DEA before opioid treatment medication can be dispensed or administered. All OTPs must have a designated Program Supervisor and Medical Director. All clinical care staff must be appropriately licensed and qualified within their respective professions, and receive specific training in MAT. Each staff member must have an annual individual training plan that includes continuing education on opioid addiction.				
Quality control	A formal quality control plan is required, which includes an annual review of program policies, an ongoing assessment of patient outcomes, and Diversion Control Plan.				
Patient admission criteria Detoxification Services Adolescents	 Admitted patients must show evidence of current dependence, have a one-year history of opioid addiction, and provide informed written consent to maintenance treatment. Patients may be exempt from meeting history criteria if they are pregnant, have been released from a penal institution within the previous six months, or have previously been admitted for treatment in the past two years. No more than two detoxification treatment episodes are allowed in a year. Patients with at least two unsuccessful detoxifications must be assessed for other forms of treatment. Patients under 18 must demonstrate at least two documented unsuccessful attempts with short-term detoxification or a drug-free treatment within a year and receive written consent from a parent or guardian before receiving treatment 				
Treatment requirements	 OTPs must provide the following services and adhere to the following treatment requirements: Initial medical evaluation within 14 days of admission that includes health screening, lab testing, physical evaluation, assessment of medical and family history, evaluation of mental health status, and comprehensive assessment of patient's social needs to determine appropriateness of treatment. Specific protocol and special services for pregnant women (e.g., prenatal care, etc.). All women of childbearing potential must be tested for pregnancy before receiving services. Patient assessment and individualized treatment plan with short-term goal setting that identifies the patient's need for social supportive services Education and training, including family planning and parent training Counseling and education, including counseling on substance abuse and HIV/AIDs Social supportive services, including vocational rehabilitation, education and employment services, etc. Treatment of co-occurring mental health and substance use disorders Random drug testing (at least 8 per patient per year for patients on MAT, and monthly for patients receiving long-term detoxification) 				

	Discharge planning, relapse prevention, and procedures for continued care			
	* If services are not able to provided at the main treatment facility, patients may be referred for treatment elsewhere			
Recordkeeping and	OTPs must comply with recordkeeping and confidentiality standards at the state and federal level, and make efforts to review that			
patient confidentiality	entiality patients only receive care at one OTP. Policies and procedures must be in place to comply with DEA standards for storage, dispensing			
	labeling, and administering of opioid medication.			
Medication	Patients receiving methadone must take medication under observation. Only adequately licensed professionals or practitioners under			
administration and	supervision of an appropriately licensed professional can administer or dispense medication. OTPs shall only use opioid agonist			
dispensing	medications approved by the FDA (methadone, buprenorphine, and buprenorphine combination products). Methadone must only be dispensed in the oral form, the initial dose of which shall not exceed 30mg or a total dose of 40mg in the first day.			
Detoxification and	Programs may initiate involuntary or voluntary supervised withdrawal from MAT. Medically supervised withdrawal must follow a			
Tapering	humane schedule following best clinical judgment. Patients may decide to taper and withdraw from treatment voluntarily, even if			
	against the advice of physicians. Programs may also administratively discharge a patient from MAT in the event of nonpayment of fees,			
	disruptive patient conduct, or incarceration or other confinement. Under these circumstances, programs should refer or transfer the			
	patient to a suitable alternative program.			
Take-home use The medical director may dispense methadone or buprenorphine-containing medications for take-home use after asset				
	documenting a patient's responsibility and stability to receive unsupervised treatment. The following criteria must be met for each			
	modality:			
Methadone	The nations must be absent of recent drug or alcohol use, serious behavioral problems, and recent criminal activity; attend clinic			
wethdone	regularly: have a stable home and social environment; and he able to store the medication safely. OTPs must also consider the length of			
	time the national has narticinated in comprehensive MAT			
	A standard dosing schedule applies, ranging from a single dose a week for take home use in the first 90 days to a month supply after two			
	years of continuous treatment. Further exemptions may be permitted on occasion for patients with transportation hardships,			
	disabilities, employment issues, etc.			
Buprenorphine and	The patient must be able to store medication safely.			
Suboxone				
Interim Maintenance	The medical director may place patients on a treatment on an interim maintenance program for 120 days allowing patients to receive			
	administered medication daily under observation without meeting other requirements for counseling, or other rehabilitative or social			
	services. OTPs must receive special approval from SAMHSA before establishing an interim maintenance program.			

State	Required Program	Required Services/Treatment Protocol	Required Program Policies/Procedures	Agency Oversight
СТ	All: • Adequate supervision by licensed practitioners for all staff • Clinical supervisor • Executive Director Facilities providing detoxification, residential treatment, or MAT: • Medical director • Registered nurse • Licensed pharmacist • Licensed counselors • Psychiatrist or psychologist	 <u>All</u>: Comprehensive patient assessment Individualized treatment plan with continuous review <u>Facilities providing detoxification or MAT:</u> Physical examination and medical history within 24 hours of admission Diagnostic testing within 72 hours of admission Initial drug urinalysis and eight additional random urine tests in the first year. Patients receiving treatment for <1 year receive a minimum of four urine tests annually. 	 <u>All</u>: Annual program evaluation Admissions, discharge, and referral protocols Rules for medication administration, including policies for supervision, record keeping, inspection, monitoring, labeling, and disposing Treatment documentation and data reporting 	Department of Public Health: Source
ME	All: • Adequate supervision by licensed practitioners for all staff • Medical director • Licensed counselors • Minimum of 1.5 clinical staff with adequate training Detoxification facilities and OTPs • Interdisciplinary team, including 24-hour physician support • Alcohol and drug counselor • Pharmacist	 <u>All</u>: Comprehensive patient intake assessment to determine appropriateness of treatment, patient's mental health history, and patient health risks Individualized treatment plan with continuous review Case management/ referrals for continued care Drug and alcohol education Monitoring Individual/Group/Family counseling <u>Residential treatment:</u> Vocational and life skills training Transportation <u>OTPs:</u> Comprehensive initial physical medical examination 	 <u>All</u>: Patient admission criteria Rules for medication administration, including policies for supervision, record keeping, inspection, monitoring, labeling, and disposing Risk management and quality improvement procedures Waiting list that ensures patients are screened, referred, and prioritized Procedures for care coordination and referrals, including policies for treatment plan reviews Discharge planning and treatment termination policies Plan for treatment follow-up and aftercare 	Office of Substance Abuse: <u>Source</u>

Table 2B. Overview of state licensing requirements for facilities providing substance abuse treatment in New England.*+

	 All staff required to complete intensive training on opioid dependence Required ratio of counselor to patients (no more than 50 patients per counselor) 	 Individual treatment plan with dosage program Drug testing every 30 days Maximum take-home dose allowed is for 6 days of treatment (after 361 days of continuous treatment) Phase 1 (Induction): 45 day duration; 4 hours of counseling; goal to manage withdrawal symptoms Phase 2 (Acute): 60 day duration; 6 hours of counseling; goal to increase dose to eliminate cravings/withdrawal Phase 3 (Rehabilitation): 90 day duration; 6 hours of counseling; drug testing; goal to eliminate illicit drug use and amelioration of withdrawal Phase 4 (Supportive care): ongoing 90 day intervals; 3 hours of counseling; goals of stable living situation and income, with no criminal involvement Phase 5 (Medical Maintenance): ongoing 90 day intervals; 1 hour of counseling; goals of 2 years of continuous treatment, adequate social support system and stability in life 	 Treatment documentation and data reporting OTPs: Maximum of 500 patients, unless a waiver is permitted Confirmation from State that patient is not being treated by any other OTP 	
MA	 <u>All</u>: Adequate supervision by licensed practitioners for all staff Monthly training sessions Multi-disciplinary care team <u>Detoxification</u>: Medical Director Clinical supervisor Licensed psychiatrists or psychologist 	 <u>All</u>: Comprehensive patient intake assessment to determine appropriateness of treatment, patient's mental health history, and patient health risks Individualized treatment plan with continuous review Plan for discharge, transitional, and after care supports Case management/referrals for continued care Drug and alcohol education Mental health services, including psychopharmacology Relapse prevention/Recovery maintenance 	 <u>All</u>: Risk management and quality improvement plan Patient admission criteria Rules for medication administration, including policies for supervision, record keeping, inspection, monitoring, labeling, and disposing Discharge planning and treatment termination policies Plan for treatment follow-up and aftercare after discharge Treatment documentation and data reporting 	Department of Public Health: <u>Source</u>

- Desistand number number	Detevification	
• Registered nurse, nurse	Detoxincation.	OTDe
practitioner, or physician	Comprehensive biopsychosocial assessment	
assistant	including appropriate screening, mental health	Confirmation from State that patient is
Case managers, case	evaluation, and assessment of substance use	not being treated by any other OTP
aides, or practical nurse	 Outpatient: 9 hours of detoxification per week 	
• Ob/gyn if serving pregnant	 Inpatient: 4 hours of detoxification programming 	
women	daily	
Outpatient Counseling:	Outpatient counseling:	
Senior clinician	 Individual/Group/Family therapy 	
• Licensed psychiatrist or	Day treatment:	
psychologist	• 3.5 hours of services daily, including counseling,	
	psychoeducational groups, and family therapy	
	OTPs:	
	 Annual comprehensive physical examination 	
	including appropriate screening, mental health	
	evaluation and assessment of substance use	
	Waiting period of one week between	
	detoxifications	
	 Monthly drug screens for patients receiving 	
	detoxification for more than 30 days	
	15 drug screens a year for notionts receiving MAT	
	15 drug screens a year for patients receiving MAT	
	Maximum take-nome dose for treatment is 13	
	doses every two weeks following 18 months of	
	treatment. Take home doses must be dispensed	
	in locked containers.	
	 Patients that voluntarily terminate treatment 	
	must be provided with supervised withdrawal	
	services, relapse prevention, and referrals for	
	continued care	
	 Medical withdrawal rate must be determined by 	
	the medical director and consider the patient's	
	preferences and clinical record	
	Adult Residential Rehabilitation:	
	Daily clinical services	
	Advocacy/Social support	

		 4 hours of nursing services daily (transitional homes only) Transportation Monitoring Education and crisis services 		
NH	 <u>All:</u> Medical director responsible for all medical services All practitioners must be adequately trained and certified <u>Residential Facilities providing</u> <u>detoxification services or MAT:</u> Full-time administrator Required medication dispensation training for all non-practitioners supervising medication All personnel must complete annual continuing education/in- service Required orientation procedures for all personnel Director of program services with at least 2 years experience in substance abuse rehabilitation and meets qualifications for a licensed clinical supervisor 	 <u>All:</u> Patients must be given opportunity to participate in a methadone or buprenorphine detoxification program versus a maintenance therapy program at time of admission and every 6 months thereafter <u>Residential Facilities providing detoxification services</u> <u>or MAT:</u> Preliminary needs assessment within 24 hours after admission, and comprehensive evaluation within 7 days Individualized care plan with continuous review Progress notes written monthly <u>OTPs:</u> Participants in long-term detoxification should receive methadone or buprenorphine to reach a drug-free state within 180 days. Participants in short-term detoxification should reach drug-free state within 90 days. Patients in methadone maintenance must attend the program 7 days per week and participate in 8 hours of counseling per month for first 90 days. Reduction in required hours of counseling and possibility for take home doses considered after 90 days, with the possibility of up to 6 weekly take home doses and 1 required hour of monthly counseling after 910 days. 	 <u>Residential Facilities providing</u> <u>detoxification services or MAT:</u> Protocol for maintaining accurate client records Rules for medication administration, including prescription, record keeping, labeling, storage, supervision, and disposal Assessment at time of admission using an evaluation tool Procedures for discharge and transfer <u>OTPs:</u> Procedures for re-admission in the event of a relapse following discontinuance of methadone 	New Hampshire Department of Health and Human Services Source The New Hampshire General Court Source

 At least one licensed nurse in the facility 24 hours a day Licensed nursing assistants 	Individual/Group/ Family counseling		
 RI Adequate supervision by licensed practitioners for all staff 50% of direct care staff will be licensed in mental health and addictions Psychiatrist (on site or through consultation) Required overdose prevention education Detoxification facilities and <u>OTPs:</u> Medical director Registered nurse with 2 years experience in substance abuse At least 1 licensed nurse per 25 patients Counseling staff must be licensed chemical dependency professionals Required annual training in detoxification for nurses Case managers 	 <u>All</u>: Initial clinical phone screening to determine need for assessment Comprehensive patient intake assessment to determine appropriateness of treatment, patient's mental health history, and patient health risks Individualized treatment plan with continuous review Comprehensive social supports for patients with co-occurring disorders Case management <u>Outpatient facilities:</u> Individual/group/family counseling Psychotherapy Medication treatment and review Education <u>Intensive outpatient facilities:</u> Minimum of nine hours per week of treatment services, including at least one individual counseling session on a daily basis <u>OTPs:</u> Monthly pregnancy testing for women receiving buprenorphine Annual medical examination Individual/group/family counseling 	 <u>All</u>: Patient admission criteria Rules for medication administration, including policies for supervision, record keeping, inspection, monitoring, labeling, and disposing Procedures for care coordination and referrals, including policies for treatment plan reviews Discharge planning and treatment termination policies Plan for treatment follow-up and aftercare Treatment documentation and data reporting Detoxification facilities: Each patient must be assigned to a primary counselor OTPs: Confirmation from State that patient is not being treated by any other OTP No person under 16 may be admitted without prior written approval from the State Methadone Authority Written policies for drug testing Daily reports on admissions, transfers, and discharges 	Department of Behavioral Healthcare, Developmental Disabilities, and Hospitals Source

		 Minimum of one hour individual counseling monthly in the first year of treatment Two hours of monthly individual counseling for individuals receiving long-term detoxification After two years of treatment, patient may receive up to six doses of medication. After three years, patients may reduce program attendance to twice monthly (14-day take-home dose). After four years, patient may receive monthly take-home doses of medication. 	 Standardized method that includes use of photograph to identify each individual before dispensing medication Buprenorphine must be dispensed in sub-lingual tablets 	
VT	 <u>Facilities providing</u> <u>detoxification services or MAT:</u> All practitioners must be adequately trained and certified Practitioners providing direct behavioral health services must be a licensed clinical professional (e.g psychologist, psychiatrist, LICSW, etc.) and must possess certification in substance abuse training 	 Facilities providing detoxification services or MAT: Comprehensive patient intake assessment to determine appropriateness of treatment, patient's mental health history, and patient health risks. Comprehensive psychosocial assessment Individualized treatment plan with continuous review Comprehensive social supports for patients with co-occurring disorders Opportunities for family involvement in therapy, as clinically appropriate Provision or referral to parenting skills training or childcare services Dosing of MAT cannot be adjusted to reinforce positive behavior or punish negative behavior, unless the patient is non-compliant with program expectations and taper forms part of a medically-assisted withdrawal from treatment. Patients that voluntarily terminate treatment should be referred to increased counseling services. Medical withdrawal rate must be determined by the medical director and consider the patient's preferences and clinical record 	 Facilities providing detoxification services or MAT: Risk management and quality improvement procedures Programs must register with the <i>Vermont Prescription Drug Monitoring</i> <i>System</i> Recordkeeping Discharge planning, continued care, and treatment termination policies 	Vermont Dept. of Health: <u>Source</u>

* Substance abuse facilities include OTPs, outpatient facilities providing MAT with buprenorphine-containing products, counseling, and/or detoxification services, residential rehabilitation programs, and inpatient detoxification programs.

† Requirements listed in Table are in addition to conditions for licensing set forth by federal agencies, including SAMHSA and the DEA. All federal requirements for OTPs and DATA 2000 apply to substance abuse facilities providing MAT or detoxification in New England states.

Appendix C. Treatment Centers in New England

Figures 1-6. Map of available substance abuse facilities and office-based Suboxone programs in New England states



<u>Connecticut</u>





Massachusetts



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New Hampshire



Rhode Island



<u>Vermont</u>



Appendix D. Meeting Participants

CEPAC Members (in attendance)	Policy Roundtable Participants
Robert H. Aseltine, Jr., PhD	Rebecca Boss, MA
Professor, Division of Behavioral Sciences and Community Health,	Deputy Director,
University of Connecticut Health Center	Department of Behavioral Healthcare, Developmental Disabilities and
Deputy Director, Center for Public Health and Health Policy	Hospitals (BHDDH),
Director, Institute for Public Health Research, University of Connecticut	State of Rhode Island
Stacey L. Brown, PhD	John Brooklyn, MD
Director, Community-based Education	Physician, Community Health Centers of Burlington
Assistant Professor, Community Medicine	
University of Connecticut School of Medicine	
Teresa Fama, MD, MS	Barbara Cimaglio
Physician, Central Vermont Rheumatology	Deputy Commissioner for Alcohol and Drug Abuse Programs, State of
	Vermont
Austin Frakt, PhD	TJ Donovan, JD
Health Economist, VA Boston Healthcare System	State Attorney for Chittenden County
Associate Professor, Boston University School of Public Health	State of Vermont
Associate Professor, Boston University School of Medicine	
Claudia B. Gruss, MD, FACP, FACG, CNSC (Chair)	Kevin Flanigan, MD
Physician, ProHealth Physicians	Medical Director, MaineCare Services
Claudio Gualtieri, JD	John Hammel, MD
Associate State Director of Advocacy, Connecticut AARP	Director, Substance Abuse Services
	White River Junction VA (New Hampshire and Vermont)
Felix Hernandez, MD, MMM	Lisa Muré, MEd, CPS
Medical Director, Surgical Services	Director, Prevention, New Hampshire Center for Excellence Senior
Medical Director, Undergraduate Medical Education,	Consultant, Community Health Institute
Eastern Maine Medical Center	
Toni Kaeding, MS, RN	Stacey Sigmon, PhD
Special Projects, Green Mountain Care Board	Associate Professor of Psychiatry
	University of Vermont
	Director, The Chittenden Clinic
Stephen Kogut, PhD, MBA, RPh	Jeff Simmons, MD
Associate Professor, University of Rhode Island College of Pharmacy	Medical Director for Behavioral Health
	Blue Cross Blue Shield of Massachusetts
Sandhya Rao, MD	Tom Simpatico, MD
Associate Medical Director, Quality Improvement	Chief Medical Officer, Vermont Department of Health Access
Massachusetts General Physicians Organization	
Julie Rothstein Rosenbaum, MD	Jacquelyn Starer, MD, FACOG, FASAM
Associate Professor, Yale School of Medicine	Associate Attending Physician, Faulkner Hospital
	Associate Director, Physician Health Services, Inc.
	President, Massachusetts Chapter of ASAM
Cynthia N. Rosenberg, MD (ex-officio)	Joycelyn Woods, MA, CMA
Senior Medical Director, Harvard Pilgrim Health Care	Executive Director, National Alliance for Medication Assisted Recovery
Jeanne Ryer, MS	
Tom Simposing MD (av. efficie)	
Chief Medical Officer. Vermont Department of Health Access	
Mitchell Stein, MBA (Vice-Chair)	
Independent Health Care Consultant	

Appendix E. Summary Evidence Tables

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Randomized Cor	ntrolled Trials			
Woody GE	RCT	Patients aged 14-21	1) N=78	Number of positive urine tests at 12 weeks
2008		years entering		• Detox: 53
	Primary analysis: 12	outpatient treatment	2) N=74	• Maint: 49
United States	weeks	for opioid dependence		p-value, NR
Also applicable to	Post-treatment f/u: 12	1) Detoxification		Retention in trial at 12 weeks
discussion of	months	w/Suboxone		• Detox: 21%
adolescent				• Maint: 70%
populations		2) Maintenance		p<.001
		treatment (Suboxone)		
				• Detox patients reported more opioid use (OR 4.30, p<.001), marijuana use (OR
		All patients received		6.15, p=.001), cocaine use (OR 16.39, p=.001), with cocaine use remaining significant
		counseling		up to 1 year (OR 3.84, p=.004)
				• Side effects: headache reported in both groups, 16-21%
				1 death (maintenance)

Table 1E. Detoxification versus Maintenance.

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Weiss RD	RCT	Patients with	Phase 1	Patients with successful treatment outcomes in Phase 1: 6.6%
2011		prescription opioid-	1) N = 329	 Patients with successful treatment outcomes in Phase 2: 49.2%
	12-36 weeks	dependence initiating		 Patients in Phase 2 were significantly more likely to attain success while
United States		Suboxone treatment	2) N = 324	maintained on buprenorphine-naloxone (week 12) than after 8 weeks follow-up (week 24), controlling for counseling condition (49.2% versus 8.6%, p<.001)
Also framing		All patients entered	Phase 2	• Rate of opioid-positive urine tests in Phase 2 was significantly higher during the
question #4		Phase 1: brief (12-	1) N = 180	combined taper and post-taper periods (weeks 13–24) than
		week) Suboxone		while maintained on buprenorphine-naloxone during weeks 1–12 (58.1% vs. 39.1%,
		treatment	2) N = 180	p<.001)
				 No significant difference between groups in opioid use outcomes
		Patients		
		w/unsuccessful		
		outcomes entered		
		Phase 2: extended (36-		
		week) Suboxone		
		treatment		
		 In both phases, 		
		patients were		
		randomized:		
		1) standard medical		
		management (SMM) +		
		opioid dependence		
		counseling (ODC)		
		2) SMM alone		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Comparative Stu	Idies	·		•
Caldiero RM	Retrospective case-	Opioid-dependent	1) N = 30	Treatment retention at 12 weeks
2006	controlled	patients initiating		• Detox: 0%
		treatment	2) N = 30	• Maint: 40%
United States	12 weeks			p<.001
		1) Detoxification		
		w/tramadol		Subgroup (receiving care in particular program, Detox: n=30, Maint: n=24)
				Duration of treatment
		2) Suboxone induction		• Detox: 0.4 weeks
		and maintenance		Maint: 8.5 weeks
				p<.001
		 All patients w/follow- 		
		up counseling and		Completion of treatment program
		aftercare		• Detox: 0 patients (0%)
				Maint: 12 patients (50%)
				p<.001
Donovan DM	Non-contemporaneous	Heroin-dependent	1) N = 852	Mean length of stay in outpatient treatment
2013	case series	patients entering		• Detox: 69 days
		treatment	2) N = 144	• Maint: 99 days
United States				p-value, NR
		1) Detoxification		
		w/clonidine		Completion of outpatient treatment program
				• Detox: n=1
		2) Suboxone induction		• Maint: n=33
		and maintenance		p-value, NR
		All patients		Repeat detox admissions
		w/inpatient care,		• Detox: 1.3/year
		outpatient follow-up		• Maint: 1.1/year
		care		p-value, NR
				Subgroup analysis: significant factors associated w/program completion
				• Lower monthly income (p=.04)
				• Not concurrently using cocaine (p=.021)
				• Not having relapse during program (p=.007)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Teesson M	Prospective	Heroin-dependent	1) N = 236	Median cumulative treatment days
2006	comp cohort	patients		• Detox: 78
			2) N = 227	• Maint: 334
Australia	1 year	1) Detoxification		p-value, NR
		2) Maintenance		Median treatment episodes since baseline interview
		(buprenorphine and		• Detox: 3
		methadone)		Maint: 1
		,		p-value, NR
				• Decreases noted in heroin abstinence, days of heroin use, criminal activity in
				previous month for both groups – no statistical analyses
Detoxification Ca	se Series			
Amass L	Retrospective case	Opioid-dependent	N=234	Program completion (13-day taper): 68%
2004	series (from RCTs)	patients receiving		
		Suboxone		Adverse events
United States	6 months	detoxification, 13-day		 18 events recorded, 17 requiring hospitalization
		taper		• 1 mortality (myocardial infarction)
Gandhi DH	Prospective	Heroin users enrolling	N=123	• 96% program completion for 3 days, followed by rapid decline in retention with
2003	case series	in buprenorphine		over half dropping out over the following 3 days
		detoxification,		 Heroin abstinence at 6 months (confirmed by negative urine): 11.8%
United States	6 months	3-day taper		 Self-reported non-use or diminished use at 6 months: 41.2%
				At 30 days, 74% reported using heroin at least once
Hillhouse M	Retrospective case	Opioid-dependent	N=139	 Average number of days in program: 11 days
2010	series (from an RCT)	patients receiving		• Receipt of ancillary medication was associated with decreased retention (p<.001)
		Suboxone for		 Continued opioid use during treatment (positive urinalysis): 44%
United States	13 days	detoxification,		Abstinence from opioids during treatment: 11%
		13-day taper		
Strang J	Prospective	Opioid-dependent	N=137	Mortality at 12 months: 5 patients
2005	case series	patients enrolling in		
		methadone		Significant predictors
United Kingdom	12 months	detoxification,		• Mean dose of methadone (p=.04), mean number of days using heroin in last 30
		28 day		days (p=.03), living alone in last 30 days (p=.004), mean length of stay in program
				(p=.02), completion of full treatment program (p=.02)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Maintenance Ca	se Series			
Astals M 2009	Prospective case series	Opioid-dependent patients enrolling in methadone treatment	N=189	 Retention in treatment: 67% Co-occurring mental disorders did not impact retention (p=.622) Patients w/co-occurring mental disorders had more current diagnoses of alcohol
Spain	18 months			abuse (p=.019)
Bartu A 2002 Australia	Retrospective case series 2 years	Opioid-dependent patients treated w/oral naltrexone	N=981	 Average length of retention: 9 weeks Patients remaining in treatment after 12 weeks: 25% No significant impact of age, gender, formal psychosocial support (outpatient group or individual counseling) or presence of partner on length of time in treatment Employment (part-time or full-time) significantly associated with retention, 11 vs. 7 weeks (p<.05) Patients referred from private clinic stayed in treatment longer than referrals from other sources, 10 vs. 6 weeks (p<.01)
Bovasso G 2003 United States	Prospective case series 2 years	Opioid-dependent patients enrolled in methadone treatment	N=234	 Mean duration in treatment: 551 days Subgroup analyses based on 3 groups: high opiate use(A), high cocaine use(C) and low use of both(B) derived from urinalysis results during first 6 months of treatment) C patients had significantly more criminal charges than B patients (p<.05), no difference btwn A&C B had significantly less heroin use than A&C (p<.01) No significant differences in months of unemployment
Carrieri MP 2003 France	Prospective case series 39 months	HIV-infected, opioid- dependent patients receiving buprenorphine treatment	N=114	 Discontinuation of treatment: 40.4% Treatment continuation until 39 months: 43% Significant factors associated w/discontinuation: women (OR 2.8, 95% Cl 1.0-7.9), heroin users (OR 6.1, 95% Cl 1.9-20.0), having a detectable viral (HIV) load (OR 2.7, 95% Cl 1.0-7.7) Significant decrease in reported injection drug use (p<.001), heroin use (p<.0001), psychotropic drug use (p<.0001) at last f/u No significant changes in cocaine use, misuse of buprenorphine Significant factors associated w/buprenorphine misuse: polydrug abuse (RR 2.5, 95% Cl 1.0-6.3), depression (RR 1.05, 95% Cl 1.01-1.09), while receipt of antiretroviral medication was associated with non-misuse (BR 0.3, 95% Cl 0.1-0.8)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Cerovecki V	Retrospective case	Opioid-dependent	N=287	• 12-year mortality rate: 8%
2013	series	patients enrolled in		Annual mortality rate: 0.7%
		methadone treatment		• Significant factors associated w/fatal outcome included methadone treatment
Croatia	Variable follow-up			w/out any remission (p=.018), living in an unstable relationship (p=.002), loss of
				contact w/family physician overseeing drug status (p=.001)
Chaudhry ZA	Retrospective case	Opioid-dependent	N=142	 Completion of detoxification: 75% (variable agents)
2012	series	patients receiving		 Retention in treatment ≥17 weeks: 30%
		community-based oral		• Decreased alcohol intake (<10 units/week, p=.02) and shorter duration of addiction
United Kingdom	>4 weeks	naltrexone treatment		(<3 years, p=.01) were significantly associated w/treatment retention
Che Y	Retrospective case	Patients enrolled in	N=793	Median attendance at clinic: 61 days
2011	series	methadone treatment		• Factors significantly negatively associated w/attendance included treatment>3
				months (p<.001), being unmarried (p<.001), history of shared syringes (p=.02) and
China	9 months			self-employment (p<.001)
				 Factors significantly associated w/attending treatment included a history of
				detoxification (p=.02)
Cox J	Retrospective case	Opioid analgesic-	N=246	 Retention in treatment: 63% (1 patient w/completion)
2013	series	dependent patients		Mean time in program: 306 days
		enrolled in methadone		• Analyses of factors associated w/voluntary and involuntary discharge conducted
Canada	3 years	treatment		
De Jong CAJ	Prospective	Opioid-dependent	N=272	Continuous abstinence at 16 months: 24%
2007	case series	patients enrolled in oral		• At 16 months, significant decreases in the use of heroin, methadone, polysubstance
		naltrexone treatment		abuse
The Netherlands	16 months	w/Community		 No significant baseline differences between abstinent patients and relapses
		Reinforcement		 Abstinent patients attended significantly more CRA sessions w/physicians and
		Approach (CRA)		counselors, and received naltrexone on significantly more days (124 vs. 57, p<.001)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Deck D 2005 United States	Medicaid database Analysis of patients retained for at least 1 year	Patients in methadone treatment for opioid use	Oregon: n=3557 Washington: n=5308	Oregon • Retention rates 1994: 24.8%; disabled/welfare pts: 22.9% 1999: 49.8%; disabled/welfare pts: 55.2% Washington • Retention rates 1994: 27.9%; disabled/welfare pts: 27.4% 1999: 32.8%; disabled/welfare pts: 35.5% • Significant predictors of retention for both states included older patients (p<.01)
				 Significant predictors of not being retained included being male (p<.05), daily opiate use (p<.05), cocaine as second drug (p<.001), African American [in WA only, p<.001)], being arrested in previous 2 years (p<.05)
Dijkstra BAG 2010	Prospective case series	Opioid-dependent patients from addiction treatment centers	N=121	 Completion of detox program: 87% Mean # of detox days: 7.19 # of patients lost to f/u at 1 month post-detox: 37%
The Netherlands	1 month	enrolling in detoxification & maintenance w/oral naltrexone		• Of patients remaining in maintenance, % abstinent: 62%
Esteban J	Retrospective case	Opioid addicts	N=1487	Retention in treatment: 54%
2003	series	receiving methadone		• Survival percentage at 3 years: 83%; at 5 years: 72%
Spain	7 years	maintenance treatment		• Factors associated w/increased rate of mortality included HIV infection (p<.001), not currently receiving methadone (p=.003)
Flynn PM 2003	Retrospective case series	Patients in methadone treatment for opioid addiction	N=432	Patient status at 5 years • Recovered: 27.5% • Non-recovered: 72.5%
United States	5 years			 Significant predictors of non-recovery included alcohol use (p<.001) and illegal activity (p<.05) Patients spending between 90 and 240 days in index treatment were significantly more likely to be recovered at 5 years (p<.05)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Gossop M	Prospective	Patients enrolled in	N=276	• Significant decreases at follow-up in heroin use, non-prescribed methadone and
2003	case series	methadone treatment		benzodiazepines, injecting drugs, acquisitive crime and drug selling (all p<.001)
United Kingdom	4-5 years			
Gossop M	Prospective	Patients enrolled in	N=276	• Significant decreases in frequency of heroin, cocaine and alcohol use at follow-up
2006	case series	methadone treatment		(p<.01)
				• Factors significantly associated w/more frequent heroin use included frequency of
United Kingdom	6 months			heroin (p<.001), cocaine (p<.01) and injecting drugs (p<.05) at admission
				• Older age was significantly associated w/less frequent heroin use at follow-up (p<.05)
Harris EE	Retrospective case	Patients receiving	N=252	Patients w/at least 1 criminal charge: 38%
2012	series	buprenorphine for		
		opioid dependence		• Significant correlates of criminal activity included history of heroin abuse (p=.001),
United States	2 years			IV drug use (p=.025), HCV infection (p=.01) and prior criminal activity (p<.001)
				• Significant correlates of NO criminal activity included prescription opioid abuse
				(p<.001), recent opioid maintenance treatment $(p=.017)$, and 26 opioid-free months $(n=.004)$
Judson G	Prospective	Patients enrolled in	N=151	• Mean time in program: 6.7 years
2010	case series	methadone treatment		Methadone injection while in program: 80%
				(New Zealand study - some of injected methadone was that prescribed, some from
New Zealand	Survey of enrolled			other sources)
	patients			Alternate injecting of illicit substances: 35%
				Longer time spent in treatment associated with decreased likelihood of injecting
				methadone (p=.029) and other substances (p=.046)
				• Injection of other substances associated with more frequent observed methadone
				dosing (days/wk) (p=.005)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Kamal F	Retrospective case	Opioid-dependent	N=440	Mean duration in treatment: 42 months
2007	series	patients enrolled in		Abstinent from illicit opiate use: 34%
		methadone		Patients w/positive urinalysis for cocaine: 39%
Ireland	Patients enrolled over	maintenance		Patients w/positive urinalysis for benzodiazepines: 65%
	a 3-month period			 Patients w/positive urinalysis for alcohol misuse: 17%
				Patients w/positive urinalysis for amphetamines: 5%
				 Factors associated with greater opiate abstinence included methadone ≥60 mg (p=.02) Factors associated w/less episte abstinence included section (a < 001) and
				• Factors associated w/less oplate abstinence included cocaine (p<.001) and honsediazoning use (n= 002)
Lanovro Mostro M	Potrospostivo caso	Patients newly enrolled	N-202	Petention in trootmont: 27%
2003	sorios	in hunrenornhine	N-202	• Retention in treatment. 57%
2003	361163	treatment		
France	24 weeks	treatment		
Leonardi C	Retrospective case	Opioid-dependent	N=979	Retention in treatment: 51%
2008	series	patients receiving		Relapsed patients: 33%
		buprenorphine		Abstinent patients (no heroin): 15%
Italy	Up to 2 years	treatment		
LiL	Prospective	Heroin-dependent	N=168	Mean duration in treatment: 25 months
2011	case series	patients receiving		• Significant decreases after 1 year of treatment in the use of heroin, alcohol,
		methadone treatment		tramadol and triazolam (p<.01)
China	1 year			• Significant increase in the use of ephedrine (p<.001)
				• Higher education and history of heroin use in the 6 months prior to treatment
				independently increased risk of heroin use during treatment
				Abstinence rate of heroin use after 1 year: 6%
Lin C	Prospective	Patients receiving	N=560	Average duration of treatment: 13.5 months
2011	case series	methadone treatment		• Concurrent illicit drug use (self-report or positive urinalysis): 38%
China	Crease continuel			• Factors negatively associated w/illicit drug use included family support (p<.01),
China	cross-sectional			psychological and environmental nearth (p<.001) • Easters associated w/likelibood of consurrent illigit drug use included longer
	anaiysis			duration of onioid use pre-treatment ($n < 05$)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Lucas GM 2012 China & Thailand	Prelim safety data (4 weeks) from ongoing RCT	Opioid-dependent patients receiving Suboxone treatment	N=150	 Completion of induction: 97% 2 clinical adverse events reported: grade 3 gastroenteritis, grade 3 osteomyelitis Grade 3 assessments in hemoglobin and platelet count observed in 1 patient each; 6 grade 3 changes in liver enzyme (ALT) observed
Moore BA 2007 United States	Secondary analysis of RCT (Fiellin, 2006; see framing question #4) 24 weeks	Patients w/heroin and/or prescription opioid dependence enrolled in Suboxone treatment	N=200	 Prescription opioid users were significantly more likely to complete treatment than heroin-only patients (59 vs. 38%, p=.01) Prescription-only (21 weeks) and combined-use patients (19 weeks) remained in treatment longer than heroin-only (14 weeks, p=.002) Prescription-only patients had a higher percentage of opioid-negative urines compared to other groups (p=.03)
Mullen L 2012 Ireland	Retrospective case series 12 months	Patients newly enrolled in methadone treatment	N=1269	 Retention in treatment: 61% Mortality: 5 patients (0.3%) Factors significantly associated w/retention included female (p=.03), attendance at a primary care physician (p=.01), methadone dose ≥60 mg (p=.0001)
Neumann AM 2013 United States	Retrospective case series 6 months	Opioid-addicted patients receiving Suboxone treatment	N=356	 Patients completing treatment (6 months): 36% Factors significantly associated w/treatment completion included attendance in counseling program (p=.002), and past emotional or physical trauma/injury (p<.001)
Ohlin L 2011 Sweden	Retrospective case series >4 weeks treatment	Patients receiving Suboxone/ buprenorphine treatment for opioid dependence	N=123	Retention in treatment >1 year: 50%
Pade PA 2012 United States	Retrospective case series	Patients w/chronic non-cancer pain and opioid dependence treated w/Suboxone	N=143	Retention in treatment: 65% Mortality: 2 patients (1%)
Peles E 2010 Israel	Retrospective case series Up to 15 years	Patients enrolled in methadone treatment	N=613	 Overall mortality: 94 patients (15%) (2.0 deaths/100person-years) (multiple predictors evaluated) Retention in treatment: 285 (46%) Factors significantly associated w/longer retention included no opiate or BZD abuse after 1 year (p<.0005), methadone dose ≥100mg after 1 year (p<.0005), or direct admission to the bosnital (n= 02)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Soeffing JM	Retrospective case	Patients receiving	N=255	Retention in treatment: 57%
2009	series	maintenance treatment		• Factors significantly associated w/retention included concurrent use of cocaine
		w/Suboxone/		(p=.011) and alcohol (p=.041), and patients assigned to residents/physicians
United States	12 months	buprenorphine		compared to nurse practitioners (p=.012)
				Opioid negative patients at 1 year: 16%
				Mortality: 5 patients
Somers CJ	Retrospective case	Patients enrolled in	N=123	Retention in treatment at 15 months: 46%
2012	series	methadone treatment		• Positive urinalysis for heroin: 31%; for cocaine: 12%; for BZDs: 18%; for cannabis:
				21%; for alcohol: 5%
Ireland	15 months			• Positive urinalyses for cocaine(OR 0.69, 95% CI 0.59-0.81) and BZDs (OR 0.7, 95%
				CI 0.53-0.93) significantly associated w/poorer outcomes while methadone dose
				<60mg associated w/improved outcomes (OR 1.67, 95% CI 1.16-2.41)
Sung HE	Retrospective case	Patients enrolled in	N=318	Retention in treatment: 55%
2011	series	methadone treatment		Increase in employment rate from baseline: 30%
United States	12 months			
Tkacz J	Prospective	Newly enrolled patients	N=703	Patients w/relapse within 3 months: 20%
2011	case series	in buprenorphine		• Factors significantly associated w/relapse included noncompliance (p<.001)
		treatment		
United States	3 months			
Wang EA	Secondary analysis of	Opioid-dependent	N=166	Comparison of patients w/a history of incarceration vs. none
2010	RCT (Fiellin, 2006; see	patients receiving		• No significant difference in outcomes based on incarceration history: treatment
	framing question #4)	Suboxone treatment		completion, treatment retention, continuous opioid and cocaine abstinence,
United States				percent negative cocaine/opioid urinalyses
Wu LT	Secondary analysis of	Patients w/continued	N=383	• No difference in number of days in treatment between patients with and
2008	RCT (Peirce, 2006; see	stimulant abuse		without past-month illicit use of methadone (79.3 vs. 78.6 days)
	framing question #4)	enrolled in methadone		• Younger age (13-34 years), a history of outpatient treatment for psychological
United States		treatment		problems and past-year dependence on marijuana all significantly associated
				w/past-month illicit methadone use (p<.05)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Randomized Cont	trol Trials	·		
Giacomuzzi S	RCT	Evaluation opioid users	1) N = 120	Use of other substances of abuse
2006		enrolled in outpatient		• Significant difference between addicts at admission and methadone, slow-release
	6 months	maintenance treatment	2) N = 120	oral morphine, and buprenorphine patients in illicit cocaine use (p<.001)
Austria			Morphine,	 Sublingual buprenorphine and methadone maintenance treatment showed more
		1) Opioid users seeking	N = 40	favorable values compared with clients at admission for consumption of opioids
		initial treatment	Methadone,	(p≤.004)
			N = 40	 Patients on a slow-release oral morphine program showed significantly more
		2) Opioid-dependent	Buprenorphin	consumption of benzodiazepines than subjects treated with methadone or
		patients retained for 6	е,	sublingual buprenorphine (p=.021)
		months	N = 40	
		 Slow-release oral 		Treatment retention/Continued use of illicit opioids
		morphine		 Comparable efficacy with buprenorphine 8–12 mg/day and methadone 30– 90
		Methadone		mg/day in promoting retention in treatment and reducing illicit opioid use
		Buprenorphine		
				<u>Notes</u>
				 Except age (p=.039), no statistical differences b/w groups
Jagsch R	RCT	Patients with opioid	1) N = 31	Treatment retention
2005		dependence seeking		• Drop-out rate significantly higher for methadone patients vs. buprenorphine
	24 weeks	treatment	2) N = 29	patients (71% vs. 38%, p=.01)
Italy				
		1) Methadone		Dosing
				 Average methadone dose of 54.05 mg/day was compared with an average daily
		2) Buprenorphine		buprenorphine dose of 6.11mg (ratio 8.85)

Table 2E. Comparative Effectiveness of Methadone, Buprenorphine, and Naltrexone.

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Krupitsky E	RCT	Detoxified patients	1) N = 126	Continued use of opioids
2011		with opioid		Median weeks of confirmed abstinence for naltrexone was 90% vs. 35% for
	24 weeks	dependence disorder	2) N = 124	placebo (p=.0002)
Russia				• Self-reported median opioid-free days was 99.2% for naltrexone vs. 60.4% for
		1) Injectable naltrexone		placebo (p=.0004)
				• Opioid craving was significantly lower for naltrexone than placebo (p<.0001)
		2) Placebo		• Reduced rates of relapse for Vivitrol vs. placebo (0.8% vs. 13.7%, p<.0001)
		• Patients received 12		Other substances of abuse
		bi-weekly counseling		Median weeks of confirmed abstinence for naltrexone was 90% vs. 35% for
		sessions		placebo (p=.0002)
				• Patients with total confirmed abstinence was 35.7% for Vivitrol vs. 22.6% for
				placebo (p=.022)
				Treatment retention
				• Retention was 168 days for naltrexone vs. 96 days for placebo (p=.004)
				• Every patient had a significant other who supervised their compliance with study
				procedures
Krupitsky E	RCT	Patients with opioid	1) N = 102	Treatment retention (without relapse)
2012		dependence		• Implant: 52.9%
	24 weeks		2) N = 102	• Oral: 15.7%
Russia		1) Naltrexone implant +		Placebo: 10.8%
		oral placebo	3) N = 102	p<.001
		2) Oral naltrexone +		Continued use of illicit opioids
		implant placebo		• Implant: 63.6% (95% CI, 60%-66%)
				• Oral: 42.7% (95% Cl, 40%-45%)
		3) Oral/implant placebo		• Placebo: 34.1% (95% Cl, 32%-37%)
		All received bi-weekly		Side effects
		counseling		• Implant: 4.9% (wound infections), .9% (redness + swelling)
				• Oral: 1.1% (wound infections), .8% (redness + swelling)
				 Placebo: .7% (wound infections), .8% (redness + swelling)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Lintzeris N	RCT	Patients currently on	1) N = 44	• No significant difference between groups for plasma levels, treatment outcomes,
2013		Suboxone treatment		or adverse events
	31 days		2) N = 48	• Film took significantly less time to dissolve (p=.007) and produced higher patient
Australia		1) Sublingual film		satisfaction scores
		(buprenorphine/		
		naloxone)		
		2) Oral tablet		
		(hupreporphine/		
		naloxone)		
Otiashvili D	RCT	Patients with opioid	1) N = 40	• Both study arms resulted in reduction in opioid use, opioid craving, and/or
2013		dependence		elimination of unsafe HIV risk injecting behaviors
	20 weeks		2) N = 40	 Significantly fewer participants who remained in treatment used illicit opioids
Republic of Georgia		1) Methadone		(5.6% vs. 27.6%; p<.001)
		2) Suboxone		
		 12-week treatment 		
		w/follow-up at week 20		
Saxon AJ	RCT	Opioid-dependent	1) N = 529	Treatment retention
2013		patients seeking		 Suboxone group completed fewer weeks of treatment than did the methadone
	24 weeks	treatment	2) N = 740	group, (mean = 25.8, p<.0001) but had excellent clinical responses
United States				
		1) Methadone		Significant differences in baseline characteristics included, Suboxone group had
				less non-heroin opioid use than the methadone groups (9.3 vs. 7.3 days, p=.043),
		2) Suboxone		and the methadone group reported more injection drug use in the past 30 days as
				compared to the Suboxone group (69.3% vs. 61.8%, p = 0.032)
				No evidence of liver damage during the initial 6 months of treatment in either
				condition

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Schottenfeld RS	RCT	Detoxified heroin-	1) N = 43	Treatment Retention
2008	[part of Cochrane	dependent patients		• Buprenorphine was found to be superior in terms of mean days in treatment
	review (Mattick,		2) N = 44	compared to naltrexone (117 vs. 84, p=.022) and placebo (117 vs. 70, p=.0009)
Malaysia	2014)]	1) Oral naltrexone		
			3) N = 39	Continued illicit opioid use
	24 weeks	2) Buprenorphine		• Buprenorphine was found to be superior in terms of mean days in treatment
				without heroin use compared to naltrexone (51 vs. 24, p=.028) and placebo (51 vs.
		3) Placebo		18, p=.0058)
				Notes
				Differences between naltrexone and placebo were not significant for any
				outcomes
Case Series				
Comer SD	Randomized, double-	Evaluation of the abuse	N=12	Higher mean "drug liking" measures for heroin, high-dose
2010	blind crossover study	potential of Suboxone		buprenorphine/naloxone, and low- and high-dose buprenorphine than for placebo
		vs. buprenorphine for		(p<.0001)
United States	8-9 wks	intravenous heroin		• Buprenorphine/naloxone has less abuse potential than buprenorphine alone
		users maintained on		(p<.0005)
		varying doses of		 Participants reported that they would pay significantly less money for
		buprenorphine (2, 8 or		buprenorphine/naloxone than for buprenorphine or heroin (p<.05)
		24 mg)		
Gibson A	Secondary analysis of	Heroin-dependent	1) N = 205	<u>Mortality</u>
2008	Mattick 2003 [part of	patients enrolled in		No significant difference in mortality between methadone and buprenorphine
	Cochrane review	maintenance treatment	2) N = 200	participants
Australia	(Mattick, 2014)]			
		1) Methadone		Treatment Retention
	10 years			• Participants in both groups were significantly more likely to spend longer time in
		2) Buprenorphine		treatment episodes lasting longer than 14 days (p<.0001)
				• No significant differences between the groups in demographics or drug use
				variables

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Hser YI	Secondary analysis of	Evaluation of	N=1,269	• Treatment completion rate was better for methadone (74% vs. 46%, p<.01)
2014	RCT (Saxon, 2013)	medication dose, urine		• Of those remaining in treatment, buprenorphine patients submitted significantly
		drug screens, and days		fewer opioid positive urine screens (p<.01) during the first 9 weeks of treatment
United States		in treatment		• Higher completion rate and lower opiate use were associated with higher doses for
				both buprenorphine (30-32mg/d) and methadone (60mg/d)
Also framing				
question #3				
Potter SJ	Secondary analysis of	Evaluation of baseline	N = 1,269	 Injectors were more likely to be using at end of treatment compared with non-
2013	RCT (Saxon, 2013)	clinical characteristics		injectors
		and impact on		Opioid-users users were more likely to complete treatment compared with heroin
United States		treatment outcomes		users and combined users
				• No evidence of superiority of buprenorphine over methadone for treating opioid-
				users versus heroin users
Table 3E. Dosing and Duration Protocols.

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Randomized Cont	rolled Trials			
Comer SD	RCT	Heroin-dependent	1) N = 20	Treatment retention
2006		patients		Placebo: 39% with drop out at 27 days
	8 weeks		2) N = 22	 192mg: 60% with drop out at 36 days
United States		1) Sustained-release		 384mg: 68% with drop out at 48 days
		depot naltrexone, 192mg	3) N = 18	p=.002
				Continued use of illicit opioids (as determined by opioid-negative urine)
		2) Sustained-release depot naltrexone,		• Mean % lowest in placebo and highest at 384mg (25.3% vs. 61.9%, p=.002)
		384mg		Other substances of abuse
				• Cocaine-negative samples significantly lower in placebo group than in 192mg (0%
		3) Placebo		vs. 100%, p= .01) and in the 384mg group (0% vs. 84.6%, p=.04) through week 7
				Adverse Events (AE)
		Patients		• No significant difference between groups for # of AEs, treatment-related AEs or
		received		discontinuation due to AEs
		relapse		
		prevention		
		therapy 2x		
		week		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Epstein DH	RCT	Outpatients admitted	1) 70mg	Continued use of illicit opioids
2009		for methadone	N = 126	 Percent of negative urines was greater in 100mg groups than in 70mg groups
	5 week baseline,	treatment		(42% vs. 20%, p=.01)
United States	12 week intervention		2) 100mg	• Number of urines negative for cocaine for opiates and cocaine simultaneously did
		1) Randomization by	N = 126	not differ by dose
		methadone dose, 70mg		 Contingency groups had the longest duration of opioid-negative urines for both
		vs. 100mg		opiates and cocaine (p=.01)
		2) Randomization by		Treatment retention
		voucher arm:		Mean retention was 15.1 (out of possible 17 weeks)
		 Non-contingent 		• Drop-out rate was 44%
		 Contingent on 		 Retention did not differ significantly by dose or contingency
		cocaine-negative urine		
		screen		
		 Contingent on 		
		cocaine + opiate		
		negative urine screens		
		w/voucher value "split"		
		Daily methadone and		
		weekly counseling		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Kennedy AP 2013 United States	RCT 40 weeks	Opioid- and cocaine- dependent patients enrolling in methadone treatment	1) Neither, N = 16 2) CM, N = 29	 <u>Continued use of illicit opioids</u> Abstinence from opioid/cocaine use was greater in group <i>CM</i> than in group <i>Both</i> (p=.018) and did not differ between groups <i>Both</i> and <i>Neither</i> (p =.70) <u>Treatment retention</u> Pange from 19.9 wks to 21.1 wks with no significant difference across groups
		2) 100mg fixed + cocaine-abstinent vouchers	3) Flexible, N = 6 4) Both, N = 13	 Dosages of methadone over 100 mg/day, even when prescribed based on specific signs and symptoms, were not better than 100 mg/day
		 3) >100mg flexible + non-contingent vouchers 4) >100mg flexible + cocaine-abstinent vouchers 		
Krupitsky E 2012	RCT 24 weeks	Patients with opioid dependence	1) N = 102 2) N = 102	Treatment retention (without relapse) • Implant: 52.9% • Oral: 15.7%
Russia		 1) Naltrexone implant + oral placebo 2) Oral naltrexone + implant placebo 3) Oral/implant placebo Participants received bi-weekly counseling 	3) N = 102	 Placebo: 10.8% p<.001 <u>Continued use of illicit opioids</u> Implant: 63.6% (95% CI, 60%-66%) Oral: 42.7% (95% CI, 40%-45%) Placebo: 34.1% (95% CI, 32%-37%) <u>Side effects</u> Implant: 4.9% (wound infections), .9% (redness + swelling) Oral: 1.1% (wound infections), .8% (redness + swelling) Placebo: .7% (wound infections), .8% (redness + swelling)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Ling W	RCT	Patients initiating	1) N = 255	Continued use of illicit opioids
2009		Suboxone treatment		• More people were opioid-free at end of 7-day taper (44.3% vs. 29.9% for 28-day
	2 years	with 1 month of	2) N = 261	taper, p=.0007)
United States		stabilization followed		• No statistically significant differences were found at 1-month and 3-month follow-
		by a taper		ups
		1) 7-day taper		• Groups did not differ at baseline or through stabilization in terms of demographics
				of drug characteristics
		2) 21-day taper		 If the goal is discontinuation of all treatment, shorter taper is better
Marsch LA	RCT	Opioid-dependent	1) N = 45	<u>Continued use of illicit opioids (% of urines that were opioid-negative)</u>
2005		outpatients enrolling in		• Daily, 73%
	24 weeks	buprenorphine	2) N = 44	• 3x weekly, 70%
United States		treatment		• 2x weekly, 73%
			3) N = 45	p-value, NS
		1) Daily dosing		
				Treatment retention
		2) 3x/week dosing		• Daily, 69%
				• 3x weekly, 73%
		3) 2x/week dosing		• 2x weekly, 64%
				p-value, NS
				• Employment predicted cocaine/opioid abstinence (p=.04)
				Number years of regular use predicted cocaine/opioid abstinence for participants
				in 3x dosing condition (p=.005)
				All dosing regimens were of comparable efficacy in promoting treatment retention
				and opioid and cocaine abstinence

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Montoya ID 2004 United States	RCT 13 weeks	Patients enrolling in buprenorphine maintenance treatment for concurrent opioid and cocaine addiction 1) 16mg daily 2) 16mg every other day 3) 8 mg daily 4) 2 mg daily	1) N = 46 2) N = 43 3) N = 46 4) N = 46	 <u>Continued use of illicit opioids/cocaine</u> 8mg & 16mg daily groups associated with statistically significant decreases in urine morphine (p=.0135, p<.001) and benzo (p=.0277, p=.006) concentrations Urine benzoylecgonine concentrations did not increase significantly during the withdrawal phase (p=.16 for 2 mg/d, p=.85 for 8 mg/d, p=.48 for 16 mg every other day, and p=.59 for 16 mg/d) Low dose (2 mg/d) not associated with reduction in opioid use Not significantly different among medication groups for treatment retention and adverse events
Nava F 2008 Italy	RCT 1 year	Heroin addicts with alcohol dependence enrolled in opioid maintenance treatment 1) Methadone • Dosed at 80, 120, 160 or 200 mg/day 2) Buprenorphine • Dosed at 8, 16, 24 or 32 mg/day	1) N = 108 2) N = 110	 <u>Treatment retention</u> At the 3rd and 6th month of treatment, methadone showed a less percentage of drop-outs than buprenorphine (6 vs. 10 drop-outs at both points) <u>Continued use of illicit opioids</u> At highest dose, the treatments were equally in effective reducing both heroin craving and positive-opioid urine After the 6th month the effects of the dose of 16 mg/day were statistically significant (p<.01) in comparison with the effect of the dose of 8 mg/day Groups were similar at baseline characteristics

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Rea F	RCT	Evaluation of low-dose	1) N = 22	Treatment retention (measured at 3 and 6 months)
2004		oral naltrexone for		• Difference was not statistically significant b/w groups, but trended towards higher
	6 months	treatment of patients	2) N = 23	retention for 50 mg day
Australia		with heroin		
		dependence	3) N = 21	Continued use of illicit opioids
		1) 50		• Regardless of dose group, heroin use was significantly reduced over time
		1) 50 mg		(p=.5285).
		2) 0.5 mg		 Study was terminated because there was a trend favoring 50mg/day
		3) 0.05 mg		
Sigmon SC	RCT	Prescription opioid-	1) N = 22	Continued use of illicit opioids
2013		dependent patients		• Abstinence at the end of phase 2 was significantly greater (p=.03) in the 4-week
	12 weeks	initiating Suboxone	2) N = 24	group with 50% compared with the 2- and 1-week conditions (16% and 20%,
United States		treatment		respectively)
		. Fallendare Culture	3) N = 24	Toucher and and and in a
		Following Suboxone		Ireatment retention
		randomized to taper		• Retention and native compared w/17% and 21% for 2, and 1, week dependences $n = 0.0$
		(phase 1) followed by		
		naltrexone		• Participants were primarily white and reported oxycodone as their primary drug of
		maintenance (phase 2)		abuse
		Phase 1		
		1) 4-week taper		
		2) 2-week taper		
		3) 1-week taper		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Weiss RD	RCT	Patients with	Phase 1	Patients with successful treatment outcomes in Phase 1: 6.6%
2011		prescription opioid-	1) N = 329	 Patients with successful treatment outcomes in Phase 2: 49.2%
	12-36 weeks	dependence initiating		 Patients in Phase 2 were significantly more likely to attain success while
United States		Suboxone treatment	2) N = 324	maintained on buprenorphine-naloxone (week 12) than after 8 weeks follow-up (week 24), controlling for counseling condition (49.2% versus 8.6%, p<.001)
Also framing		 All patients entered 	Phase 2	• Rate of opioid-positive urine tests in Phase 2 was significantly higher during the
question #1		Phase 1: brief (12-	1) N = 180	combined taper and post-taper periods (weeks 13–24) than
		week) Suboxone		while maintained on buprenorphine-naloxone during weeks 1-12 (58.1% vs. 39.1%,
		treatment	2) N = 180	p<.001)
				 No significant difference between groups in opioid use outcomes
		Patients		
		w/unsuccessful		
		outcomes entered		
		Phase 2: extended (36-		
		week) Suboxone		
		treatment		
		• In both phases.		
		patients were		
		randomized:		
		1) standard medical		
		management (SMM) +		
		opioid dependence		
		counseling (ODC)		
		2) SMM alone		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Comparative Stud	lies			
Carreno JE	Prospective	Outpatients with	1) N = 56	Treatment retention comparison
2003	comparative cohort	opioid-dependence		• Implant: 80% at month 6, 65% after 1 year
		receiving detoxification	2) N = 284	• Oral: 42% at month 6, 17% after 1 year
Spain	1 year	followed by naltrexone		p<.05
		1) Naltrexone implant		Continued use of illicit opioids
				Opioid-negative urine in all tested
		2) Oral naltrexone		
				Side Effects
				 Allergic reactions including rash and wound infection
Fareed A	Retrospective	Patients enrolled in	1) N = 56	• High-dose group had significantly higher percentage of positive urine drug screens
2012	comparative cohort	buprenorphine		after admission (p=.0001) compared to the moderate-dose group, but the later four
United States	At least 1 month in	maintenance treatment	2) N = 21	urine drug screens did not show statistically significant difference between the two groups (p=.74)
	treatment	1) High dose, >16mg		• Severity and duration of opioid addiction may reflect the need for higher or lower buprenorphine doses to prevent relapse • Dropout rate between the high-dose and
		2) Moderate dose,		moderate-dose groups (15.3 vs. 18.2 months) was not statistically significant
		≤16mg		
Fonseca F	Prospective comp	Opioid-dependent	1) N = 169	Responders and non-responders were defined by illicit opioid consumption
2011	cohort	patients enrolled in a		detected in random urinalysis.
		community program of	2) N = 76	• Methadone dosage – responders on 109 mg/day vs. non-responders on 72 mg/day
Spain	At least 4 months in	methadone treatment		(consumption detected in random urinalyses)
	treatment			• Responders stayed in treatment 52 months vs. 21 months for non-responders
		1) Responders		
		2) Non-responders		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Gerra G 2003	Prospective comp cohort	Heroin-dependent MMT patients randomly selected from	1) N = 89 2) N = 176	 Responders and non-responders were defined by were defined by detection of illicit and non-prescribed drugs in urinalysis Higher doses of methadone (more than 80 mg) in comparison with the patients
Italy	1 year	20 addiction services program		who received lower doses (less than 40 mg) produced significantly more responders (p<.02)
		2) Non-responders		
Nielsen S 2013	Secondary analysis of RCT (Ling, 2009)	Evaluation of outcomes following a Suboxone	1) N = 90	• More PO users were stabilized on: 8mg (18%) or 16mg (32%) vs. heroin users (8%, 26%, respectively) (p = .002)
United States		taper between prescription opioid &	2) N = 426	• Those in 7-day taper group were twice as likely to complete the taper and provide an opioid-negative urine sample (p=.01)
		heroin users		• More of the heroin group was present at the end of the taper compared to PO users (317 vs. 57, p=.20)
		1) Prescription opioid users (PO)		• Results were not significant when controlling for demographics and drug use at baseline (heroin group reported more years of use)
		2) Heroin users		
Case Series				
Dickinson GL	Retrospective case	Evaluation of	N=301	• Statistically significant relationship b/w dosing and treatment retention with the
2006	series	methadone prescribing		best relationship being found for maximum dose (r=.1637)
United Kingdom	5 vears	practices over time		Max dose associated w/greatest retention is 96mg/day; higher doses associated w/decreased patient retention
onned kingdom	5 years	Prescription database		• Every extra mg dose received, the patient remained in treatment 3.3 days
		was used to identify		
		entry length of stay		
		(first prescription to		
		last day recorded)		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Dunn J	Retrospective case	Patients receiving long-	N=169	Proportion of urines positive for illicit opiate was inversely and significantly
2003	series	term methadone		associated with:
		maintenance		1) Methadone dose (p=.004)
United Kingdom	7 months			2) Duration of treatment (p=.001)
		Evaluation of		
		methadone prescribing		
		over time		
		Data collected from 3		
		electronic databases	N 004	
Hillhouse M	Secondary analysis of	Evaluation of correlates	N=894	• Non-daily opioid use for the past 30 days at baseline, previous drug abuse
2013	RCT (LINg, 2009)	or treatment success		treatment, and marital status were significant predictors of abstinence as measured by a single toyicology test at the end of the stabilization phase $(n = 54)$
United States				• Potentian was significantly associated with non-daily oniate use in the past
United States		therapy		• Recention was significantly associated with non-daily optate use in the past 20days lifetime arrest for criminal activity, and employment (past 20days) (p= 71)
		therapy		Solarys, method arest for christian activity, and employment (past solarys) ($p=.71$).
		• 4 week stabilization		
		on Suboxone followed		
		by 7 or 28 day taper		
Hser YI	Secondary analysis of	Evaluation of	N=1,269	• Treatment completion rate was better for methadone (74% vs. 46%, p<.01)
2014	RCT (Saxon, 2013; see	medication dose, urine		• Of those remaining in treatment, buprenorphine patients submitted significantly
	framing question #2)	drug screens, and days		fewer opioid positive urine screens (p<.01) during the first 9 weeks of treatment
United States		in treatment		• Higher completion rate and lower opiate use were associated with higher doses
				for both buprenorphine (30-32mg/d) and methadone (60mg/d)
Also framing				
question #2				

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Leonardi C 2008	Retrospective case series	Opioid-dependent patients enrolling in buprenorphine	N=979	 Over half of all treatments induced with 2mg of buprenorphine relapsed (51.2%), vs. 39.2% on 4mg, 31.5% on 8mg, and 20.6% on 10mg Patients treated with buprenorphine doses ≥16 mg less-than-daily dosing resulted
Italy	2 years	treatment 3 days buprenorphine induction followed by maintenance 		in better compliance and retention in treatment compared with daily dosing • Inverse relationship between urines positive for illicit drugs and duration of treatment with most notable reductions in patients treated with >16mg
		 Participants also received non- compulsory psychosocial support 		
Liao DL	Retrospective case	Database of nationwide	Groups based	• For treatment-related factors, the higher-dosage group (>60mg/d) has lower
2013	series	enrolled opioid-	on average	mortality risk than the lower-dosage group (p=.03).
Taiwan	2 1/02/16	dependent patients at	daily dose:	• Dosage effect is significant in shorter duration (<=365 days) and not significant in
laiwaii	2 years		1) ≤30mg, N = 7,675 2) 30-45mg,	 Trend indicating doses higher than 60 mg/d further lowers the mortality risk in 80 mg/d (p=.02) and 100 mg/d (p=.07) subgroups For treatment duration, the dosage effect is significant in short duration (<365 days) subgroup (p=.002) but not significant in the long duration (>365 days)
			N=10,400	subgroup
			3) 45-60mg, N=8,124	
			4) >60mg, N=7,350	

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Nosyk B 2010 Canada	Retrospective case series 11 years	Study of dosing patterns in MMT patients from provincial drug dispensation database	N=31,724 "episodes" or treatment durations	 Higher daily maintenance dose associated with longer treatment Risk of fatal overdose during first 2 weeks of treatment is 6.7x higher than those not receiving treatment and 98x higher than those on maintenance doses of methadone Although slower tapers are more effective, most patients relapse or discontinue treatment (5% success rate) Statistical significance was not measured
Nosyk B 2012	Retrospective case series	MMT tapering outcomes from provincial drug	N=4,183 tapering "episodes"	 Longer tapers had substantially higher odds of success (12–52 weeks vs. <12 weeks: Odds ratio: 3.58; 95% CI: 2.76 – 4.65) Reaching a maximum dose of between 60–100mg and more than 100mg had 44%
Canada	11 years	dispensation database		and 60% lower odds of sustained success in tapering compared to those maintained on lower doses
Reece A 2007 Australia	Non- contemporaneous case series 12 months	Evaluation of naltrexone for treatment of patients with heroin addiction 1) Naltrexone implant 2) Oral naltrexone (treated 2000-2001) 3) Historical oral naltrexone (treated 1999-2000)	1) N = 102 2) N = 113 3) N = 161	 Amphetamine use was significantly greater in the implant group than either the tablet (p=.0075) or historical (p< 0.001) groups Pair wise comparisons of type of implant used including no implant, there was a significant difference (p=.001); however, when the two implants alone were compared the difference was not significant (p=.43). There was a significant improvement in work status for the implant and tablet groups (p<.001), but not in the historical group
Willenbring ML 2004 Also framing question #5	Retrospective case series 12 months	Impact of concordance with evidence-based practice on patient outcomes among patients enrolled in opioid-agonist treatment at V.A. clinics	N=1,175	• While not statistically significant, the percent of patients receiving doses of at least 60 mg was negatively correlated with percent of opioid positive urine drug screens (r= -0.64, p=.06)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Randomized Cont	rolled Trials	·		
Barnett PG	RCT	Opioid-dependent	1) N= 32	Enrollment in long-term methadone at 6 months
2006		injection drug users		1) 91% (p<.001 vs. groups 3 & 4)
	6 months		2) N= 30	2) 90% (p<.001 vs. groups 3 & 4)
United States		1) Vouchers + case		3) 44%
		management	3) N= 32	4) 22%
				No significant differences between groups 3 & 4
		2) Vouchers for	4) N= 32	
		methadone treatment		• No significant differences among the groups in self-reported heroin use at 6
				months
		3) Case management		
				Total health care costs at 6 months
		4) Usual care		1) \$10, 411 (p<.05 vs. group 4)
				2) \$13,087 (p<.05 vs. group 4)
				3) \$7,400
				4) \$5,620
				No significant differences between groups 3 & 4
				No significant differences among the intervention groups
Bickel WK	RCT	Opioid-addicted	1) N= 45	Weeks of continuous cocaine and opioid abstinence
2008		outpatients enrolled in		1) 8.0
	23 weeks	Suboxone maintenance	2) N= 45	2) 7.8
United States		treatment		3) 4.7
			3) N= 45	Groups 1 & 2 significantly greater than group 3 (p<.05); no significant difference
		1) Community-		between groups 1 & 2
		reinforced treatment		
		(CRT) + vouchers		Treatment retention at 23 weeks
				1) 53%
		2) Computer-assisted		2) 62%
		therapy + vouchers		3) 58%
				p=.69
		Standard treatment		

Table 4E. Important Components of Treatment.

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Brooner RK	RCT	Newly admitted	1) N = 65	Overall counseling attendance in all types
2004		patients in an		1) 83%
	90 days	ambulatory methadone	2) N = 62	2) 44%
United States		treatment program		p<.001
		1) Motivated stepped		Rates of poor treatment response
		care		1) 46%
				2) 79%
		2) Standard stepped		p<.001
		care with methadone		
				Adjusted rates of any drug-positive urine screens
				1) 49%
				2) 54%
				p=.370
Brooner RK	RCT	Newly admitted	1) N = 59	Rates of any drug-negative urine screens at 9 months
2007		patients for methadone		1) 48%
	6 months w/ 3-month	maintenance	2) N = 59	2) 46%
United States	follow-up			3) 53%
		1) Motivated Stepped	3) N = 59	4) 33%
		Care (MSC)		p-value, NR
			4) N = 59	
		2) Contingent Voucher		 MSC+CVI was associated with the highest proportion of drug negative urine
		Incentives (CVI)		samples during both the study period (OR 3.04, 95% CI 1.75-5.30) and at 3 month
				follow-up (OR 2.16, 95% Cl 1.04-4.48)
		3) MSC + CVI		
				Mean proportion of counseling sessions attending at 6 months
		4) Standard care		1) 0.52
				2) 0.35
				3) 0.58
				4) 0.33
				p<.05
				• No significant difference among groups in treatment retention over 9 months, but
				patients enrolled in voucher arms were significantly more likely to complete the
				study (HR 1.74, 95% CI 1.16-2.61) compared to MSC alone and standard care

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Carpenter KM 2008 United States	RCT 24 weeks	Methadone maintained patients with a depressive disorder 1) Behavioral Therapy for Depression in Drug	1) N = 18 2) N = 20	Number of treatment sessions attended 1) 11.6 2) 15.3 p<.10
		2) Structured relaxation intervention (REL)		 Rate of change in Hamilton Depression Scale score from baseline was high and similar in both groups (B = .02; t₍₃₅₎ = .19; p<.86) <u>Proportion of weeks opiates used</u> 0.29 0.18 10.19 0.09 2.29 <u>Proportion of weeks benzodiazepines used</u> 0.17 0.15 -41
Chawarski MC 2008 Malaysia	RCT 24 weeks	Patients seeking treatment with buprenorphine for opioid dependence 1) Enhanced services with contingent take- home dosing and behavioral counseling 2) Standard services with pon-contingent	1) N = 12 2) N = 12	Overall opiate-negative urine screens 1) 87% 2) 69% p=.04 • Continuous opiate abstinence was not significantly different between groups 1 & 2 (10.3 vs. 7.8 weeks, respectively; p=.154) • Completion rate was high for both groups (100% vs. 92%, groups 1 & 2, respectively) p-value, NR
		2) Standard services with non-contingent take-home dosing		respectively) p-value, NR

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Chawarski MC	RCT	Heroin-dependent	1) N = 20	• Patients enrolled in the MMT + BDRC groups had a significantly greater decrease in
2011		patients enrolling in		opiate use compared to MMT only (p<.001) (data in figure only)
	3 months w/3-months	methadone	2) N = 17	
China	follow-up	maintenance treatment		 Participants in MMT+BDRC had significantly greater reductions in HIV risk
		(MMT)		behaviors during the study and at 3-month follow up compared to MMT only (p<.01)
		1) MMT with manual-		
				Treatment retention at 6 months
		behavioral drug and		1) 76%
		HIV risk reduction		2) 80%
		counseling (BDRC)		n= 8
		counseiing (bbite)		
		2) MMT only		
Chopra MP	RCT	Opioid-dependent	1) N = 42	Treatment retention at 12 weeks
2009		patients seeking		1) 58%
	12 weeks	treatment with	2) N = 41	2) 85%
United States		buprenorphine/Suboxo		3) 76%
		ne	3) N = 37	p=.009, group 1 vs. group 2
				 No significant differences between groups 1 or 2 vs. group 3
		1) Buprenorphine with		
		medication		Average percent of drug-free urines (opioid + cocaine)
		contingency + therapy		1) 79%
				2) 76%
		2) Voucher		3) 69%
		contingencies		p=.067
		3) Standard care		• After adjusting for baseline characteristics, medication contingency group had 1.5
				more continuous weeks of continuous opioid/cocaine abstinence (p=.029) and
				voucher group had 2 more total weeks than standard care (p=.048)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Czuchry M	RCT	Patients enrolled in	1) N = 22	Mean proportion of opiate use based on urinalysis
2009		methadone		1) 0.55 (p<.05 vs. group 3)
	Up to 12 months of	maintenance treatment	2) N = 33	2) 0.76
United States	treatment			3) 0.85
		1) Standard treatment	3) N = 27	
		w/free mapping		Mean proportion of opiate use based on self-report
				1) 0.45 (p<.05 vs. group 3)
		2) Standard treatment		2) 0.67
		w/ free plus guide		3) 0.81
		mapping		
		3) Standard treatment		
DeFulio A	RCT	Opioid-dependent	1) N = 19	Acceptance of naltrexone injections
2012		patients detoxified and		1) 87%
	6 months	receiving naltrexone	2) N = 19	2) 52%
United States				p=.002
	Therapeutic	1) Employment –based		
	workplace setting	reinforcement		Retention in the contingency group was significantly greater than in the
	(employment-based	contingency		prescription group (p=.008) (data in figure only)
	intervention for drug	management		 No significant differences across interventions in the percentages of samples
	addiction			negative for opiates (72% vs. 65%, p=.56) and for cocaine (58% vs. 54%, p=.75)
	and unemployment)	2) Prescription		• Opioid-positive urines associated w/cocaine-positive urine, independent of
		management		naltrexone blockade (p=.002)
		All patients eligible to		
		earn vouchers		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Dunn KE	RCT	Unemployed opiate-	1) N = 35	Completion of naltrexone treatment
2013		dependent and		1) 54%
	26 weeks	cocaine-using injection	2) N = 32	2) 16%
United States		drug users maintained		p<.01
	Therapeutic	on oral naltrexone		
	workplace setting			Naltrexone-positive urinalyses
	(employment-based	1) Employment –based		1) 72%
	intervention for drug	reinforcement		2) 21%
	addiction	contingency		p<.01
	and unemployment)	management		
				• No statistical differences between contingency and prescription groups in opiate-
		2) Prescription		negative urine screens (71% vs. 60%, respectively, p=.19) or cocaine-negative
		management		urinalyses (56% vs. 53%, p=.82)
Epstein DH	RCT	Cocaine- and opiate-	1) N = 47	Percentage of patients completing 12-week intervention
2003		using methadone		1) 81%
	12 weeks with 12-	maintained outpatients	2) N = 48	2) 79%
United States	month follow-up			3) 69%
		1) Contingency	3) N = 49	4) 76%
		Management (CM)		p=.45
			4) N = 49	
		2) Cognitive Behavior		Duration of cocaine abstinence at 12 weeks
		Therapy (CBT)		1) 11.3
				2) 3.7
		3) CM + CBT		3) 8.3
				4) 2.3
		4) Standard care		p<.0001
				Results not sustained at follow-up
				Solf reported coccine use at 12 weeks (uses /day)
				3 - (1 - 1)
				$Groups 1 \approx 3. Lonical nonininkeu regression - 0.55, SEIVI - 0.04$ $Groups 2.8.4: ISmean - 0.45, SEIM - 0.04$
				n = 0.17
				Pesults not sustained at follow-up
				- Results not sustained at 1010w-up

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Everly JJ	RCT	Unemployed opioid-	1) N = 18	Retention in naltrexone treatment
2011		dependent adults		1) 66%
	26 weeks	maintained on	2) N = 17	2) 35%
United States		naltrexone		p=.026
	Therapeutic			
	workplace setting	1) Employment –based		• No statistical differences between contingency and prescription groups in opiate-
	(employment-based	reinforcement		negative urine screens (74% vs. 62%, respectively, p=.41) or cocaine-negative
	intervention for drug	contingency		urinalyses (56% vs. 54%, p=.94)
	addiction	management		
	and unemployment)			
		2) Prescription		
		management		
	DOT			
Fals-Stewart W	RCI	Opioid-dependent male	1) N = 62	Mean counseling sessions attended
2003	24	patients living with a		1) 34
Linited States	24 Weeks with	family member	2) N = 62	2) 27
United States	maximum 1-year			p<.05
	tollow-up	1) Benavioral Family		Manual data of a discourse the second
		Counseling (BFC) +		<u>Mean days of haltrexone therapy</u>
		Individual treatment		1) 103
		2) Individual based		2) 79
		2) Individual-based		
		treatment (IBT)		• Detients in group 1 had significantly more enjoid free (79%) vs. (00%) n (01%) and
				• Patients in group 1 had significantly more opioid-free (78% vs. 69%, p<.05) and drug free (60% vs. 61% , p< 0%) uring screeps compared to group 2
				During treatment (72% vs. 65% ns. 65) and after the 1 year follow vs. (50% vs.
				• During treatment (72% vs. 05%, p <.05) and after the 1-year follow-up (59% vs.
				45%, p<.05), group 1 had significantly more days of abstinence from all drugs than
				group z

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Fiellin DA	RCT	Opioid-dependent	1) N = 70	• No significant difference between groups in self-reported opioid use (p=.96) (data
2013	24 wooks	patients in a primary	2) N - 71	not snown)
United States	24 weeks	Suboyone	2) N - 71	• No significant difference between groups in maximum consecutive weeks of opioid
United States		Suboxone		abstinence (p=.84) (data in figure only)
		1) Physician		
		management (PM)+		
		Cognitive Behavior		
		Therapy (CBT)		
		2) PM		
Fiellin DA	RCT	Opioid-dependent	1) N = 54	Percentage of opioid-negative urine screens
2006		patients in a primary	,	1) 40%
	24 weeks	care clinic receiving	2) N = 56	2) 40%
United States		Suboxone	,	3) 44%
			3) N = 56	p=.82
		1) Enhanced medical		
		management +		Percentage of cocaine-negative urine screens
		3x/week medication		1) 73.6%
		dosing		2) 71.1%
				3) 75.5%
		2) Standard care +		p=.79
		3x/week medication		
		dosing		Maximum duration of continuous opioid abstinence (weeks)
				1) 5.5
		3) Standard care +		2) 5.7
		1x/week medication		3) 6.7
		dosing		p=.54
				Mean percentage of days with Suboxone adherence
				1) 69%
				2) 73%
				3) 75%
				p=.87

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Grabowski J	2 parallel RCTs	Heroin- and cocaine-	Total N = 240	Study 1
2004		dependent patients		 Reduction in cocaine use was significant for the 30/60mg dose of d-
	26 weeks	enrolled in methadone	• 120 cocaine	amphetamine compared to the 15/30mg and placebo (p=.018)
United States		treatment	and heroin dependent	 Opioid use was reduced in all groups with a trend toward greater reduction in the 30/60 mg d-amphetamine group
		Study 1) D-	patients in	• Significant relationship b/w d-amphetamine dose and decreasing opioid use
		amphetamine vs.	each study	(p=.018)
		placebo	randomized	
			to different	Study 2
		Study 2) Risperidone	doses of each	• No significant reductions in cocaine use among groups (p>.9) or in opioid
		vs. placebo	drug	use (p>.9)
		Behavior therapy		 No adverse medication interactions noted for both studies
		1x/wk		• Retention was not significantly different between groups in study 1 (p=.107) or in
				study 2 (p=.12)
Groß A	RCT	Opioid-dependent	1) N = 20	Average treatment retention (weeks)
2006		patients maintained on		1) 11.3
	12 weeks	buprenorphine	2) N = 20	2) 10.4
United States				3) 11.8
		1) Voucher contingency	3) N = 20	p=.29
		2) Medication		Mean continuous abstinence from opioids and cocaine (weeks)
		contingency		1) 2.9
				2) 5.9 (p<.05 vs. group 1)
		3) Standard treatment		3) 4.0
				 No significant differences between standard care and groups 1&2

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Hayes SC	RCT	Polysubstance abusing	1) N = 42	Percent of patients with opiate-negative urinalyses at 6-month f/u
2004		methadone-maintained		1) 61% (p=.03 vs. group 3)
	16 weeks with 6-	addicts	2) N = 44	2) NR (in figure only, p=NS)
United States	month follow-up			3) 28%
		1) Methadone	3) N = 38	
Also framing	Patients were housed	maintenance (MM) +		Percent of patients with negative-total drug use assessments at 6 months
question #5	in community-based	acceptance and		1) 50% (p=.006 vs. group 3)
	clinic separation from	commitment therapy		2) 38% (p=.03 vs. group 3)
	methadone clinic	(ACT)		3) 12%
		2) MM + 12 step		Psychological distress improved across all conditions but no evidence of
		facilitation (ITSF)		differential improvement among groups
		2) NANA		• Comparisons between ACT or TISE is underpowered in this trial
Lialland D	DCT	3) IVIIVI Opiata dapandant	1) N=10	\sim Treatment retention was better for nations, receiving unsupervised thereas (80%)
	KCI	opiale-dependent	1) N=19	• Treatment recention was better for patients receiving unsupervised therapy (89%)
2012	6 months	methadone	2) N-21	vs. twice-weekly supervision (80%) and daily supervision (75%) but the differences were not significant ($n = 440$)
Scotland	0 11011113	(all natients received 3	2/11-21	• While all groups demonstrated decreased use compared to baseline in the use of
Scotland		months of initial daily	3) N=20	illicit drugs the difference was statistically significant for the daily supervised group
		supervised treatment)	5/11-20	only (n= 046)
		supervised treatmenty		• No significant differences in the groups between baseline and follow-up heroin use
		1) No supervision		
		w/daily medication		
		pick-up		
		2) 2 days of supervision		
		w/daily medication		
		pick-up		
		3) Continued daily		
		supervision		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Hser YI	RCT	Patients enrolled in	1) N = 159	• Better retention in treatment w/incentives found Kunming (81% vs. 67%, p < .05)
2011		methadone treatment		but not Shanghai (75% vs. 44%, p< .05)
	12 weeks		2) N = 160	 Negative urine samples (p<.0001) and longest duration of sustained abstinence
China		1) Usual care		was more common in incentive group
	Community-based	w/contingency		
	methadone	incentives		
	maintenance clinics in			
	Shanghai and	2) Usual care		
	Kunming			
Kidorf M	RCT	Patients w/current	1) N = 62	Mean overall mental health sessions (including individual, group and psychiatric
2013		psychiatric disorder		counseling) during month 3
	12 weeks	enrolled in methadone	2) N = 63	1) 5.7
United States		maintenance		2) 2.4
				p<.001
		1) Reinforced on-site		 ROIC patients attended significantly more sessions at months 1 &2 compared to
		integrated care (ROIC)		standard care (p<.001)
		with vouchers		
				 No differences in study retention between groups (p=.96)
		2) Standard on-site		• No significant differences between groups in opioid-positive (p=.88) or cocaine-
		integrated care(SOIC)		positive urine screens (p=.51)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
King VL	RCT	Highly stabilized	1) N = 32	• No significant differences in treatment retention at 12 months among groups
2006		methadone		(p=NS)
	12 months	maintenance patients	2) N = 33	 No significant differences in drug-positive urinalyses among groups (p=NS)
United States				
		1) Office-based	3) N = 27	Initiation of new vocational or social activities
Also framing		methadone treatment		1) 97%
question #5				2) 81%
		2) Clinic-based		3) 46%
		methadone treatment		p<.001
		3) Routine care		
		Methadone treatment		
		patients received more		
		take-home doses than		
		routine care		
		(28 days vs. 5-6 days)		
King VL	RCT	Partial responders to	1) N = 20	Overall treatment adherence (group & individual sessions)
2009		methadone		1) 89%
	6 weeks	maintenance (patients	2) N = 17	2) 74%
United States		testing positive for an		p=.07
		illicit substance)		
Also framing				 No significant differences between group 1 and group 2 in drug-positive urine
question #5		1) e-GetGoing internet-		screens (37% vs. 42%, respectively, p=NS)
		based		
		videoconferencing		
		2) Unsite group		
		counseling		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Ling W 2013	RCT	Opioid-dependent participants maintained	1) N = 53	• No significant differences among groups in mean opioid use during all phases of study including 52-week follow-up (p=.83)
United States	16 weeks w/up to 52 weeks of follow-up	on buprenorphine	2) N = 49	Analyses revealed no significant differences across groups for any secondary
		buprenorphine	3) N = 49	outcome (retention, withdrawal symptoms, craving, other drug use and adverse
		phase	4) N = 51	
		1) Cognitive behavioral therapy (CBT)		
		2) Contingency management (CM)		
		3) CBT and CM		
		4) No additional		
		behavioral treatment (NT)		
Lucas GM	RCT	Patients enrolling in	1) N=46	Average estimated participation in opioid agonist therapy
2010		Suboxone induction		1) 74%
	12 months	and maintenance	2) N=47	2) 41%
United States		1) LUV clinic based		p<.001
		1) HIV CIIIIC-Dased		Average percentage of opicid positive urine tests
		management		1) 44%
Also framing		munugement		2) 65%
question #5		2) Referral to an opioid treatment program		p=.015
				Average percentage of cocaine-positive urine tests
				1) 51%
				2) 66%
				p=.012

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Miotto K	RCT	Patients enrolled in	1) N = 28	Proportion of opioid-negative urine tests at 20 weeks
2012		buprenorphine		1) 0.22
	1 year	treatment	2) N = 33	2) 0.33
United States				3) 0.17
		1) Opioid-treatment	3) N = 33	p=.08
Also framing		program (OTP) offering		
question #5		individual counseling		Treatment retention at 20 weeks
				1) 21.4%
		2) Group counseling		2) 51.5%
		program utilizing the		3) 33.3%
		manualized Matrix		p=.05
		Model (MMM) of		
		cognitive-behavioral		Mean weeks of treatment retention
		treatment		1) 14
				2) 25
		3) Private clinic setting		3) 19
		mirroring standard		p=.11
		medical management		
		for buprenorphine		
		treatment provided		
		specifically at a		
		psychiatrist's private		
		practice (PCS)		
Neufeld KJ	RCT	Opioid-dependent	1) N = 51	Percentage of patients attending counseling
2008		patients with antisocial		1) 83%
	6 months	personality disorder	2) N = 49	2) 53%
United States		(APD) receiving		p<.0001
		methadone		
				Rates of study completion were not significantly different between groups
		1) Highly structured		
		contingency		
		management		
		intervention (n=51)		
		- (-)		
		2) Control (n=49)		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Newbern D	RCT	Patients enrolled in	1) N = 55	Average session attendance by patients with high levels of ADHD-related problems
2005		methadone treatment		1) 1.9
	12 months		2) N = 56	2) 2.4 (p<.05 vs. group 1, group 2)
United States		1) Free-map counseling		3) 1.9
		(f-map)	3) N = 55	
Also framing				Number of patients in treatment at 12 months
question #5		2) Free- and guide-map		1) 35 (p<.05 vs. group 3)
		counseling (f/g-map)		2) 31
				3) 24
		3) Standard counseling		
		Secondary factor:		
		evaluation of self-		
		reported levels of		
		ADHD-related		
		behaviors		
Nunes EV	RCT	Heroin-dependent	1) N = 36	• BNT improved retention compared to control over 6 months (log rank = 4.28,
2006		patients receiving oral		p=.04)
	6 months	naltrexone	2) N = 33	
United States				Weeks of completed treatment
		1) Behavioral		1) 11.9
		Naltrexone		2) 7.2
		Therapy (BNT)		p=.04
		w/vouchers		
				• No significant differences between groups in naltrexone adherence, or in number
		2) Standard treatment		of any drug-positive urinalyses
		[Compliance		• One death reported in group 2; one patient with suicidal ideation in group 2
		Enhancement		
		(CE)]		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Peirce JM	RCT	Patients w/continued	1) N = 198	Submission of stimulant- and alcohol-negative samples was twice as likely for
2006		stimulant abuse		incentive as for usual care group participants (odds ratio, 1.98; 95% confidence
	12 weeks	enrolled in methadone	2) N = 190	interval, 1.42-2.77)
United States		maintenance programs		
		for at least 1 month		Percent opioid-negative urine samples
		and no more than 3		1) 71.4%
		years		2) 62.4%
				• OR 1.49 (1.09-2.08)
		1) Usual care with low-		
		cost abstinence		Odds of continuous stimulant and alcohol abstinence (Group 1 vs. 2)
		incentives		• \geq 4 weeks: OR 3.1 (1.7-5.7)
				• ≥ 8 weeks: OR 9.3 (3.2-26.7)
		2) Usual care alone		• 12 weeks: OR 11.1 (11.4-86.5)
				 No significant differences between groups in study retention or counseling
				attendance
Pollack MH	RCT	Patients enrolled in	1) N = 12	• All analyses evaluated by effect size (Cohen's d)
2002		methadone		• No significant difference between groups in percentage of negative illicit substance
	6 months	maintenance treatment	2) N = 11	urine screens
United States				
		1) Novel cognitive		
		behavioral treatment		
		(CBT-IC) program		
		2) Enhanced treatment-		
		as-usual care		
		(increased counseling)		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Ruetsch C	RCT	Opioid-dependent	1) N = 987	Overall, no significant difference between groups in treatment compliance
2012		patients new to		
	12 months	buprenorphine	2) N = 439	 Patients receiving telephonic support (≥ 3 calls) were more compliant than the
United States		treatment		standard care group at month 12 (64.4% vs. 56.1%, p<.025)
		1) Standard care plus		• Number of calls significantly associated with treatment compliance at 12 months
		HTH patient support		(p<.001)
		program (telephonic		
		patient support		Attendance at 12-step/self-help therapy
		program known as		1) 34.2%
		HereToHelp)		2) 27%
				p<.05
		2) Standard care		
Schottenfeld RS	RCT	Patients with cocaine	1) N = 40	Patients receiving methadone stayed in treatment longer than those receiving
2005		and opioid dependence		buprenorphine (log rank=6.4, df=1, p<.05) with no significant differences between
	24 weeks	enrolling in opioid	2) N = 40	intervention groups
United States		agonist treatment		
			3) N = 39	Mean weeks of continuous abstinence from cocaine and opioids
		1) Methadone with		• Methadone vs. buprenorphine: 4.6 vs. 2.3, p<.05
		contingency	4) N = 43	 Contingency vs. maintenance: 3.6 vs. 3.3, p=NS
		management		
				Percentage of patients w/8 weeks of abstinence
		2) Methadone with		• Methadone vs. buprenorphine: 23% vs. 10%, p<.05
		performance feedback		• Contingency vs. maintenance: 20% vs. 12%, p=NS
		3) Buprenorphine with		
		contingency		
		management		
		4) Buprenorphine with		
		performance feedback		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Stotts AL	RCT	Opioid-dependent	1) N = 30	No significant differences between groups in percentage of patients completing
2012		patients attending a		treatment, reported opioid use during treatment and patients with successful
	6 months	methadone	2) N = 26	detoxification at 6 months
United States		maintenance clinic		
		1) Assessments and		
		1) Acceptance and		
		(ACT)		
		(ACT)		
		2) Drug Counseling (DC)		
Tetrault JM	RCT	HIV patients	1) N = 22	No significant differences between the two groups in percentage of opioid-
2012		maintained on		negative urines, maximum duration of continuous abstinence or retention at 12
	12 weeks	Suboxone	2) N = 25	weeks
United States				
		1) Physician		While percentage of subjects with detectable HIV viral loads decreased throughout
		management (PM) plus		the study, no significant differences were evident between interventions at
		enhanced medical		completion
		management (EMM)		
		2) PM alone		
Weiss RD	RCT	Treatment-seeking	1) N = 329	Patients with successful treatment outcomes in Phase 1: 6.6%
2011		outpatients dependent	,	• Patients with successful treatment outcomes in Phase 2: 49.2%
	36 weeks	on prescription opioids	2) N = 324	• Patients in Phase 2 were significantly more likely to attain success while
United States				maintained on buprenorphine-naloxone (week 12) than after 8 weeks follow-up
		1) Standard medical		(week 24), controlling for counseling condition (49.2% versus 8.6%, p<.001)
Also framing		management (SMM)		• Rate of opioid-positive urine tests in Phase 2 was significantly higher during the
question #1		+opioid dependence		combined taper and post-taper periods (weeks 13–24) than
		counseling (ODC)		while maintained on buprenorphine-naloxone during weeks 1–12 (58.1% vs. 39.1%,
				p<.001)
		2) SMM alone		No significant difference between groups in opioid use outcomes

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Comparative Stud	dies			
Gerra G 2011	Prospective comp cohort	Newly enrolled patients in methadone	1) N=100	Retention in treatment • Supervised daily (1): 58%
Italy	12 months	treatment	2) N=100	Contingent take-home (2): 74%Non-contingent take-home (3): 50%
Also framing		1) Supervised daily consumption	3) N=100	 p-value, NR Group 2 patients: 46% lower risk of dropping out compared to group 1 (p= 02): no
		2) Contingent take home incentives		significant difference between groups 1 & 3 (p=.561)
		3) Non-contingent take home		• Risk of positive urinalysis 5-times higher in group 3 compared to group 1 (p=.001); no difference between groups 1 & 2
				• Risk of criminal activity more than 3-times higher in group 3 vs. 1 (p=.007); no difference between groups 1 & 2
				 Risk of self-diversion more than 6-times higher in group 3 vs. 1 (p<.001); no difference between groups 1 & 2
Greenwald MK 2008	Retrospective comp cohort	Non-treatment-seeking heroin-dependent	1) N = 10	Median time to opioid relapse 1) 15 days
United States	Duration: NR	volunteers maintained on buprenorphine	2) N = 12	2) 1 day p<.001
Also framing question #5		1) Abstinence reinforcement		No significant difference between groups in time to cocaine relapse
		2) Control		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Moore BA 2012	Prospective comp cohort	Opioid-dependent patients receiving buprenorphine (BUP) in	1) N=28 2) N=27	• Adjusted analyses showed no significant differences between groups on retention or drug use based on self-report or urines
United States	12 weeks	a primary care setting	,	• Higher number of CBT sessions attended was significantly associated with maximum continuous weeks of opioid abstinence ($r=0.50$, $p = .007$), and higher
Also framing question #5		1) Physician Management (PM) with weekly BUP dispensing		number of opioid-negative urine screens (r=0.37, p=.05)
		2) PM and directly observed, thrice- weekly BUP and cognitive behavioral therapy		
Case Series				
Ball SA 2004	Secondary analysis of RCT (Carroll 2001)	Recently detoxified opioid-dependent outpatients receiving	N = 175	• No significant psychiatric subtype main effects found on treatment retention, medication compliance or abstinence at study completion
United States	12 weeks	naltrexone treatment 1) No incentive vouchers		• Patients with non-affective subtype in the no-incentive group had decreased probability of opiate use compared to those receiving vouchers (p<.02) (data in figure only)
		2) Incentive vouchers		• Patients of the antisocial-narcissistic subtype had greater reduction in probability of opiate use in the no-incentive voucher than in
		alone		the two (combined) incentive voucher conditions, p<.01) (data in figure only)
		3) Incentive vouchers + counseling		
Bickel WK	Prospective case	Impact of increasing	N = 152	• The only correlation for redemption type that approached significance among the
2010	series	amounts of money with negative urine screens		three demographic predictors was between age and income (r=.148, p=.074); the correlations between age and education and between income and education were
United States	12 weeks	in patients enrolled in buprenorphine treatment		not significant
				• Delayed discounting (larger-later reward versus changing immediate reward) was related to more frequent voucher redemptions for providing drug-free urine samples in a contingency management procedure

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Comiskey CM	Prospective case	Opiate users entering	N = 404	• At follow-up, 70% of patients in treatment (201/289)
2010	series	treatment for		• Significantly more patients who were drug-free at 3 years or in treatment started
Ireland	3 years	methadone		one-on-one counseling (23% and 38%) compared to patients not in treatment and still using (11%) (p< 001)
il claria	S years			• Number of previous treatment episodes at recruitment was a significant predictor
				of treatment outcome status at 3 years with those who were drug free at 3 years
				having almost twice as many previous treatment episodes (6.7) than those who were
				not drug free and using at 3 years (3.5) (p=.03)
Crist RC	Secondary analysis of	Evaluation of effects of	1) N = 77	No significant difference in average percentage of opioid-positive urine tests
2013	Saxon 2013	genetic variants in		between patients treated with methadone or buprenorphine
	(see framing question	OPRD1 on the	2) N = 566	African-Americans had significantly more opioid-positive urines than European-
United States	#2)	prevalence of opioid-		Americans treated with methadone (52% vs. 37%, p=.02) and buprenorphine (48%
		positive urine tests in		vs. 35%, p=.02)
		patients randomized to		• African-American patients with the CC genotype at rs678849 receiving
		methadone or		buprenorphine were more likely to have opioid-positive drug screens than
		buprenorphine		• African American methodono patients with the CC genetype, were
		1) African-Americans		ess likely to have opioid-positive urine drug screens than
		1) Annean-Annenicans		those in the combined CT and TT genotypes group (RR 0.52, 95%CI 0.44–0.60)
		2) European-Americans		
Dunn J	Retrospective case	Evaluation of	N = 630	• About 30% of patients missed at least one dose vs. 70% who were fully adherent
2009	series	adherence to		• Correlates of methadone non-adherence were supervised consumption (adjusted
		prescription treatment		OR 1.65, 95% CI 1.11-2.45), shorter duration of treatment episode (adjusted OR 0.99,
	28 days	by dose pick-up in		95% CI 0.98-0.99), and mean lower methadone dose (adjusted OR = 0.99, 95% CI
England		patients enrolled in		0.98-1.00)
		opioid substitution		
Also framing		treatment		
question #5				
Harris KA	Retrospective case	Patients enrolled in	N = 177	Overall treatment retention: 98%
2006	series	methadone		 Average duration of enrollment: 2.7 years No adjustment in dose since enrollment for 72% of notion to
United States	5 years	receiving monthly take		No aujustinent in dose since enrollment for 72% of patients One patient deaths recorded during treatment period
United States	Jyears	home medication		- 5 patient deaths recorded during treatment period

Also framing question #5				• Extremely low level of illicit substance use: 0.8% of the aggregate urine samples were positive for non-prescribed opiates, and 0.4% were positive for cocaine
Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Kidorf M 2004 United States	Retrospective case series 2 months	Integrating Motivated Stepped-Care (MSC) to Behavioral Reinforcement to	N = 228	 70% of patients with full-time employment; 19% of patients with part-time employment At follow-up, 7% of patients unemployed compared to 50% at admission Unemployed patients were 6.9 times more likely to be referred to intensified
Also framing question #5	All patients in a Addiction Treatment Services (ATS) program	promote employment to improve adherence to treatment in opioid- dependent patients		 Intervention for drug use in the past year than employed patients (x²=13.3, p<.01) Multiple indices of improved employment stability and functioning, including months of work (r=-0.23, p<.05), hours of work (r=-0.37, p<.05), and annualized salary (r=-0.28, p<.05), were associated with better drug use outcomes
Montoya ID 2005 United States	Secondary analysis of Montoya 2004 (see framing question #3)	Evaluation of the impact of psychotherapy attendance on treatment outcome in patients completing the scheduled 70-day maintenance buprenorphine treatment period	N = 90	 Higher psychotherapy attendance was associated with lower urine benzodiazepine levels, and this association grew more pronounced as the study progressed (p = 0.04) Inverse relationship between psychotherapy attendance and urine morphine levels was most pronounced for subjects receiving 16 mg every other day (p = 0.02)
Stitzer ML 2007 United States	Secondary analysis of Peirce 2006 (see framing question #4)	Evaluation of the association between baseline urine test result and treatment outcome in stabilized methadone maintenance patients with ongoing stimulant use	N = 386	 Patients testing negative at entry submitted 82% negative urines during the study vs. 36% for those testing positive at entry (OR=8.67; CI=5.81–12.94) Addition of abstinence incentives resulted in a significant increase in stimulant-negative urine samples submitted during the study both for those testing negative at study entry (OR= 2.27; CI=1.13– 4.75) and for those testing positive (OR=1.84; CI=1.25–2.71)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Strong DR	Secondary analysis of	Predictive validity of a	N = 48	• Lower persistence time remained a significant predictor of lapse risk (B= -0.005,
2012	an RCT	behavioral index of		SE= 0.002, p=.02)
	(Stein 2010)	persistence during a		 Lower persistence time on the PASAT was related to higher odds of a positive
United States		stress-challenge test		opiate toxicology over the 11-week assessment period (p=.04)
	3 months	called Paced Auditory		
		Serial Addition Task		 Persistence on the stress challenge task prior to initiating buprenorphine
		(PASAT) as a way to		treatment was associated with successful transition to early abstinence, and lower
		identify lapse risk in		rates of opiate use during the initial three months of buprenorphine treatment
		opioid-dependent		across antidepressant and placebo groups
		patients		

Table 5E. Delivery Models.

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest			
	Duration	Interventions	Patients				
Randomized Controlled Trials							
Bell J	RCT	Patients enrolled in	1) N=58	Treatment retention at 3 months			
2007		outpatient treatment		• Unobserved: 57%			
	3 months	for heroin addiction	2) N=61	Observed: 61%			
Australia		with Suboxone		p=.84			
		1) Unobserved dosing		Survival			
		at home (pick-up		• Unobserved: 70.1 days			
		1x/week)		• Observed: 68 days			
				p-value, NR			
		2) Usual care					
		w/observed dosing at		Self-reported heroin use, mean reduction in days			
		clinic (daily, every 2- or		• Unobserved: 18.5			
		3-day dosing,		Observed: 22.0			
		depending on stability)		p=.13			
				Patients w/negative urine tests in those reporting abstinence			
				• Unobserved: 62%			
				•Observed: 60%			
				p-value, NR			
				Overall cohort: no differences reported in use of non-opioid drugs at follow-up			
				Adverse events			
				• Unobserved: 5 events (chest painx2, urinary tract infection, liver biopsy, sexual			
				assault)			
				Observed: 1 event (cellulitis)			
				Diversion: reported for entire cohort only			
Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest			
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	Duration	Interventions	Patients				
Bell JR	F/u to Bell, 2007	Continued	1) N=45	Treatment retention at 6 months			
2008		maintenance		• Overall: 29%			
	3 months following	w/Suboxone	2) N=25	• Unobserved: 22%			
Australia	completion of original			Observed: 34%			
	study	1) Unobserved		p=.15			
		2) Observed		Median survival			
		-, -, -, -, -, -, -, -, -, -, -, -, -, -		• Unobserved: 95 days			
				• Observed: 107 days			
				p-value, NR			
				 Subjects in observed treatment twice as likely to drop out compared to 			
				unobserved (OR 2.14; 95% Cl 1.09-4.19)			
				• Subjects remaining in treatment at 6 months more likely to be abstinent (p<.001)			
				and using heroin on fewer days (p<.001)			
Gibson AE	RCT	Detox (buprenorphine)	1) N=56	Completion of detox program (8 days)			
2003		followed by		Primary care: 71%			
	91 days	maintenance therapy	2) N=59	Specialist clinic: 78%			
Australia		(multiple options)		p=.42			
		1) Primary care		Retention in treatment at 91 days			
		. ,		Primary care: 34%			
		2) Specialist clinic		Specialist clinic: 36%			
				p=.27			

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
King VL	RCT	Highly stabilized	1) N = 32	• No significant differences in treatment retention at 12 months among groups
2006		methadone		(p=NS)
	12 months	maintenance patients	2) N = 33	 No significant differences in drug-positive urinalyses among groups (p=NS)
United States				
		1) Office-based	3) N = 27	Initiation of new vocational or social activities
Also framing		methadone treatment		1) 97%
question #4				2) 81%
		2) Clinic-based		3) 46%
		methadone treatment		p<.001
		3) Routine care		
		Methadone treatment		
		patients received more		
		take-home doses than		
		routine care		
		(28 days vs. 5-6 days)		
King VL	RCT	Partial responders to	1) N = 20	Overall treatment adherence (group & individual sessions)
2009		methadone		1) 89%
	6 weeks	maintenance (patients	2) N = 17	2) 74%
United States		testing positive for an		p=.07
		illicit substance)		
Also framing				 No significant differences between group 1 and group 2 in drug-positive urine
question #4		1) e-Get-Going		screens (37% vs. 42%, respectively, p=NS)
		internet-based		
		videoconferencing		
		2) Onsite group		
		counseling		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
LiL	Cluster RCT	Patients enrolled in	1) N= 89	• No significant differences between groups at 9 months in heroin use during past
2013		methadone		month or positive urine results
	9 months	maintenance	2) N= 90	
China				
		1) MMT CARE		
		intervention (group &		
		individual sessions)		
		2) Standard care		
Lidz V	RCT	Patients enrolled in	1) N= 167	• No significant differences among groups in mean days worked at 12 months
2004		methadone		
United States	12 months	maintenance treatment	2) N= 68	 Increased rate of full-time employment noted for all 3 groups at 12 months but no statistical differences identified
		1) Vocational Problem	3) N= 66	
		Solving (VPS)		• Marijuana use declined at 12 months for patients in the VPS group while cocaine
				and heroin use decreased at 12 months for the VPS+JSW group (no statistical
		2) Job Seekers		analyses reported)
		Workshop (JSW)		
				Crime rates decreased among the 3 groups but without any clear demonstration of
		3) VPS + JSW		effect by intervention (no statistical analyses reported)
Lucas GM	RCT	Patients enrolling in	1) N=46	Average estimated participation in opioid agonist therapy
2010		Suboxone induction		1) 74%
	12 months	and maintenance	2) N=47	2) 41%
United States				p<.001
		1) HIV clinic-based		
Also framing		treatment with case		Average percentage of opioid-positive urine tests
question #4		management		1) 44%
		2) Defensel te en enicid		2) 65%
		2) Referral to an opioid		p=.015
		treatment program		Average percentage of eccening pacifiles write tests
				Average percentage of cocame-positive unifie tests
				2) 66%
				n= 012

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Magura S	RCT	Unemployed patients	1) N=78	• Significantly more CES participants had informal paid employment (27% vs. 14%,
2007		enrolled in methadone		p<.05) and any paid employment (41% vs. 26%, p<.05) compared to the control
	12 months	treatment	2) N=90	group
United States				
		1) Innovative		 Patients randomized to CES had significantly better odds of obtaining paid
		vocational		employment compared to standard counseling patients (OR 2.3, p=.03)
		rehabilitation model-		
		Customized		
		Employment Supports		
		(CES)		
		2) Standard vocational		
		counseling		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Miotto K	RCT	Patients enrolled in	1) N = 28	Proportion of opioid-negative urine tests at 20 weeks
2012		buprenorphine		1) 0.22
	1 year	treatment	2) N = 33	2) 0.33
United States				3) 0.17
		1) Opioid-treatment	3) N = 33	p=.08
Also framing		program (OTP) offering		
question #4		individual counseling		Treatment retention at 20 weeks
				1) 21.4%
		2) Group counseling		2) 51.5%
		program utilizing the		3) 33.3%
		manualized Matrix		p=.05
		Model (MMM) of		
		cognitive-behavioral		Mean weeks of treatment retention
		treatment		1) 14
				2) 25
		3) Private clinic setting		3) 19
		mirroring standard		p=.11
		medical management		
		for buprenorphine		
		treatment provided		
		specifically at a		
		psychiatrist's private		
		practice (PCS)		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Newbern D 2005	RCT 12 months	Patients enrolled in methadone treatment	1) N = 55 2) N = 56	Average session attendance by patients with high levels of ADHD-related problems 1) 1.9 2) 2.4 (p<.05 vs. group 1, group 2)
United States		1) Free-map counseling (f-map)	3) N = 55	3) 1.9
Also framing question #4		 2) Free- and guide-map counseling (f/g-map) 3) Standard counseling Secondary factor: evaluation of self-reported levels of ADHD-related babaviers 		Number of patients in treatment at 12 months 1) 35 (p<.05 vs. group 3) 2) 31 3) 24
Nyamathi AM	RCT	Patients w/moderate –	1) N= 90	 No significant differences among groups in patients reporting a 50% reduction in
2010		heavy alcohol use		alcohol use or in abstinence from alcohol at 6 months
United States	6 months	enrolled in methadone treatment 1) Motivational Interviewing – single patient session 2) Motivational Interviewing – group session	2) N= 79 3) N= 87	 Factors significantly associated with a 50% reduction in alcohol use included female gender (adjusted OR 1.95, p=.021), more education (adjusted OR 1.16, p=.045) and having at least one dose of the hepatitis B vaccine (adjusted OR 1.84, p=.013) Recent marijuana use was significantly associated with lower odds of reduced alcohol use (adjusted OR 0.34, p=.013)
		3) Nurse-led group education		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Ruetsch C 2012	RCT	Opioid-dependent patients new to	1) N = 987	Overall, no significant difference between groups in treatment compliance
	12 months	buprenorphine	2) N = 439	 Patients receiving telephonic support (≥ 3 calls) were more compliant than the
United States		treatment		standard care group at month 12 (64.4% vs. 56.1%, p<.025)
Also framing		1) Standard care plus		Number of calls significantly associated with treatment compliance at 12 months
question #4		HTH patient support		(p<.001)
		patient support		Attendance at 12-step/self-help therapy
		program known as		1) 34.2%
		HereToHelp)		2) 27%
				p<.05
		2) Standard care		
Schwartz RP	RCT	Heroin-dependent	1) N = 199	Patients enrolled in methadone maintenance at follow-up
2006	1 months	patients seeking	2) N = 120	1) / 6% 2) 21%
United States	4 11011113	maintenance treatment	2) N - 120	p<.001
		1) Interim treatment		Mean days of heroin use in 30 days prior to follow-up
		w/methadone and		1) 4.2
		emergency counseling		2) 26.4
				p<.001
		2) Waiting list		
				Mean days of cocaine use in 30 days prior to follow-up
				1) 2.4
				2) 5.8
				p<.001
				Mean illegal income in past 30 days prior to follow-up
				1) \$36
				2) \$412
				p<.02

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Silverman K	RCT	Newly admitted	1) N=26	Treatment retention at 52 weeks
2004		patients to methadone		• Take home: 62%
	52 weeks	treatment	2) N=26	• Take home + voucher: 73%
United States				• Usual care: 54%
		1) Take home doses,	3) N=26	p=NS
		contingent on negative		
		urine screens		 Rate of cocaine and opiate negative urines was greater for patients in the take
				home+voucher group compared to take home only and usual care (p≤0.05); for
		2) Take home doses		study completers, results sustained during 9-week post-intervention period (p≤0.05)
		with vouchers for		(data in figures only)
		negative urine screens		
				Longest duration of sustained abstinence from cocaine and opiates during 52-week
		3) Usual care, including		intervention (mean, weeks)
		daily methadone and		• Take home: 6.3
		counseling		• Take home + voucher: 18.8
				• Usual care: 2.3
				p<.001 (take-home + voucher compared to other groups)
Comparative Stud	lies			
Buhl L	Retrospective comp	Legislative change	• 1995	• Age was a significant predictor of change in the treatment institution (RR 0.915,
2004	cohort	moving problem drug	N=1020	p<.05) with older people less likely to transition
		users from private		
Denmark		clinics to county-based	• 1996	• Age (RR 1.035, p<.05) and previous hospitalization (RR 2.211, p<.05) as significant
		treatment centers	N=941	predictors of death
		4 cohorts of patients	• 1997	• No adverse effect on crime, hospital admissions or death attributed to legislative
		treated in methadone	N=893	change
		clinics, 1995 - 1998		
			• 1998	
			N=856	

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Gerra G	Prospective comp	Newly enrolled patients	1) N=100	Retention in treatment
2011	cohort	in methadone		Supervised daily (1): 58%
		treatment	2) N=100	Contingent take-home (2): 74%
Italy	12 months			• Non-contingent take-home (3): 50%
		1) Supervised daily	3) N=100	p-value, NR
Also framing		consumption		
question #4				• Group 2 patients: 46% lower risk of dropping out compared to group 1 (p=.02); no
		2) Contingent take home incentives		significant difference btwn groups 1 & 3 (p=.561)
				• Risk of positive urinalysis 5-times higher in group 3 compared to group 1 (p=.001);
		3) Non-contingent take home		no difference btwn groups 1 & 2
				• Risk of criminal activity more than 3-times higher in group 3 vs. 1 (p=.007); no
				difference btwn groups 1 & 2
				• Risk of self-diversion more than 6-times higher in group 3 vs. 1 (p<.001); no
				difference btwn groups 1 & 2
Gossop M	Prospective comp	Patients receiving	1) N=79	• While both groups experienced significantly decreased use of heroin, alcohol, non-
2003a	cohort	methadone		prescribed methadone and acquisitive crime over time, no significant differences
		maintenance treatment	2) N=161	between groups
England	2 years			
		1) General practitioners		• Patients treated by general practitioners had significantly less benzodiazepine
		2) Specialist drug clinics		course of the study compared to patients enrolled in drug clinics
		Differences in		
		dispensing: more daily		
		dosing and observed		
		consumption at clinics		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Greenwald MK	Retrospective comp	Non-treatment-seeking	1) N = 10	Median time to opioid relapse
2008	cohort	heroin-dependent		1) 15 days
		volunteers maintained	2) N = 12	2) 1 day
United States	Duration: NR	on buprenorphine		p<.001
Also framing		1) Abstinence		No significant difference between groups in time to cocaine relapse
question #4		reinforcement		
		2) Control		
Mintzer IL	Retrospective comp	Patients enrolled in	1) N= 45	Patients sober at 6 months
2007	cohort	Suboxone treatment		Hospital-based: 58%
			2) N= 54	Neighborhood center: 51%
United States	6 months	1) Hospital-based clinic		p-value, NR
		2) Neighborhood		• In an analysis adjusted for duration of treatment, having private insurance was
		health center		correlated with sobriety (p=.03)
				Adverse events included one death in a sober patient
Moore BA	Prospective comp	Opioid-dependent	1) N=28	Adjusted analyses showed no significant differences between groups on retention
2012	cohort	patients receiving		or drug use based on self-report or urines
		buprenorphine in	2) N=27	Higher number of CBT sessions attended was significantly associated with
United States	12 weeks	primary care setting		maximum continuous weeks of opioid abstinence (r=0.50, p = .007), and higher number of opioid-negative urine screens (r=0.37, p=.05)
Also framing		1) Physician		
question #4		Management (PM) with		
		weekly BUP dispensing		
		2) PM and directly		
		observed, thrice-		
		weekly BUP and		
		cognitive behavioral		
		therapy		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Sorensen JL	Prospective comp	Opioid users admitted	1) N=125	Mean number of days in treatment
2009	cohort	to a residential		• Methadone + TC: 166.5
		treatment program	2) N=106	• TC: 180.2
United States	24 months			p-value, NR; determined to be statistically equivalent
		1) Methadone +		
		therapeutic community		Proportion of patients testing positive for illicit opioid use, cocaine and
		(TC)		amphetamine use was statistically equivalent between groups (data in figures only)
		2) TC alone		Benzodiazepine use at 24 months
				Methadone + TC: 7%
				• TC: 0%
				p<.05
Case Series				
Alford DP	Retrospective case	Patients enrolled in	N = 382	Treatment retention at 12 months: 51%
2011	series	office-based opioid		
		treatment with		• At 3-, 6-, 9- and 12-month intervals, ≥93% of patients in treatment had negative
United States	12 months	buprenorphine in an		urine screens for illicit opioids and cocaine.
		urban academic		
		primary care practice		• Significant correlates of treatment success included age (OR 1.40, p<.01), being
				employed (OR 2.24, p<.01), and illicit use of buprenorphine (OR 3.04, p<.01)
				• Patients of African-American (OR 0.50, p<.05) or Hispanic (OR 0.45, p<.05) race had
				significantly lower odds of treatment success
Campbell Cl	NDATSS survey data	Evaluation of tailored	•1999/2000	Mean treatment duration
2009		women's programming	N=125	• 1999/2000: 22.0 months
		and organizational		• 2005: 24.1 months
United States		constructs in	• 2005	
		outpatient methadone	N=154	• Private for-profit (p<.01) and non-profit (p<.05) ownership significantly associated
		treatment, 2 cohorts		w/longer treatment duration compared to public ownership
				Hospitals associated w/longer treatment duration compared to freestanding
				facilities (p<.0001)
				Higher percentage of dual diagnosis patients associated w/shorter duration of
				treatment (p<.05)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Deck D	Medicaid database	Methadone	1) N=3557	<u>Oregon</u>
2005		maintenance treatment		Retention rates
	Analysis of patients	(MMT)	2) N=5308	1994: 24.8%; disabled/welfare pts: 22.9%
United States	retained for at least 1			1999: 49.8%; disabled/welfare pts: 55.2%
	year	1) Oregon:		
		Full coverage of MMT		Washington
		provided through		Retention rates
		prepaid health plans		1994: 27.9%; disabled/welfare pts: 27.4%
		w/waiver to cover all		1999: 32.8%; disabled/welfare pts: 35.5%
		patients falling below		
		federal poverty line		 Significant predictors of retention for both states included older patients and
				stable Medicaid eligibility
		2) Washington		
		State-administered		 Significant predictors of not being retained included being male, daily opiate use,
		services		cocaine as second drug, African American (in WA only), being arrested in previous 2
		w/reimbursement		years
		through fee-for-service		
Dunn J	Retrospective case	Evaluation of	N = 630	• About 30% of patients missed at least one dose vs. 70% who were fully adherent
2009	series	adherence to		• Correlates of methadone non-adherence were supervised consumption (adjusted
		prescription treatment		OR 1.65, 95% CI 1.11-2.45), shorter duration of treatment episode (adjusted OR 0.99,
England	28 days	by dose pick-up in		95% CI 0.98-0.99), and mean lower methadone dose (adjusted OR = 0.99, 95% CI
		patients enrolled in		0.98-1.00)
Also framing		opioid substitution		
question #4		treatment		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Haddad MS	Retrospective case	Patients enrolled in	N = 266	• Treatment retention at 6 months was 57%, and at 12 months: 62%
2013	series	buprenorphine		Patients remaining in treatment at 12 months had significantly more negative
		maintenance treatment		urine screens for opioids and cocaine compared to patients no longer receiving
United States	12 months	at a federally qualified		buprenorphine (66% vs. 21%, p<.01)
		health centers		• Correlates significantly associated with treatment retention at 12 months included
				receipt of psychiatric medications (p<.01) and on-site substance abuse counseling
				(p<.01)
Harric KA	Potrospostivo saso	Dationts oprolled in	N – 177	Baseline cocarrie use was negatively associated with treatment retention (p<.01)
2006	series	methadone	N = 177	• Overage duration of enrollment: 2.7 years
2000	301103	maintenance treatment		No adjustment in dose since enrollment for 72% of natients
United States	5 years	receiving monthly take-		• 9 national deaths recorded during treatment neriod
office states	5 years	home medication		• Extremely low level of illicit substance use: 0.8% of the aggregate urine samples
Also framing				were positive for non-prescribed opiates, and 0.4% were positive for cocaine
question #4				
Kidorf M	Retrospective case	Integrating Motivated	N = 228	• 70% of patients with full-time employment; 19% of patients with part-time
2004	series	Stepped-Care (MSC) to		employment
		Behavioral		 At follow-up, 7% of patients unemployed compared to 50% at admission
United States	2 months	Reinforcement to		 Unemployed patients were 6.9 times more likely to be referred to intensified
		promote employment		intervention for drug use in the past year than employed patients (X^2 =13.3, p<.01)
Also framing	All patients in a	to improve adherence		 Multiple indices of improved employment stability and functioning, including
question #4	Addiction Treatment	to treatment in opioid-		months of work (r=-0.23, p<.05), hours of work (r=-0.37, p<.05), and annualized
	Services (ATS)	dependent patients		salary (r=- 0.28 , p<. 05), were associated with better drug use outcomes
	program	Chrysets and lessel feature		
	Prospective case	Structural-level factors	N=560	• Provision of 22 comprehensive services (e.g., individual/group/family counseling,
2010	501105	recruitment treatment		(58%) vs $51%$ p= 0001)
China	Average time in clinic:	outcomes in natients		 Datients receiving > 2 comprehensive services were less likely to simultaneously
Cinità	13 5 months	enrolled in methadone		use illicit drugs (OR 0.42 nc 05)
		maintenance		

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Nyamathi AM 2011	Secondary analysis of Nyamathi (2010)	Patients w/moderate – heavy alcohol use	1) N= 90	 No significant differences among groups in reported average daily drug intake at 6 months
United States		enrolled in methadone treatment	2) N= 79	• Factors correlated with decreased daily drug use included no lifetime traded sex (mean square=7.23, p=.05) and no intravenous drug use at baseline (mean
			3) N= 87	square=9.71, p=.03)
		1) Motivational	-, -	
		, Interviewing – single		
		patient session		
		2) Motivational		
		Interviewing – group		
		session		
		3) Nurse-led group		
		education		
Trafton JA	Prospective comp	Patients enrolled in	N=255	• Patients enrolled in concordant clinics had significantly better heroin abstinence at
2007	cohort	opioid substitution		1 year compared to those at non-concordant clinics (OR 3.01, 95% CI 1.39, 6.51)
		treatment at V.A.	No data	Patients in concordant clinics also had significantly better cocaine abstinence that
United States	12 months	clinics	provided on	patients in non-concordant clinics (OR 1.85, 95% CI 1.41, 2.42)
			patient	Patients enrolled in concordant clinics had significantly better improvement in
		1) Clinics concordant	groups	rates of positive opiate urine screens compared to those at non-concordant clinics
		w/practice guidelines		(β _{curve} =0.003; se(β) =0.001, p<.02)
		2) Clinics non-		
		concordant		
		w/guidelines		
Willenbring ML	Retrospective case	Impact of concordance	N=1,175	While not statistically significant, frequency of counseling was negatively
2004	series	with evidence-based		correlated with non-opioid positive urine screens($r = -0.61$, $p = .08$)
		practice on patient		
Also framing	12 months	outcomes among		
question #3		patients enrolled in		
		opioid-agonist		
		treatment at V.A.		
		clinics		

Table 6E. Adolescent Studies.

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Randomized Cont	rolled Trials			
Woody GE	RCT	Patients aged 14-21	1) N=78	Number of positive urine tests at 12 weeks
2008		years entering		• Detox: 53
	Primary analysis: 12	outpatient treatment	2) N=74	• Maint: 49
Also framing	weeks	for opioid dependence		p-value, NR
question #1				
	Post-treatment f/u: 12	1) Detoxification		Retention in trial at 12 weeks
	months	w/Suboxone		• Detox: 21%
				• Maint: 70%
		2) Maintenance		P<.001
		treatment (Suboxone)		
				• Detox patients reported more opioid use (OR 4.30, p<.001), marijuana use (OR
		 All patients received 		6.15, p=.001), cocaine use (OR 16.39, p=.001), with cocaine use remaining significant
		counseling		up to 1 year (OR 3.84, p=.004)
				 Side effects: headache reported in both groups, 16-21%
				1 death (maintenance)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest		
	Duration	Interventions	Patients			
Comparative Stud	lies					
Bell J	Retrospective comp	Patients aged 14-17	1) N= 20	Mean days in treatment		
2006	cohort	years presenting for		• Methadone: 354		
		opioid dependence	2) N= 25	Buprenorphine: 58		
Australia	Variable	treatment		p<.01		
	(data collected on					
	patients entering	1) Methadone		Ireatment drop-outs		
	August 2000 April	2) Duproporphipo		Methadone: 53% Puproporphine: 76%		
	August, 2000 – April,	2) Buprenorphine				
	2003)			p=143		
				Treatment completion		
				• Methadone: 24%		
				Buprenorphine: 12%		
				p-value, NR		
				Patients still in treatment		
				Methadone: 24%		
				• Buprenorphine: 12%		
				p-value, NR		
				• Trastment retention significantly longer in patients receiving methodone		
				\sim meatinent retention significantly longer in patients receiving methadone compared to hyperporphine (pc 01)		
Case Series						
Smyth BP	Retrospective	Patients aged ≤18 years	N = 100	Mean treatment duration: 14.5 months		
2012	case series	receiving methadone		• Patients remaining in treatment at 12 months: 50%		
		and buprenorphine for		• Treatment drop-outs: 32%		
Ireland	12 months	dependence treatment		• Patients transferred to ongoing treatment (adult clinic): 39%		
Analyses related to Woody, 2008						
Chakrabarti A	Secondary analysis of	Evaluation of predictors	N = 69	• Baseline severity of pain and withdrawal significantly correlated w/dosing amounts		
2010	RCT (Woody, 2008)	of Suboxone dosing		of Suboxone (significance level not provided)		
Hill KP	Secondary analysis of	Association of cannabis	N = 152	• History of or current use of cannabis not associated w/opioid treatment outcomes		
2013	RCT (Woody,	use with treatment				
	2008)Woody, 2008	outcomes				

Author, Year	Study Design/ Duration	Comparators/ Interventions	Number of Patients	Outcomes of Interest
Meade CS 2010	Secondary analysis of RCT (Woody, 2008)	Assessment of HIV risk behavior	N = 150	• Patients receiving Suboxone had significantly decreased intravenous drug use throughout the study compared to patients undergoing detoxification (Wald χ^2 =6.83, p=.03)
Polsky D 2010	Secondary analysis of RCT (Woody, 2008)	Evaluation of cost- effectiveness of Suboxone maintenance vs. detoxification	N = 152	 One-year total direct medical cost of maintenance therapy compared to detoxification was \$83 higher (\$9,293 vs. \$9,210, p=.97) Outpatient treatment program cost/QALY of maintenance vs. detox: \$25,049
Subramaniam GA 2011	Secondary analysis of RCT (Woody, 2008)	Predictors of abstinence	N = 152	 Patients reporting previous intravenous drug use in past 30 days (OR 0.32, 95%CI 0.127-0.802) and those with more active medical/psychiatric problems (OR 0.766, 95%CI 0.599-0.980) were less likely to have opioid-positive urine screens at 12 weeks Patients with negative urine screens during weeks 1&2 (OR 0.241, 95%CI 0.089-0.656), and those receiving non-study treatment services (OR 0.114, 95%CI 0.031-0.426) were less likely to have opioid-positive urine screens at 12 weeks
Warden D 2012	Secondary analysis of RCT (Woody, 2008)	Predictors of attrition	N = 152	 Factors associated with a decreased likelihood of dropping out among maintenance patients included increased use of prescribed or over-the-counter medications in the month prior to treatment (OR 0.03, p=.002), lifetime non-heroin opioid abuse (OR 0.18, p=.013) and adherence to treatment medication (≥5 days/week in first 2 weeks) (OR 0.07, p=.04) Factors associated with dropout among maintenance patients included use of hallucinogens in the month prior to treatment (OR 28.87, p=.023) and having an opioid-positive urine during weeks 1&2 of treatment (OR 4.83, p=.019)
Wilcox CE 2012	Secondary analysis of Woody, 2008	Evaluation of compensation effects on study data collection	N = 152	 Higher compensation (Z-value=6.96, p<.01) and assignment to maintenance treatment (Z-value=6.62, p<.01) were associated with decreased likelihood of missing data during the study High compensation increased the likelihood of positive urine screens among detoxification patients more than maintenance patients (Z-value=-2.91, p<.01) The probability of negative urine samples increased with maintenance therapy assignment (Z value=6.25, p<.01) and higher componention (Z value=2.55, p<.01)

Author, Year	Study Design/	Comparators/	Number of	Outcomes of Interest
	Duration	Interventions	Patients	
Wilcox CE	Secondary analysis of	Evaluation of	N = 152	• Self-report drug use was generally concordant with urine drug screens; however
2013	Woody, 2008	concordance between		factors such as treatment assignment, compensation and concurrent drug use may
		self-report and urine		affect the validity
		drug screen data		