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

Final Report – July 2014

Authored by:

INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW

Table of Contents

Executive Summary

Abstract

On June 20, 2014 the New England CEPAC held a public meeting in Burlington, VT at which the Council discussed a systematic review of published evidence on options for the management of patients with opioid dependence. CEPAC held votes on the comparative clinical effectiveness and value of different management strategies, and then explored how best to apply the evidence to practice and policy with a distinguished Policy Expert Roundtable of patient advocates, clinical experts, and policy leaders from across New England.

In evaluating the evidence on different treatment options, CEPAC determined that long-term "maintenance" treatment approaches using methadone or Suboxone® to reduce the craving for opioids have been found to be more effective than short-term managed withdrawal methods that seek to discontinue all opioid use and "detoxify" patients. Short-term withdrawal management typically starts with maintenance treatment but attempts to wean patients off all opioids within 30 days, while maintenance treatment assumes that patients will remain on maintenance medication for longer periods. Studies comparing methadone and Suboxone found no major differences between them in reducing illicit drug use and preventing overdose or death. Although clinicians generally do not want to keep patients on medication indefinitely, there is little evidence or consensus on whether or how best to taper patients off maintenance therapy. Limited evidence suggests that patients who have not been addicted for long, do not inject heroin or other drugs, and who have a strong social support system may do well in "opioid withdrawal" programs that use injectable naltrexone, a drug that blocks the effects of opioids entirely.

CEPAC reviewed the results of economic modeling of different treatment options and voted that expanding access to maintenance therapy with either methadone or Suboxone represents "high value" because the added health care costs of treatment are offset by reductions in other health care costs that occur when individuals with opioid dependence begin treatment. Moreover, when broader societal costs such as criminal activity and work productivity are included, maintenance treatment is estimated to produce substantial overall savings. For every additional dollar spent on treatment, $1.80 in savings would be realized. These savings imply that moving just 10% of untreated individuals in New England into treatment would generate over $550 million in societal savings for the region.

Based on the evidence and expert input, CEPAC concluded that coordinated efforts are needed to improve access to opioid dependence treatment for the large number of individuals in New England who lack adequate access to high quality care options. An important component of achieving this goal will be to improve access for individuals in the criminal justice system by creating jail diversion programs in which non-violent offenders are assessed for addiction and referred to appropriate treatment in lieu of incarceration and by providing maintenance therapy to individuals who will be in prison for long periods. At the level of the healthcare delivery system, efforts to train and support more clinicians with capacity to treat addiction are needed. In addition, states should explore options to develop coordinated care networks to maximize existing capacity by allowing patients to receive short-term intensive outpatient care at specialized treatment units, following which they can be referred outward to other outpatient practices for lower levels of ongoing care in primary care settings or community-based practices.

Background

Opioid dependence has reached a critical level in the United States, driven by overprescribing and diversion of opioid painkillers, as well as the low cost and increased potency of heroin. The societal impact of this growing tide of opioid dependence is substantial in terms of costs related to treatment, lost work productivity, criminal activity, and social welfare expenditure (Hall, 2006).

Medication-assisted treatment options for opioid dependence

The goals of treatment for opioid dependence include a decrease in illicit opioid use, decreased mortality, and reductions in criminal activity (Thomas, 2014). Treatment options include methadone, buprenorphine (Subutex®), buprenorphine/naloxone (Suboxone®), and naltrexone (Revia®, Vivitrol®). Federal law restricts the dispensing of methadone, an opioid agonist medication that, when taken daily in sufficient doses, prevents withdrawal and blocks the effects of other opioids, to federal- and state-approved opioid treatment programs (OTPs). OTPs are licensed and accredited opioid agonist treatment programs that dispense methadone according to highly structured protocols as determined by the federal and state government, including the Department of Health and Human Services (HHS), the Drug Enforcement Agency (DEA), and various state agencies. A summary of federal and state requirements pertaining to patient admission, methadone dosing and abuse concerns, patient evaluation, and the provision of social supportive services is included in the full report.

Office-based prescriptions of opioid replacement therapy with buprenorphine alone or Suboxone is also restricted by federal and state regulations. Buprenorphine is a partial opioid agonist similar to methadone but with a "ceiling effect" that limits its efficacy at high doses but also is felt to limit its adverse effects. Buprenorphine is available as a combination product with naloxone (Suboxone), which is included as an abuse deterrent feature and may precipitate withdrawal in some opioid users if they use buprenorphine via injection. The passing of the federal Drug Addiction Treatment Act (DATA) of 2000 allows qualified physicians to obtain a waiver (also known as an "X" license) to prescribe and/or dispense opioid replacement therapy after receiving special training. Due to abuse and diversion concerns, physicians with a waiver may not treat more than 30 patients concurrently, but can apply for a second waiver after one year to treat up to 100 patients at one time.

Access to Treatment in New England

Current provider capacity in New England is not sufficient to meet patient need for opioid dependence treatment. For example, data from SAMHSA's National Survey on Drug Use and Health (NSDUH) from 2009-2012 indicates that 133,000 New Englanders are abusing or dependent on opioids, of whom 70% meet criteria for treatment but are not currently receiving it (SAMHSA, 2013c). The NSDUH survey indicates that approximately 2,000 individuals in New England were wait-listed for treatment in 2012; interviews with regional experts and policymakers suggest that this is a conservative estimate.

Geographic barriers to access are an important consideration across New England. Maps showing the wide gaps between the locations of available OTPs and office-based Suboxone programs for each New England state are shown in Appendix C of the report.

To help understand the status of treatment for opioid dependence in New England, ICER surveyed 32 federally certified OTPs, independent office-based Suboxone and buprenorphine prescribers, residential treatment providers, outpatient counseling programs, and centers specializing in the provision of opioid withdrawal management services.   When asked to rank the extent to which different factors served as a barrier to providing treatment, respondents listed insurance coverage, efficiency of referral pathways (e.g., emergency room, court system), and regulatory structure and restrictions for practice (e.g., physician education and patient management caps for buprenorphine, regulation of methadone clinics) as the most significant obstacles. Many respondents also noted that patients lack the ability -- for geographic, financial, or other reasons -- to gain rapid access to treatment with either methadone or buprenorphine/Suboxone. The treatment choice selected, therefore, is usually the option that the patient can best afford and access. Complete survey results are described in the full report.

Evidence Review

We conducted a review of published evidence on the comparative effectiveness and value of MAT for the treatment of opioid dependence, which was framed according to multiple questions of policy interest in New England. Where available, considerations regarding adolescents were highlighted, as this was felt to be a subpopulation of high interest to clinicians and policymakers. The evidence is summarized briefly below; details on review methods as well as specific systematic reviews and key studies identified can be found in the full report.

Maintenance versus Short-Term (<30 Days) Opioid Withdrawal Protocols

A 2009 Cochrane systematic review of clinical trials found consistently superior outcomes for maintenance treatment approaches compared to short-term (i.e., <30 days) opioid withdrawal protocols. Maintenance was associated with better treatment retention and lower rates of illicit drug use compared to patients undergoing opioid withdrawal management. Other studies not included in the Cochrane review have produced similar findings. However, while maintenance treatment appears to be effective for most opioid-dependent patients, there may be a meaningful subset of individuals who are good candidates for a trial of opioid withdrawal management. The characteristics of these patients are described in detail in the full report. Retention in therapy at approximately one year varies widely across studies, but on average approximately two-thirds of patients on maintenance therapy remain in treatment, although approximately 50% of patients have evidence of illicit drug use during that time.

Comparative Effectiveness of Methadone, Buprenorphine, and Naltrexone

Both a recent Cochrane review as well as additional studies of maintenance treatment options consistently found that there are no major differences in mortality or illicit drug use achieved with methadone versus Suboxone or buprenorphine in any form. However, methadone appears to be associated with greater retention in treatment compared to buprenorphine in either flexible or low, fixed doses. Importantly, we note that the RCTs comparing these two drugs controlled for treatment setting (i.e., patients in both arms received the same ancillary services) so that the effects seen appear to be drug- and not setting-related. However, this does not reflect reality in the U.S., where methadone is used in a tightly-controlled environment and Suboxone is typically received in an office-based setting with less structured oversight.

Naltrexone appears to be no better than placebo at retaining patients in treatment, although limited data suggest that long-acting forms (injectable or implantable) may have advantages over oral naltrexone in this regard. The performance of these three medications across key measures of effectiveness over 3-12 months of follow-up is summarized in Table ES1 below.

Table ES1. Summary measures of effectiveness of medications for opioid dependence treatment over 3-12 months of follow-up.

Outcome	Methadone	Buprenorphine/Suboxone	Naltrexone/Vivitrol
Mortality (%)	< 1% (range: 0-6%)	<1% (range: 0-2%)	No deaths reported
Use of Illicit opioids (mean # positive urine tests)	12 (range: 3-25)	12 (range: 3-25)	Not reported (% of patients not achieving abstinence: 40-60%)
Retention in treatment (%)	63% (range: 54-71%)	52% (range: 40-65%)	28% (range: 16-30%)

Dosing and Duration Protocols

Studies examining dosing and duration of maintenance treatment have found both methadone (~100 mg/day) and Suboxone (16-32 mg/day) have clear dose thresholds above which clinical outcomes no longer improve. In terms of dosing frequency, daily methadone appears to produce better outcomes than less frequent dosing, while the dosing frequency of buprenorphine appears to make little difference in outcomes. Data suggest that dose tapering regimens with either methadone or Suboxone have limited success, but that longer tapers are superior to shorter-duration tapers.

Important Components of Treatment

Available evidence suggests that several types of positive incentives (e.g., contingency vouchers and rewards), as well as negative incentives (e.g., mandatory medication tapers for missed appointments), appear to improve patient retention in treatment. Evidence on the effectiveness of active, goal-oriented therapy such as cognitive-behavioral and interpersonal therapy is mixed; however, interventions to improve counseling adherence and the use of visual aids for goal-setting and tracking may improve treatment compliance. Supervised medication consumption and more frequent dispensing do not appear to improve adherence to treatment, in part because these interventions tend to be reserved for individuals with existing non-adherence patterns.

Delivery Models

Alternative delivery mechanisms for counseling in opioid dependence management (e.g., telephonic coaching, group therapy by videoconference) appear to produce similar rates of treatment retention and illicit drug use relative to in-person counseling. Wait-list maintenance interventions and pilot, office-based methadone programs appear to produce outcomes comparable to clinic-based care. Provision of opioid dependence management in alternative settings (e.g., primary care, office-based clinics) with adjunct services appears to retain patients at comparable or better rates relative to standard treatment approaches.

Economic Outcomes of Different Opioid Dependence Treatment Strategies

We estimated the outcomes of different opioid dependence management options using two simulation models: a cohort model and a population-based budget impact model for New England.

Cohort Model

The cohort model assessed the comparative value of different approaches to treating opioid dependence among 1,000 hypothetical patients entering treatment. Model outcomes and costs were calculated over a two-year time horizon. Six strategies of interest were evaluated: maintenance treatment with either methadone or Suboxone; stabilization on Suboxone followed by a 4-week taper to either oral naltrexone or Vivitrol; and opioid withdrawal management using either oral naltrexone or Vivitrol alone.

The model took into consideration different types of costs. For each different opioid dependence treatment strategy we used the simulation model to estimate the following: 1) the costs to Medicaid of substance abuse drug therapy and related services using Medicaid payment benchmarks; 2) other health care expenditures; and 3) the "social costs" of dependency in law enforcement, victimization, and productivity loss, with estimates for each component of social cost taken from the peer-reviewed literature.

Model results for two-year costs among 1,000 hypothetical individuals entering different treatment strategies are shown in Table ES2 on the following page. Two-year costs of methadone drug therapy

(~$700) were much lower than the drug costs for all other strategies except oral naltrexone alone. But the costs of other substance abuse services for methadone maintenance (~$14,000) were 2-7 times higher than costs of maintenance with other strategies, reflecting the regulated intensity of methadone-based care. The sum of all two-year health care costs did not substantially differ across maintenance treatment strategies because even though methadone maintenance treatment costs are higher, this maintenance strategy keeps more patients in treatment, and treatment retention has been found to be associated with a 50% reduction in the costs of other health care services among patients with opioid dependence. Of note, the two-year health care costs for relapsed patients are estimated to be nearly $40,000, suggesting that the additional health care costs for substance abuse treatment, with _any_ form of treatment, will be entirely offset within the first two years by reductions in other health care costs.

When the impact of maintenance therapy on broader social costs was added to the calculations, maintenance therapy options produced significant overall cost savings. The two-year social costs associated with opioid dependence are estimated to be over $200,000. All versions of opioid dependence treatment therefore reduced social costs substantially compared to no treatment. Methadone maintenance therapy is projected to produce the lowest average total costs over a two-year period, a sum approximately $100,000 less, per patient, than would be expected without treatment.

Table ES2. Two-year costs among 1,000 hypothetical patients treated for opioid dependence.

Outcome/Cost	MMT	BMT	SUB/VIV Taper	SUB/Oral NTX Taper	Vivitrol Alone	Oral NTX Alone
Treatment outcome (per 1,000):						
In treatment	630	523	550	500	416	277
Relapsed	185	292	265	315	400	538
Drug –free	177	176	177	176	173	169
Died	8	9	8	9	12	16
Cost ($, per patient):						
Drug therapy	699	3,655	8,553	1,249	6,585	665
Other SA services	14,017	7,043	4,146	4,297	2,985	2,446
Other health care	23,926	25,993	25,454	26,441	28,109	30,844
SUBTOTAL	_38,642_	_36,691_	_38,153_	_31,988_	_37,679_	_33,954_
Social costs	92,068	102,337	98,033	105,917	119,239	141,076
TOTAL	_130,710_	_139,028_	_136,187_	_137,905_	_156,918_	_175,030_

MMT: methadone maintenance treatment; BMT: buprenorphine maintenance treatment; NTX: naltrexone; SUB: Suboxone; VIV: Vivitrol

## New England Clinical and Budget Impact Analysis

A budget impact analysis was also conducted over a two-year period. The analysis focused attention on the potential clinical outcomes (i.e., substance abuse-related deaths averted) and budgetary impact of moving different proportions of currently untreated individuals into maintenance treatment with Suboxone. Suboxone was assumed to be the modality of interest for expanded access to maintenance therapy given the regulatory hurdles required to expand access to methadone.

Currently, it is estimated that, of the 133,000 New Englanders with opioid dependence, 40,000 receive maintenance treatment. At baseline, approximately 2,800 opioid-related deaths would be expected to occur across New England in a two-year period, 450 of which would be among adolescents. Expanding treatment access by 10% would reduce the number of deaths by nearly 150 (30 of whom would be adolescents). A 50% expansion of patients brought into treatment would be expected to save nearly 700 lives in two years, including over 100 adolescents.

As noted earlier, even when considering health care costs alone, the additional costs associated with expanding access to maintenance treatment have been found to be fully offset by savings in the cost of other health care services. Moving 5% of untreated individuals in New England into treatment would increase treatment expenditures by $73 million, but result in reductions in the cost of other health care services by about $80 million. Greater levels of expansion would result in greater net cost savings. For example, a 10% expansion would increase treatment costs by $183 million, but reductions in the cost of other health care services of nearly $200 million would result in net cost savings of $15 million.

The effects of expanded access to maintenance treatment on total (health care plus social) costs are more dramatic, as presented in Figure ES1 on the following page. At baseline, total costs of opioid dependence in the region are estimated to be approximately $29 billion over two years, 81% of which is generated by dependent individuals not currently in treatment. At each level of treatment expansion, net savings are substantial, given that costs of health care services are already offset by treatment and reductions in social costs are pronounced. For example, expanding treatment by as little as 5% would decrease total costs by approximately $220 million. A 25% expansion would decrease overall costs by approximately $1.3 billion, and a 50% expansion would decrease overall costs by $2.6 billion. Put another way, each additional health care dollar spent on expanding maintenance treatment would return approximately $1.80 in savings. Importantly, all of these savings are realized even under the assumption that only slightly more than 50% of individuals newly-accessing Suboxone treatment would remain in treatment after two years.

Figure ES1. Total costs (health care plus social costs of opioid dependence) of persons with opioid dependence in New England, assuming different levels of increase in percentage of individuals brought into treatment. Total costs go down with each incremental increase in the percentage of patients in medication-assisted treatment programs.

Total Cost (Billions)

Increase in Percentage of All Individuals with Opioid Dependence in Treatment
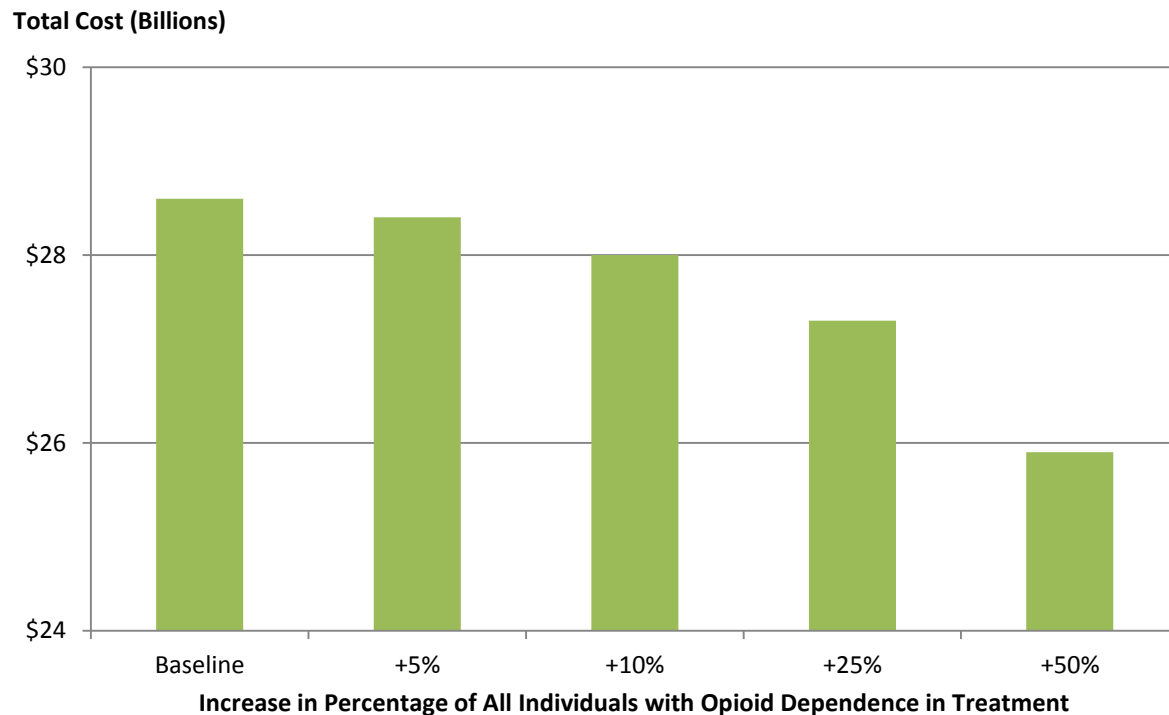
CEPAC Votes on Comparative Clinical Effectiveness and Value

During CEPAC public meetings, the Council deliberates and votes on key questions related to the review of the evidence produced by the Institute for Clinical and Economic Review (ICER). At the June 20, 2014 meeting, CEPAC discussed and placed votes assessing the comparative clinical effectiveness and value of various treatment approaches addressed in this evidence review. When voting on comparative value, CEPAC was asked to assume the perspective of a state Medicaid program that must make resource decisions within a relatively fixed budget for care. For each question on value, CEPAC placed two separate votes: one considering only the direct medical costs associated with each intervention, and one considering both the societal and medical costs associated with each intervention. The voting results are presented on the next page.

1. **Is the evidence adequate to demonstrate that long-term maintenance therapy with any medication is superior to short-term detoxification for most patients with opioid dependence?**

   12 yes (92%)   1 no (8%)

2. **From the perspective of a state Medicaid program, would you judge the value of long-term maintenance therapy with any medication compared to detoxification to be high, reasonable, or low?**

   Considering only direct medical costs:
   10 high (77%)   1 reasonable (8%)   1 low (8%)   1 abstain (8%)

   Considering medical costs and societal costs together:
   11 high (85%)   1 reasonable (8%)   1 low (8%)

3. **From the perspective of a state Medicaid program, would you judge the value of expanded access to maintenance therapy with any medication versus the status quo to be high, reasonable, or low?**

   Considering only direct medical costs:
   9 high (69%)   3 reasonable (23%)   1 low (8%)

   Considering medical and societal costs together:
   12 high (85%)   1 low (8%)

4. **Is the evidence adequate to demonstrate that maintenance therapy with methadone is at least functionally equivalent to maintenance with Suboxone in treating patients with opioid dependence?**

   12 yes (92%)   1 no (8%)

5. **From the perspective of a state Medicaid program, would you judge the value of methadone treatment compared to Suboxone treatment to be high, reasonable, or low?**

   Considering only direct medical costs:
   2 high (15%)   **8 reasonable (62%)**   2 low (15%)   1 abstain (8%)

   Considering medical and societal costs together:
   3 high (23%)   **8 reasonable (62%)**   1 low (8%)   1 abstain (8%)

6. **Among patients who can be successfully tapered from maintenance therapy with any medication (e.g., Suboxone, methadone) to opioid antagonist treatment, is the evidence adequate to demonstrate that Vivitrol is as good as or superior to oral naltrexone for patients with opioid dependence?**

1 yes (8%)   **12 no (92%)**

Recommendations to Guide Practice and Policy in New England

Before the CEPAC public meeting, ICER staff conducted unstructured interviews with 15 policy experts to explore real world perspectives on recent practice and delivery system innovations, potential policy changes, and other opportunities to improve how patients utilize and access treatment for opioid addiction in New England. There were interviewees from each New England state, with positions in OTPs, patient advocacy organizations, state agencies, clinical societies, academic institutions, and office-based addiction treatment centers.

The results from these interviews were used to frame a set of policy and practice recommendations that are presented in the body of the report and which informed a moderated Policy Roundtable discussion during the CEPAC meeting between Council members and a panel of regional policy experts. Roundtable panelists are shown below:

Rebecca Boss, MA	Rhode Island	Deputy Director, Department of Behavioral Healthcare, Developmental Disabilities and Hospitals (BHDDH), State of Rhode Island
John Brooklyn, MD	Vermont	Physician, Community Health Centers of Burlington
Barbara Cimaglio	Vermont	Deputy Commissioner, Alcohol and Drug Abuse Programs, State of Vermont
TJ Donovan, JD	Vermont	State Attorney for Chittenden County, State of Vermont
Kevin Flanigan, MD	Maine	Medical Director, MaineCare Services, State of Maine
John Hammel, MD	New Hampshire & Vermont	Director, Substance Abuse Services, White River Junction VA
Lisa Muré, MEd, CPS	New Hampshire	Director for Prevention, New Hampshire Center for Excellence Senior Consultant, Community Health Institute
Stacey Sigmon, PhD	Vermont	Associate Professor of Psychiatry, University of Vermont Director, The Chittenden Clinic
Jeff Simmons, MD	Massachusetts	Medical Director for Behavioral Health, Blue Cross Blue Shield of Massachusetts
Tom Simpatico, MD	Vermont	Chief Medical Officer, Vermont Department of Health Access
Jacquelyn Starer, MD, FACOG, FASAM	Massachusetts	Associate Attending Physician, Faulkner Hospital Associate Director, Physician Health Services, Inc. President, Massachusetts Chapter of ASAM
Joycelyn Woods, MA, CMA	National	Executive Director, National Alliance for Medication Assisted Recovery

Combining the insights gained from the earlier policy expert interviews with the votes on the evidence by CEPAC and the ensuing Policy Expert Roundtable discussion, the following set of recommendations are presented to guide the application of evidence to improve opioid dependence management practice and policy in New England. The rationale for these recommendations is presented in the body of the report beginning on page 81, where we also present further nuance on different practice and policy options along with benchmarking information on recognized best practice organizations and approaches.   The Policy Expert Roundtable discussion reflected multiple perspectives and opinions and therefore none of the recommendations below should be taken as a consensus view held by all participants.

1. **Coordinated efforts are needed across New England to improve access to opioid dependence treatment for the large number of individuals who lack adequate access to high quality care options. Mechanisms that should be considered to help accomplish this goal include:**

   - Change regulations that isolate methadone treatment from the rest of clinical care and consider allowing the extension of methadone treatment to office-based settings.
   - Provide more resources to develop the skills and expertise of DATA 2000 waivered physicians in order to increase their capacity and willingness to serve more patients with addiction.
   - In appropriate organizational settings, relax limits on the number of patients that can be treated by qualified clinical teams.
   - Broaden the scope of DATA 2000 to allow qualified nurse practitioners to prescribe buprenorphine-containing medications.
   - Develop stronger peer networks to help organizations and specialties treating patients with addiction manage care more effectively.
   - Revise highly restrictive entry criteria for some medication-assisted treatment programs that add another barrier to entry for patients.
   - Screen for opioid addiction in primary care settings in order to support early interventions for recovery.

2. **Develop innovative strategies that connect individuals in the criminal justice system to treatment for their addiction.**

   - Create jail diversion programs in which non-violent offenders are assessed for addiction and referred to appropriate treatment in lieu of incarceration.
   - Expand treatment to incarcerated individuals by providing Suboxone to individuals who will be in prison for more than a short period and making MAT available to individuals who are waiting for sentencing.
   - Avoid the indiscriminate use of naltrexone in individuals exiting the corrections system given that many individuals who are believed to be opiate-free are not, and some individuals that exit incarceration with Vivitrol are likely to never return to treatment and will be at higher risk for overdose.

3. **Clinicians should individualize treatment, including decisions about medication choice, counseling, and supportive social services, according to an initial assessment of a patient's baseline severity and unique health care needs. For most patients, medication-assisted maintenance therapy will be more effective than attempts at short-term managed withdrawal. However, short-term managed withdrawal may be a reasonable consideration for a subset of patients with relatively short-term histories of addiction and less intravenous opioid use.**

   - The results of a patient's initial assessment and evaluation should determine the medication selected for treatment.
   - Patients with higher opioid tolerance, longer histories of use, and unstable living situations are likely to benefit from a more structured program with methadone. Conversely, individuals with mild-to-moderate levels of dependence and greater life stability who require less treatment oversight are often considered for first-line treatment with buprenorphine-containing medications. Naltrexone may be an effective first-line treatment option for individuals with short histories of opioid use who access treatment early.
   - Specialty societies, states, and other stakeholders should work together to develop evidence-based screening tools, questionnaires, or algorithms to help identify the most appropriate initial treatment based on individual patients' unique factors.

4. **Develop systems to triage patients entering treatment to the level of care most appropriate for their individual needs in order to support patient-centered treatment and allow for more capacity in the system.**

   - Consider developing coordinated care networks in which patients receive short-term intensive outpatient care until stabilized, and then are referred outward to other outpatient practices for lower levels of ongoing care and MAT in primary care settings or community-based practices.

5. **Mandatory requirements for certain kinds of counseling can have unintended consequences and should be reconsidered to ensure they are not negatively affecting patient outcomes.**

   - State and health insurer medical policies that require that treatment plans provide counseling in order for patients to receive MAT should be reconsidered. Although social support and counseling are critical for many patients, there are not enough counselors to serve every patient with addiction, and therefore these policies can sometimes "bottleneck" treatment and serve as an additional barrier to care.
   - Many counselors are not specifically trained in addiction and individuals with dependence may be better served through peer-led recovery support that addresses techniques for relapse prevention from a patient's perspective.

6. **Provide treatment for opioid dependence through comprehensive, team-based care with collaboration across health care providers.**

   - All patients should have access to comprehensive health care services that can address the full range of co-occurring clinical, social, and environmental factors surrounding dependence. Housing support, wellness services, occupational rehabilitation, transportation, reproductive counseling, parenting support, and legal support are among the social services most important for patient success.
   - Treatment programs that are unable to provide the full spectrum of services that opioid-dependent patients require on-site should maintain a strong referral network with local mental health providers and other social agencies, as well as a robust case management system that tracks patients' progress and helps coordinate services for them as they access treatment.

7. **Clinical strategies for dosing and tapering of medication-assisted therapy should adopt an individualized approach that engages the patient in setting goals.**

   - Although clinicians generally do not want to keep patients on medication indefinitely, there is little consensus on whether or how best to taper patients off maintenance therapy. Standardized treatment cut-offs are generally regarded as counterproductive.
   - Some programs with success implementing a tapering strategy suggest adopting a gradual approach that slowly weans patients off medication over the course of several months. Patients should be engaged to determine their level of motivation to attempt a taper, and frequent re-assessments should be performed to decide if the taper should be halted or reversed.
   - Stakeholders in Maine, where treatment programs are required to attempt to wean patients on Suboxone to a lower dose within two years as a condition for reimbursement, have found that when tapering is framed as a sign of success it boosts patients' self-confidence and engagement in their treatment plan.

8. **Evidence-based insurance coverage policies for opioid dependence services should support efficient clinical practice and provide enough flexibility to help clinicians appropriately support the care needs of a diverse group of patients.**

   - Insurers should attempt to institute efficient prior authorization processes for Suboxone and Vivitrol to achieve intended policy goals while minimizing the burden to patients, clinicians, and pharmacists. "Fast-track" prior authorization processes for reliable prescribers should be considered.
   - Insurers and providers share the burden of balancing concerns for diversion with the desire to provide a dose high enough to ensure a patient does not experience withdrawal and drop out of treatment. No standardized approach for dosing (or

tapering) will work for all patients, and therefore the level at which patients receive medication must be individualized. Mechanisms to facilitate rapid consideration of requests for dosing beyond established dosing limits should be instituted.

- Exemptions for some patients from specific coverage criteria should be considered, such as exemptions from requirements for patients with long histories of successful maintenance therapy.
- Policies for compliance monitoring and random "call backs" to prevent abuse and diversion are reasonable but as with other policies there should be some mechanism for consideration of exempting some patients demonstrating long-term adherence to treatment.
- Increases to reimbursement rates for addiction treatment in order to bring them on par with payment for other clinical services should be considered to reduce the stigma that still affects addiction medicine specialists.

9. **Policymakers should develop long-term solutions to recruit, train, and retain qualified physicians to the field of addiction medicine in addition to fostering greater awareness and skills for recognizing opioid addiction among primary care clinicians.**
   - Require that physicians in training receive more exposure to addiction medicine in medical school and that treatment of substance abuse be incorporated as a standard part of residency training to help recruit more professionals to the field.
   - Implement greater efforts to train and support primary care physicians in recognizing addiction disorder, leveraging training and physician mentorship programs from ASAM and AAAP that assist primary care providers to incorporate screening, brief interventions, and referrals to substance abuse treatment centers as a standard part of care.

10. **Funders and the clinical research community should focus future study on key areas where further evidence is needed to appropriately manage patients with opioid dependence.**
   - Further research is needed to help clinicians identify those patients for whom abstinence may be an appropriate short, medium, or long-term goal, and how best to achieve and maintain abstinence in this population.
   - Future RCTs should test the comparative effectiveness of different dosing and tapering protocols. In particular, significant questions remain in the clinical community on how best to identify patients for potential tapers who have been on treatment for many years.
   - The existing literature shows promise for Vivitrol as a treatment option but more research is needed to establish its effectiveness and appropriate use compared to oral naltrexone.

1. Introduction

To make informed health care decisions, patients, clinicians, and policymakers must consider many different kinds of information. Rigorous evidence on the comparative clinical risks and benefits of alternative care options is always important; but along with this information, decision-makers must incorporate other considerations. Patients and clinicians must weigh patients' values and individual clinical needs. Payers and other policymakers must consider information about current patterns of utilization, and the impact of any new policy on access, equity, and the overall functioning of systems of care. All decision-makers, at one level or another, must also take into account the costs of care, and make judgments about how to gain the best value for every health care dollar.

The goal of the New England Comparative Effectiveness Public Advisory Council (CEPAC) is to provide a forum in which all these different strands of evidence, information, and public and private values are discussed together, in a public and transparent process. Funded by a consortium of state Medicaid agencies, private payers, and integrated provider groups, and backed by a diverse set of New England state policymakers, the mission of CEPAC is to provide objective, independent guidance on how information on comparative effectiveness can best be used across New England to improve the quality and value of health care services. CEPAC is an independent body composed of clinicians and patient or public members from each New England state with skills in the interpretation and application of medical evidence in health care delivery. Representatives of state public health programs and of regional private payers are included as ex-officio members of CEPAC. The latest information on CEPAC, including conflict of interest policies and guidelines for submitting comments, is available online: cepac.icer-review.org.

The Institute for Clinical and Economic Review (ICER) manages CEPAC and is responsible for developing evidence reviews for CEPAC consideration. ICER is a trusted non-profit organization that evaluates scientific evidence on the value of medical tests, treatments, and delivery system innovations and helps translate that evidence into action to improve patient care and control costs. By working collaboratively with patients, clinicians, manufacturers, insurers and other stakeholders, ICER develops tools to support patient decisions and medical policy that share the goals of empowering patients and improving the value of health care services. More information about ICER is available at www.icer-review.org. ICER has produced this evidence review and policy analysis in response to increasing stakeholder interest in strategies for managing opioid dependence, driven in large part by the growing opioid addiction epidemic in New England and across the country.

This report will support CEPAC's deliberation and attempts to answer some of the key issues confronting patients, providers, payers, and other policymakers. The goals of this review are to: 1) document the federal and New England state regulations affecting treatment options; 2) provide an

overview of existing clinical guidelines and payer coverage policies; and 3) summarize the evidence on the different management approaches for opioid dependence, including special considerations for adolescents. ICER's report for CEPAC also includes the results of a survey performed by ICER of treatment centers across New England in order to capture regional practice patterns, delivery system innovations, and policy opportunities to improve outcomes while controlling costs, as well as an overview of lessons learned from regional and national experts in the field of addiction medicine. ICER also developed a simulation model to explore the clinical and economic impact of various management strategies for patients with opioid dependence. The overall purpose of this report is to help enhance the use of evidence in practice and policy, and comments and suggestions to improve the work are welcome.

2. Background

Physical dependence on and/or addiction to prescription narcotics has reached a critical level in the U.S., due to the growing national epidemic of prescription drug abuse. Approximately 12 million Americans reported using prescription painkillers for nonmedical purposes in 2010, the most recent year for which data are available [National Institute on Drug Abuse (NIDA), 2014].   Heroin use is also on the rise. In 2012, the percentage of people using heroin in the past year had more than doubled since 2003 (Substance Abuse and Mental Health Services Administration, 2013). Fatal drug overdoses have more than tripled in the United States since 1999, with pharmaceutical overdoses – particularly from opioid pain medications such as oxycodone, hydrocodone, and methadone – driving the increase [Centers for Disease Control and Prevention (CDC), 2011]. In fact, death from drug overdose is now the leading cause of injury-related death in the United States, outpacing deaths from homicide, suicide, and traffic fatalities (CDC, 2013a). The problem of opioid addiction has recently received significant national and regional attention. Governors in New Hampshire, Massachusetts, Maine, and Vermont have all noted that combating growing opioid abuse is a major priority in their state, and they are searching for solutions for managing the growing affected population while addressing concerns regarding access and costs.

Several factors are cited for contributing to the escalating levels of opioid addiction in the U.S., including overprescribing and diversion of opioid painkillers, as well as the low cost, increased potency, and widespread availability of heroin. In 2010, enough prescription painkillers were prescribed in the U.S. to medicate every American adult continuously for one month (CDC, 2013b). Although most of these medications are prescribed for clinically indicated purposes, many are ultimately diverted to friends and family members without a prescription for non-medical use. Given the low cost of heroin relative to opioid painkillers, many individuals transition to using heroin once addicted to opioid medication (NIDA, 2014). The societal impact of opioid dependence is substantial in terms of costs related to treatment, lost work productivity, criminal activity, and social welfare expenditure (Hall, 2006). The total cost of illicit drug use and abuse in the U.S. was estimated to total nearly $200 billion in 2011 (U.S. Department of Justice National Drug Intelligence Center, 2011).

Even with rising levels of opioid abuse and dependence, treatment resources are limited in the U.S. and many individuals requiring treatment are unable to access care.   Medication-assisted treatment (MAT) for opioid dependence in clinic-based settings requires highly structured treatment protocols and special licensing by federal and state entities that isolate treatment from the rest of the health care system and serve as a barrier to entry for many patients and physicians (an explanation of federal and state regulations is provided in the next section). Meanwhile, federal and state regulations restrict the number of patients physicians can treat with opioid treatment medication in office-based settings. The highly restrictive treatment setting for patients with opioid dependence reinforces the stigma many people associate with treatment for substance abuse, and helps

perpetuate the misconception that opioid dependence is a willful choice and not a long-term chronic medical disorder.

Pharmacology

The goals of treatment for opioid dependence include decreased use or abstinence from illicit opioid use, reduced nonopioid drug use, decreased mortality, reductions in criminal activity, and lower incidence of overdose as well as communicable diseases common among injection drug users such as HIV and hepatitus (Thomas, 2014). Pharmacological treatment options include methadone, buprenorphine, buprenorphine/naloxone (Suboxone®), and naltrexone (Revia®, Vivitrol®). These agents are described below, including their place in therapy as well as a discussion of their associated benefits and risks. A summary table comparing the different medications can be found on page 23.

Methadone

Methadone has been used in the treatment of opioid dependency for almost 50 years (Tetrault, 2012). As a full opioid agonist, methadone binds to cells in the brain and fully activates receptors, helping to control cravings and block the effects of illicit drugs such as heroin (Nosyk, 2013). Available as a branded (e.g., Methadose®) or generic medication, methadone is provided as an oral liquid for the treatment of opioid dependency (FDA, 2014). In the U.S., patients must be enrolled for treatment at a federally-licensed clinic to receive methadone, and they must go to the clinic daily for their dose (see Section 3). Advantages of methadone include documented efficacy in easing patients' cravings and feelings of euphoria, as well as blocking the euphoric effect in patients still using illicit opioids. Potential risks and adverse effects of methadone include constipation, sweating, and heart arrhythmias (Nosyk, 2013). Methadone may be used for induction therapy (initial management of withdrawal symptoms to help wean patients from illicit opioid use), or for maintenance treatment. The risk of abuse and overdose are substantial challenges with methadone treatment (Nosyk, 2013), and its use carries significant stigma as being associated with continued drug abuse (Olsen, 2014).

Suboxone®/Zubsolv® (Buprenorphine/Naloxone)

Suboxone contains buprenorphine, a partial opioid agonist/antagonist, and naloxone, an opioid antagonist in a 4:1 ratio (Suboxone® package insert, 2011). Like methadone, buprenorphine activates opioid receptors. However, as a partial agonist, buprenorphine's activity is diminished compared to methadone. Specifically, there is a "ceiling effect" with buprenorphine that limits its efficacy at high doses, but also limits adverse effects (Tetrault, 2012). Inclusion of naloxone deters diversion and abuse, as oral naloxone has poor absorption into the body but will cause withdrawal symptoms when injected intravenously. Suboxone is available as a branded film, taken sublingually, and as a generic

or branded sublingual tablet (Zubsolv). Patients take a single dose each day, and may receive a prescription for up to 30 days of medication. Unlike methadone, burprenorphine/naloxone may be used by office-based physicians who have obtained a special prescribing license (see Section 3) as well as in licensed treatment centers. Benefits of burprenorphine/naloxone include easing of patients' cravings with a decreased risk of overdose and diversion, as well as blocking feelings of euphoria with other opioids if used illicitly. Potential side effects include headache, sweating, and potential liver complications (Volkow, 2014); in addition, concurrent use of benzodiazepines may lead to significant respiratory depression and overdose (Tetrault, 2012). Naloxone should also be avoided in pregnancy (Tetrault, 2012). Suboxone may be used for therapy induction or stabilization as well as maintenance treatment. As with methadone use, Suboxone is viewed by some as a capitulation to drug addiction and not as a treatment for a chronic disease (Olsen, 2014). Further, while many prescribers adhere to federal prescribing regulations and treatment recommendations, other clinicians utilize Suboxone prescribing as a sophisticated cash-generating business opportunity (Sontag, 2013).

Subutex® (Buprenorphine alone)

Buprenorphine may also be used alone in the treatment of opioid dependence. Without the presence of naloxone, there is an increased risk of diversion with buprenorphine, but it may be an appropriate choice for the treatment of pregnant women (who should not receive naloxone). It is available as a generic sublingual tablet and is dosed once daily. Buprenorphine may also be used as an agent for therapy induction or stabilization as well as for maintenance treatment.

Revia®/Vivitrol® (Naltrexone)

Naltrexone is a complete opioid antagonist, producing blockade at receptors in the brain and preventing the euphoria that is a consequence of taking drugs like heroin and oxycodone (Tetrault, 2012). Available as a branded (Revia) and generic oral tablet, naltrexone was also approved in 2010 as an intramuscular depot injection (Vivitrol). Oral tablets require once-daily dosing, while the depot injection is given in a clinician's office once a month. Advantages of naltrexone include the absence of addicting or sedating effects as well as little to no potential for abuse or diversion (Volkow, 2014). The primary disadvantage is that naltrexone has relatively little effect on opioid cravings, which may precipitate addiction relapse in many patients (Dijkstra, 2007). Patients must also be opioid-free for approximately seven days before starting therapy with naltrexone. Serious adverse events include precipitation of opioid withdrawal symptoms and liver injury (Vivitrol® package insert, 2010). Other side effects include headache, stomach pain, nausea and fatigue (Tetrault, 2012). Naltrexone is used as a maintenance agent in patients who have undergone opioid management withdrawal and are not receiving opioid replacement therapy with methadone or Suboxone. Challenges to the use of naltrexone include poor adherence associated with absence of any euphoric effects, risks of overdose

in patients concurrently using illicit opioids, and the need for patient abstinence prior to therapy initiation (Tetrault, 2012).

Emerging Treatment Options

Investigational treatment options for opioid dependency include a buprenorphine implant (Probuphine®, Titan Pharmaceuticals), a naltrexone implant, and a heroin vaccine. Designed to slowly release buprenorphine over a 6-month period, Probuphine did not receive approval from the FDA in May 2013 despite a favorable vote from its Advisory Committee, as the FDA required further research regarding Probuphine's ability to mirror relevant doses of sublingual buprenorphine (Carroll, 2013). Initial studies of naltrexone implants that release medication over a 3-6 month period have demonstrated favorable preliminary safety profiles, but rigorous comparative clinical trials are still needed to investigate treatment outcomes (Lobmaier, 2011). Finally, animal studies of an investigational heroin vaccine involving antibodies to heroin and its metabolites have provided preliminary evidence of activity against the rewarding and reinforcing properties of heroin (Schlosburg, 2013).

In addition, a new buprenorphine/naloxone film (Bunavail®) has recently been approved by the FDA. Bunavail is able to be absorbed by the body faster than the Suboxone film allowing it to be administered in doses of 2.1mg, 4.2mg, or 6.3mg instead of the recommended 16mg/daily for Suboxone (Anson, 2014).

Table 1. Summary characteristics of medications for the treatment of opioid dependency.

Characteristic	Methadone	Buprenorphine/naloxone	Naltrexone
Brand name	Methadose	Suboxone, Zubsolv	Revia, Vivitrol
Class	Full agonist	Partial agonist/antagonist	Full antagonist
Administration	Oral liquid	Sublingual film/tablet	Oral tablet/depot injection
Use and effects	Taken once daily to alleviate cravings and withdrawal symptoms	Taken once daily to alleviate cravings and withdrawal symptoms	Taken once daily or by monthly injection to decrease rewarding effects of opioids
Usual effective dose	20 -100 mg/day	8-24 mg/day (Suboxone) 5.7 – 11.4 mg/day (Zubsolv)	50-100 mg/day (Revia) 380 mg/month (Vivitrol)
Prescription source	Federally regulated drug treatment clinics	Federally regulated drug treatment clinics; licensed physicians' offices	Federally regulated drug treatment clinics; physicians' offices
How dispensed	On site at federally regulated drug treatment clinics; take-home doses permitted for patients with documented compliance and negative drug urine screens	Community pharmacies; on site at federally regulated drug treatment clinics	Physicians' offices; on site at federally regulated treatment clinics
Advantages	High strength and efficacy	High strength and efficacy; eligible for prescription doses up to 1 month; avoidance of specialty clinics; decreased abuse liability	Not addictive or sedating, and without physical dependence; avoidance of daily dosing
Disadvantages	High abuse and diversion potential; requires daily visits to approved treatment clinics	Some abuse potential; risk of precipitated withdrawal with injection	Poor patient adherence; treatment requires initial abstinence
Price for 30 days of treatment (based on average wholesale price estimates)	Generic liquid: $15	Generic tablet: $600* Suboxone: $500 Zubsolv: $500	Generic tablet: $200 Revia: $660 Vivitrol: $1,400

* According to Red Book Online®, the average wholesale price for generic buprenorphine/naltrexone does not appear to be less than the current pricing for Suboxone.

Source: Volkow ND et al. Medication-assisted therapies – tackling the opioid-overdose epidemic. *N Engl J Med*. 2014;370(22):2063-2066; Nosyk B et al. A call for evidence-based medical treatment of opioid dependence in the United States

and Canada. *Health Aff (Millwood)*. 2013;32(8):1462-1469; Micromedex Healthcare Series. RED BOOK® Online. Greenwood Village, CO: Truven Health Analytics, 2014. http://truvenhealth.com/. Accessed May, 2014.

3. Regulations Affecting Access to Care in New England

An overview of regulations and legislative initiatives affecting treatment for opioid dependence is presented in the sections that follow. Regulations related to the prescribing of opioid medications or overdose prevention, while related to opioid dependence, are not included here in detail since they are outside the scope for this review. It is important to recognize that legislative status is an ever-changing landscape; accordingly, this section should be considered a "snapshot" of status at the time of report publication.

3.1 Federal Regulations

Opioid Treatment Programs (OTPs)

Federal law restricts the dispensing of methadone to federal- and state-approved opioid maintenance programs. OTPs, or "methadone clinics", are licensed and accredited opioid agonist treatment programs that dispense methadone according to highly structured protocols as determined by the federal and state government, including the Department of Health and Human (HHS) and the DEA, and individual states (ASAM, 2004). The Substance Abuse and Mental Health Services Administration (SAMHSA) oversees the certification and accreditation of OTPs with assistance from the Center for Substance Abuse Treatment (CSAT), which is part of SAMHSA. Federal regulation passed in 2001 outlines the conditions required for authorization, including criteria for clinical environment, safety, quality control, and community involvement. Federal regulation also sets forth conditions for patient admission, program staffing, medication dosing, patient assessment, drug testing, and provision of social supportive services.

By regulation, patients receive methadone at OTPs under observation, though many patients may progress to less structured services and may eventually earn take-home medication privileges after documenting responsibility and stability to receive opioid medication unsupervised. The provision of psychosocial services is required at the main treatment facility or through formal referrals with other providers, the frequency, intensity, and scope of which vary according to each individual patient's needs. Most OTPs only administer methadone, though following the introduction of buprenorphine some programs have expanded their services to include buprenorphine-containing products. To be admitted for treatment, adults must have a documented one-year history of opioid

addiction and provide written consent (though certain exceptions apply). For adolescents the admission criteria are stricter, requiring at least two documented unsuccessful attempts with short-term opioid withdrawal or a drug-free treatment within a year before MAT can be provided. Table 1 in Appendix B summarizes other key components of federal regulation for OTPs.

Prescribing of buprenorphine-containing medications

The passing of the Drug Addiction Treatment Act (DATA) of 2000 allowed physicians to dispense or prescribe MAT for opioid dependence in treatment settings other than the traditional OTP environment for the first time. DATA 2000 allows qualified physicians to obtain a waiver (or "X" license) to prescribe and/or dispense Schedule III, IV, and V opioid medications or combinations of such medications that the FDA has specifically approved for the treatment of opioid dependency. Buprenorphine alone and Suboxone/Zubsolv (buprenorphine/naloxone) are currently the only approved treatments by the FDA within these classifications. In order to qualify for a waiver, physicians must hold a current state medical license and a valid DEA registration number, and have adequate training with respect to the treatment and management of opioid-addicted patients.   To meet this end, physicians must either be board certified in addiction medicine or other relevant specialty, have served as the principal investigator in a clinical trial for buprenorphine-containing medications for the treatment of opioid dependence, or have completed an eight hour training course on appropriate use of buprenorphine from an approved organization. Physicians with a waiver may not treat more than 30 patients with an addiction treatment concurrently, but after one year can apply for a second waiver to treat up to 100 patients at one time. Physicians must also attest that they have the capacity to refer patients to counseling and other appropriate non-pharmacological therapies as needed. The DEA maintains oversight of certified physicians and may perform random unannounced audits of physician records to ensure compliance with regulations.

Substance abuse services and the Affordable Care Act (ACA)

The signing of the ACA in 2010 established new requirements for health insurers to cover treatment for addiction and substance use disorders. The final bill includes services for mental health and substance use disorders as an Essential Health Benefit, meaning that "health insurance sold on the Health Insurance Exchanges or provided by Medicaid to certain newly eligible adults must include coverage for substance use disorders" (Office of National Drug Control Policy, 2014). The law also requires that Medicaid insurance plans and health plans on the marketplace exchange comply with standards for mental health parity and provide services for substance use disorders and mental health to the same extent as all other covered medical benefits.

3.2 New England State Regulations

Licensing requirements for substance use disorder treatment programs

Each New England state has strict criteria pertaining to the licensing and accreditation of facilities providing services for substance use disorders. Legislation in each state outlines procedures for renewal, inspections, and other approval processes, as well as conditions for safety, conflict management, patient protection, recordkeeping, and other program components. To operate in a state, OTPs and other substance abuse treatment centers must be certified and registered with all relevant state and federal authorities. The extensive set of criteria pertaining to substance abuse centers makes establishing new treatment facilities an arduous task. Some states, like Maine, require that licensing authorities first determine the need for an OTP at a particular location and hold a public forum before establishing a program in a given area.

Each New England state requires that substance abuse facilities have standardized policies and procedures in place for ongoing quality control. All facilities must have documented protocols for program evaluation; patient admission, discharge, and referral; treatment documentation and reporting; and medication administration. Patient admission protocols at OTPs or practices providing opioid withdrawal management services ("detoxification facilities") typically follow stricter criteria than other substance abuse facilities. For example, OTPs in each state must confirm with the state that a patient is not receiving treatment at any other OTP before providing care. In Maine, OTPs may not admit more than 500 patients without a special waiver. In Rhode Island, adolescents under 16 may not be admitted for treatment without written approval from the state methadone authority, and daily reports on patient admissions, discharges, and transfers must be provided to all relevant state authorities.

As with federal regulations, substance abuse facilities in each state require that adequately licensed and trained practitioners supervise program staff. Programs providing MAT, rehabilitation, or opioid withdrawal management services in each state are required to staff a multi-disciplinary care team typically composed of a medical director, registered nurse, psychiatrist or psychologist, pharmacist, counselors, and case managers. Some states have specific requirements for clinician caseloads. For example, in Maine, counselors working at detoxification facilities or OTPs are unable to treat more than 150 patients at one time, and Rhode Island requires at least one licensed nurse per 25 patients. Most states also have standards that practitioners at substance abuse facilities receive ongoing training in addiction disorders and overdose prevention.

State licensing authorities in New England typically require that patients receive a comprehensive assessment and evaluation that informs an individualized treatment plan.   Some states set standards for the frequency and interval at which practitioners must review and update treatment

plans to ensure that services continuously adapt to a patient's specific needs. Complementary social support, mental health, education, and case management services are typically required as part of the standard treatment program at all substance abuse facilities.

State treatment requirements for programs providing MAT or opioid withdrawal management generally follow federal regulations. Some states have more specific criteria for counseling and supportive care than do federal standards. For example, Maine sets minimum counseling requirements for different phases of care (e.g., 4 hours of individual counseling during first 45 days of treatment). In Rhode Island, individuals receiving care at OTPs must attend at least one hour of individual counseling monthly in the first year of treatment. The requirement is higher for patients receiving long-term opioid withdrawal management. In Vermont, regulations around MAT in OTPs also apply to physicians prescribing buprenorphine-containing medications in office-based settings. Patients receiving MAT in either setting must receive an initial psychosocial assessment or be reffered for evaluation.

Many states have also enacted stricter medication requirements, particularly around random drug testing and dosing for take-home use. Federal regulations allow eligible patients to receive up to a monthly dose of methadone for take-home use after two years of continuous treatment. Rhode Island, however, requires patients to achieve four years of ongoing treatment before a monthly take-home dose can be administered. The maximum take-home dose in Massachusetts is 13 days given every two weeks following 18 months of treatment. In Maine, eligible patients may receive a take-home dose of 6 days following one year of continuous services. Maine and Massachusetts also require more frequent drug testing for patients receiving care at OTPs. Compared to federal standards of eight random drug screens a year, Maine and Massachusetts require 12 and 15, respectively.

Table 2 in Appendix B provides a more detailed overview of the various licensing criteria in the region, including staffing, treatment, and program conditions required for substance abuse facilities to operate in each New England state.

Legislative Initiatives

Table 2 on the following page provides an overview of legislative activity at the time of writing in New England states related to opioid dependence.

Table 2. Summary of New England state regulation affecting treatment of opioid dependence

State	Overdose prevention	Safe prescribing of opioid painkillers	Mandatory insurance coverage for MAT	Treatment duration limits for MAT	Increased regulation for Suboxone® prescribers	Jail Diversion programs	Care delivery reform
CT	■					■	
ME	■	■		■			
MA	■	■			□	□	□
NH		□					
RI	■	■	■				□
VT	■	■			■	■	■

Key: □ = Introduced   ■ = Passed

Most legislation in New England regarding opioid dependence targets opioid prescribing and overdose prevention. States have made efforts in recent years to improve the quality of opioid prescribing for pain management in order to reduce the number of individuals addicted to opioids. States have also made efforts to reduce overdose by expanding access to naloxone, by broadening prescription and administration criteria, and providing legal immunity to persons who seek medical assistance for a drug overdose. In terms of regulation surrounding MAT and treatment for opioid dependence, some states have introduced policies regulating coverage for opioid treatment medication. For example, Maine enacted legislation in 2013 that placed treatment duration restrictions on insurance coverage for MAT. Medicaid patients receiving methadone or Suboxone for opioid dependence in Maine receive coverage for treatment for a maximum of two years, except when permitted for a longer treatment duration through prior authorization. In Rhode Island, legislators recently proposed a bill that would mandate insurance coverage for methadone, Suboxone, other forms of buprenorphine, and naltrexone. The Senate Health and Human Services committee considered the bill in April 2014 and recommended further study.

Access to MAT in criminal justice settings is rare in the U.S., but some states have made efforts to improve access to MAT and the level of care provided in prisons for individuals with opioid dependence. For example, Connecticut passed legislation establishing a jail diversion program that allows for individuals in the court system to be evaluated for addiction and appropriately referred to an addiction treatment program (Connecticut General Assembly, 2014). Massachusetts lawmakers have introduced legislation that would expand addiction treatment for nonviolent drug-dependent offenders by diverting these individuals from jail into treatment (The Commonwealth of Massachusetts, 2014). In Vermont, state legislators passed a bill requiring courts to provide pretrial screening to defendants who may benefit from substance abuse treatment. The bill also creates new programs to help divert individuals with nonviolent crimes away from traditional criminal

justice protocols to reduce the numbers of individuals with addiction in penal institutions, and establishes a pilot that allows individuals who were receiving MAT prior to incarceration to continue treatment while in prison (Vermont State Legislature, 2014).

Some New England states have also considered legislation on the regulation of buprenorphine and Suboxone prescribing. Massachusetts lawmakers recently introduced legislation that would expand the power of the Department of Public Health to oversee buprenorphine-containing medications, including the ability to establish further conditions for approval, licensure, staffing, reporting, treatment requirements, and termination of its use. Vermont recently passed legislation that would require physicians treating fewer than 30 patients with buprenorphine or Suboxone to ensure patients are assessed to determine their need for substance abuse counseling or other supportive care and are appropriately referred to services as needed. (Existing legislation in Vermont requires that physicians treating more than 30 patients in office-based settings meet federal counseling requirements for OTPs). The legislation would also allow Vermont's Medicaid agency to sanction Medicaid-participating providers who are found to have prescribed buprenorphine-containing medications in violation of state or federal requirements.

Other states have supported legislation that introduces new requirements for the delivery of opioid dependence treatment. Rhode Island recently introduced legislation that would require health care facilities providing treatment for addiction to schedule a follow-up appointment within seven days of discharge and make patient contact within 30 days of discharge to assess the patient's progress. Lawmakers in Vermont approved the implementation of a new model for care delivery called the "Hub and Spoke" program that creates an integrated care continuum for patients with opioid addiction. The Hub and Spoke model links OTPs and office-based opioid treatment programs together under one system of care and triages patients to appropriate levels of treatment based on each individual's needs (the Hub and Spoke model is described in more detail in Section 8).

Access to treatment

Current provider capacity in New England is not sufficient to meet patient need for treatment for opioid dependence. For example, data from SAMHSA's National Survey on Drug Use and Health (NSDUH) from 2009-2012 indicates that 133,000 New Englanders are abusing or dependent on opioids, of whom 70% meet criteria for treatment but are not currently receiving it (SAMHSA, 2013c). The percentage of individuals not receiving treatment includes those who think there is no problem and make no effort to seek treatment, those who acknowledge their addiction but refuse treatment, and those waiting for treatment. The NSDUH survey indicates that approximately 2,000 individuals in New England were wait-listed for treatment in 2012; interviews with regional experts and policymakers suggest that this is a conservative estimate.

The current availability of both facility-based and office-based opioid dependence treatment falls far short of clinical need. State-based information from SAMHSA's National Survey of Substance Abuse Treatment Services (N-SSATS) shows that, in 2012, approximately 46,000 individuals in New England received at least one day of treatment with methadone or buprenorphine-containing medications in an OTP (SAMHSA, 2013b).

While information on the use of Suboxone outside of licensed facilities in New England is not publicly available, some indication of capacity for managing patients in an office-based setting is available from SAMHSA. A total of 1,193 physicians in New England who can prescribe Suboxone have voluntarily reported their status on SAMHSA's treatment program locator (SAMHSA, 2014). Most of these physicians are limited to a cap of 30 patients, but using a national benchmark, it is estimated that approximately one-third of physicians licensed to prescribe Suboxone have obtained a waiver to move from a patient cap of 30 to 100 (SAMHSA, 2013a). If this figure is applied to New England, the maximum number of patients who could be treated with Suboxone given current provider capacity is approximately 60,000. This number falls far short of the estimated 133,000 individuals in New England who have opioid dependence. And while it is theoretically possible that all 133,000 individuals could be treated by increasing the number of physicians with a cap of 100 patients, this is not a realistic outcome given that many physicians are not able to manage the care of a high number of opioid dependence patients (Gordon, 2011; Walley, 2008).

Restrictions on the availability of MAT in the U.S. criminal justice system also pose a significant barrier to treatment for many individuals with opioid dependence. In 2004, 13% of all inmates in state prisons reported using heroin or opiates regularly (Mumola, 2006). Even though the criminal justice system is regarded as the largest source of referral for substance abuse treatment, only 10% of individuals that require MAT receive it as part of their justice system supervision (SAMHSA, 2013a).

Finally, geographic barriers to access are also an important consideration across New England. For example, Figure 1 on the following page provides a map of available OTPs (in red) and office-based Suboxone programs (in blue) in the state of Vermont. As can be seen in the figure, patients in certain locations (e.g., Bennington and Franklin counties) have few or no treatment options available to them, and must therefore travel great distances for either prescriptions or daily facility-based treatment. Similar maps are available for the other New England states in Appendix C.

Figure 1. Map of available substance abuse facilities and office-based Suboxone programs in Vermont
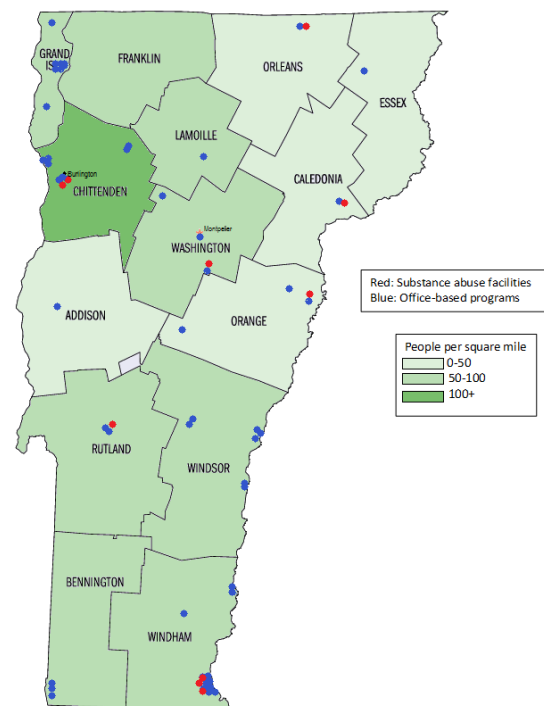
3.3 Policy Expert Survey on Status of Treatment in New England

To help understand the status of treatment for opioid dependence in New England, ICER developed a survey instrument to profile the types of services provided to opioid dependent patients at treatment locations in the region. The survey was distributed to each facility listed in the SAMHSA OTP directory in New England, as well as to regional physicians and treatment centers included on SAMHSA's treatment program locator. The survey was also sent to the leadership of each New England state chapter of the American Society of Addiction Medicine (ASAM) for broader distribution. Of the 388 treatment centers surveyed, a total of 32 unique respondents completed the instrument, of which 18 came from Massachusetts, 2 from Connecticut, 3 from Maine, 3 from New Hampshire, 4 from Rhode Island, and 2 from Vermont. Survey respondents represented federally certified OTPs, independent outpatient Suboxone and buprenorphine prescribers, detoxification centers, residential treatment providers, and outpatient counseling programs. The key survey findings are summarized in the following sections.

## Description of Responding Treatment Centers

Services Provided

Of the 32 unique treatment programs that responded to the survey nearly all provided some form of MAT. Treatment programs that did not offer MAT offered short-term opioid withdrawal management, long-term abstinence-oriented recovery support, outpatient counseling and supportive services, or residential sober-living. When offering maintenance therapy, treatment programs typically provided buprenorphine/naloxone tablets and/or Suboxone. Half of the treatment programs that responded to the survey offered methadone, and half offered naltrexone. Approximately 40% of treatment programs surveyed offered both methadone and buprenorphine or buprenorphine combination therapies.

Supportive Services

All treatment centers that responded offered some form of supportive services in addition to maintenance therapy, opioid withdrawal management , and long-term drug-free rehabilitation.   A summary of the supportive services typically provided is shown in Figure 2 below.

Figure 2. Survey results of supportive services provided at treatment centers in New England (n=32)
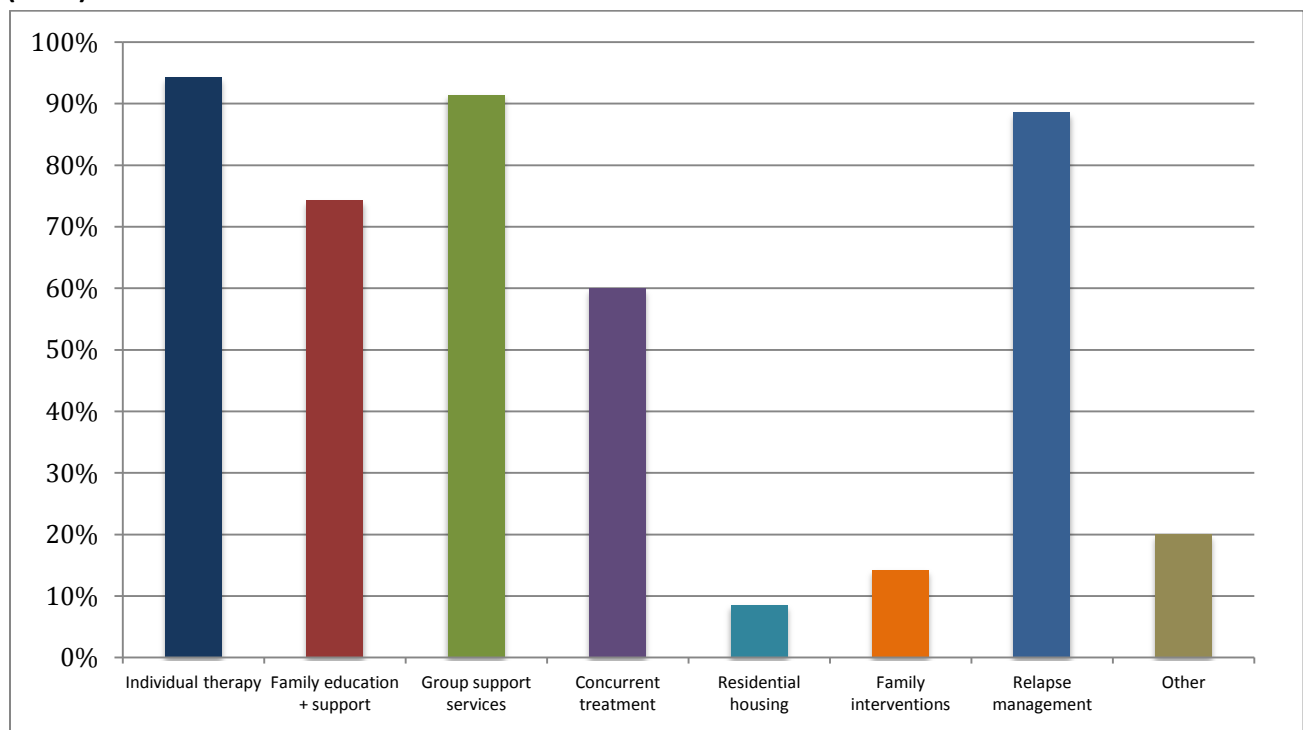
Medication requirements, protocols, and treatment choice

Of the respondents offering maintenance therapy, approximately 30% of treatment centers from across all six New England states had protocols in place that established limits on dosing and/or treatment duration.   Substance abuse programs commonly limited buprenorphine or Suboxone dosing to 16 mg a day. Other practices had higher dosing limits of 24 mg or 32 mg daily. Programs in Maine had protocols for tapering and transitioning patients off treatment by 24 months, in accordance with state regulations.

Only 29% of survey respondents offering MAT had written protocols in place to support physicians in determining which treatment agent to use for drug-assisted treatment. Some practices utilize a standard set of screening criteria to assess appropriateness of buprenorphine-containing medications, methadone, or naltrexone. When patients have documented prior success with a certain medication, efforts are typically made to continue patients with that treatment option. Some practices initiate patients with mild-to-moderate levels of dependency on buprenorphine or Suboxone, and reserve methadone for individuals with higher opioid tolerance who may benefit from a more highly structured treatment regimen. However, many practices cited access questions as driving medication selection. Many patients will lack the ability -- for geographic, financial, or other reasons -- to gain rapid access to treatment with either methadone or buprenorphine/Suboxone. The treatment choice selected is usually the option that the patient can best afford and access.

Barriers to providing high quality treatment to patients with opioid dependence

Respondents cited many challenges to providing high quality health care to patients with opioid dependence. When asked to rank the extent to which different factors served as a barrier to providing treatment, respondents listed insurance coverage, efficiency of referral pathways (e.g., emergency room, court system), and regulatory structure and restrictions for practice (e.g., physician education, patient management caps for buprenorphine-containing medications, regulation of methadone clinics) as the most significant obstacles. Prominent challenges to providing treatment are listed in rank order in Table 3 on the following page.

Table 3. Barriers to providing treatment for opioid dependence in New England

Obstacle/Treatment challenge	Significant or very significant barrier
Insurance coverage for opioid treatment	**57%**
Efficiency of referral pathways for treatment	**47%**
Regulatory structure and restrictions	**46%**
Community reaction to placement of treatment centers	**37%**
Communication/coordination across different health providers	**34%**
Recruiting/retaining qualified staff	**33%**
Staff or resource levels to address co-morbid conditions	**30%**
Availability of time and resources to assess treatment outcomes	**27%**
Patient/family attitudes regarding need for treatment	**23%**
Tailoring treatment program to client needs	**13%**

Other challenges referenced by respondents included the inability to secure safe and stable housing environments for patients, insufficient transportation services, and poor coordination of services between mental health and other health care providers. One respondent mentioned that some practices are unwilling to coordinate services and have dropped patients after learning they also receive care at an OTP. Others referenced the scarcity of mental health providers in the region with whom to coordinate care and establish systems for referral.

As shown in the table above, over half of treatment centers surveyed cited insurance coverage and reimbursement as a significant or very significant barrier to care.   In some states, programs mentioned that low Medicaid reimbursement rates, legislative actions to reduce funding for treatment centers, and lack of Medicare and private insurance coverage made it a challenge to remain open and continue to provide care. Others stated that underfunding of services made it difficult to maintain adequate staffing and recruit physicians to addiction medicine. Respondents also highlighted that the burdensome nature of existing prior authorization requirements for buprenorphine, Suboxone, and Vivitrol make it difficult to prescribe these therapies. The changing landscape of insurance coverage for substance abuse services due to federal regulations around mental health parity may ease some of these burdens over time.

4. Medicaid, Medicare, National and New England Private Insurance Coverage Policies

We examined publicly available policies for national payers, including Aetna, Anthem, Cigna, and UnitedHealthcare, and regional private and public payers.

Limited information is available regarding Medicare coverage of opioid dependency treatment. National Coverage Determinations describe longstanding policies regarding physician-provided, hospital outpatient, and freestanding clinic services for drug abuse treatment. Coverage is subject to general limitations applicable to these settings of care.

http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=29&ncdver=1&DocID=130.5&bc=gAAAAgAAAAAA%3d%3d&

http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=28&ncdver=1&DocID=130.6&bc=gAAAAgAAAAAA%3d%3d&

http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=59&ncdver=1&DocID=130.7&bc=gAAAAgAAAAAA%3d%3d&

4.1 Methadone

We found a single publicly available coverage policy for the use of methadone in opioid dependence treatment. Blue Cross Blue Shield of Massachusetts (BCBSMA) explicitly requires prior authorization for methadone treatment of opiate addiction. Survey results in a report prepared for ASAM revealed that all six New England state Medicaid agencies do provide coverage of methadone treatment (ASAM, 2013), although coverage policies are not available online. Among national private payers, Anthem provides clinical guidelines for the treatment of substance abuse but the policy does not describe individual medication treatment approaches.

4.2 Suboxone∕Zubsolv (buprenorphine/naloxone)

Medicaid

Use of Suboxone is generally limited in New England Medicaid programs through prior authorization and clinical criteria requirements as well as dosing and quantity limits (see Table 4 on page 39). Maine, Massachusetts and Vermont limit the allowable daily dose of Suboxone or the generic tablet to 16 mg, while Massachusetts places additional restrictions on higher doses based on duration of therapy. Use of non-preferred agents requires documentation of intolerance to preferred medication. Only Connecticut (Suboxone) does not require prior authorization. Use of Suboxone in Maine requires evidence of monthly monitoring (e.g., pill counts or urinalyses) and is restricted to a lifetime treatment limit of 24 months. Prior authorization for use beyond 24 months is contingent on patients' engagement in recovery services and documented attempt(s) at dose tapering. Vermont requires patients to designate a "pharmacy home" for all prescriptions, and the allowable maximum supply is 14 days for take-home doses. Prior authorization for Suboxone in New Hampshire evaluates whether patients have received a dependency assessment and if patients are enrolled in addiction counseling.

Zubsolv may be used in Connecticut, Maine and Massachusetts only with prior authorization.

Regional Private Payers

Among the major regional private payers, Blue Cross Blue Shield of Vermont (BCBSVT), ConnectiCare and Harvard Pilgrim Health Care (HPHC) place few restrictions on the use of Suboxone, Zubsolv and the generic tablet (see Table 5 on page 40). Conversely, BCBSMA, Blue Cross Blue Shield of Rhode Island (BCBSRI) and Tufts Health Plan require prior authorization for use of these medications with dose and quantity limits applied. Similar to Medicaid restrictions, BCBSMA limits the maximum daily dose of Suboxone and the generic tablet to 16 mg and to 11.4 mg for Zubsolv. Quantity limits based on medication strength vary widely for a 30-day prescription (generally 30 – 90 units for film strips or tablets). Criteria for approved use also include a treatment plan and enrollment in behavioral/psychosocial therapy.

National Private Payers

Aetna, Anthem/UniCare/Wellpoint, and UnitedHealthcare require prior authorization for the use of Suboxone, where documented enrollment in an outpatient treatment program may be necessary. Cigna and Aetna require step therapy for Zubsolv, where patients must initially fail therapy using Suboxone or the generic tablet. While Aetna allows for higher daily dosing limits (24 mg for Suboxone and 17.1 mg for Zubsolv), monthly quantity limits are similar across the national private

payers compared with regional groups. Anthem permits higher doses for initial therapy with lower limits for therapy beyond three months. Cigna places no dosing or quantity limits on the use of Suboxone.

4.3 Subutex (Buprenorphine alone)

Medicaid

Use of buprenorphine alone for opioid dependency treatment requires prior authorization among the New England Medicaid agencies (see Table 4 on page 39). Approved uses may include for patients who are pregnant or breastfeeding, or patients who have demonstrated intolerance to naloxone. Vermont allows a 14-day supply of up to 16 mg/day per prescription, with authorized use up to one year.

Regional Private Payers

BCBSMA, BCBSRI and Tufts require prior authorization for the use of buprenorphine, limiting its use to pregnant women, patients with a proven allergy to naloxone or as induction therapy only (see Table 5 on page 40). The maximum allowable dose is 16-24 mg/day while quantity limits range from 11 tablets/90 days (BCBSRI) to 120 tablets/90 days (Tufts).

National Private Payers

National private payers also limit the use of buprenorphine primarily to induction therapy (3-24 tablets/month). Aetna further restricts buprenorphine to patients concurrently enrolled in outpatient counseling, and UnitedHealthcare allows the use of buprenorphine if a patient is pregnant or breastfeeding while in maintenance treatment.

4.4 Revia/Vivitrol (naltrexone)

Medicaid

Among New England Medicaid policies, generic naltrexone tablets are the preferred therapeutic choice; use of branded tablets (Revia) requires prior authorization and demonstrated intolerance. Massachusetts and New Hampshire do not place restrictions on the use of Vivitrol; Vermont

requires prior authorization, with approved use limited to six months. Maine requires patients to have failed oral naltrexone, comply with psychosocial counseling, and submit a recent random urinalysis. Vermont limits the maximum monthly dose to one injection.

Regional Private Payers

HPHC and Tufts do not place restrictions on the use of naltrexone, Revia, and Vivitrol for opioid dependence. BCBSMA limits coverage to oral formulations, while ConnectiCare provides coverage of generic tablets and use of Vivitrol with prior authorization.

National Private Payers

Aetna, Cigna and UnitedHealthcare do not limit the use of naltrexone, Revia or Vivitrol for opioid dependence. Anthem/UniCare/Wellpoint restricts use of Vivitrol to patients unable to comply with daily oral dosing who are abstinent, currently enrolled in a rehabilitation program, and without liver disease.

Table 4. Coverage policies for medications used in opioid dependence treatment: state Medicaid agencies.

State	Brand: Suboxone (film), Zubsolv (tablet) Generic: buprenorphine/naloxone (tablet)	Buprenorphine (tablet)	Brand: Revia (tablet), Vivitrol (injection) Generic: Naltrexone (tablet)
Connecticut	+ (Suboxone only) • Use of any other agents requires PA	○	+ (generic oral only) • Use of any other agents requires PA
Maine	+ (Suboxone only, max dose = 16 mg) • Clinical criteria applied to Suboxone use • Lifetime limit of 24 months for use of Suboxone unless PA approved • Use of any other agents requires PA	+ (during pregnancy only)	+ (generic oral only) • Use of any other agents requires PA
Massachusetts	+ (generic tablet w/dose ≤16 mg per day) • PA required for generic tablet >32 mg/day, and doses between 16 and 32 mg depending on duration of therapy • PA required for Suboxone, Zubsolv	• PA required	+ (generic oral, Vivitrol) • PA required for Revia
New Hampshire	• PA required for Suboxone ○ (Zubsolv)	• PA required	○ (Revia and generic) + (Vivitrol)*
Rhode Island	• PA required	• PA required	• PA required
Vermont	+ (Suboxone, max dose = 16 mg/day) • PA required for generic tablet (max dose = 16 mg/day) • Clinical criteria applied to Suboxone use • Authorized use up to 1 year for Suboxone and buprenorphine/naloxone • Max days' supply for Suboxone and buprenorphine/naloxone = 14 days ○ (Zubsolv)	• PA required (max dose = 16 mg/day) • Authorized use up to 1 year for buprenorphine • Max days' supply for buprenorphine = 14 days	+ (generic oral only) • PA required for Revia • PA required for Vivitrol (max dose = 1 injection/30 days)

* Additional data regarding Medicaid coverage from American Society of Addiction Medicine (ASAM). Advancing access to addiction medicines (2013).

http://www.asam.org/docs/advocacy/Implications-for-Opioid-Addiction-Treatment. Accessed March, 2014.

+: coverage policy identified; ○: no coverage policy identified; PA: prior authorization

Table 5. Coverage policies for medications used in opioid dependence treatment: regional private payers.

Payer	Brand: Suboxone (film), Zubsolv (tablet) Generic: buprenorphine/naloxone (tablet)	Buprenorphine (tablet)	Brand: Revia (tablet), Vivitrol (injection) Generic: Naltrexone (tablet)
Blue Cross Blue Shield of Massachusetts	• PA required for all agents [max dose = 16 mg/day (11.4 mg for Zubsolv)] • Quantity limits = 30-90 units per prescription based on medication strength	• PA required (max dose = 16 mg/day)	+ (Revia and generic only) ○ (Vivitrol)
Blue Cross Blue Shield of Rhode Island	• PA required for Suboxone, buprenorphine/naloxone • Quantity limits = 30-90 units per 30 days based on medication strength ○ (Zubsolv)	• PA required • Quantity limit = 11-12 tablets/90 days	○
Blue Cross Blue Shield of Vermont	+ • Quantity limit = 90 units per prescription	+	+ (generic only) ○ (Vivitrol)
ConnectiCare	+ • Quantity limit for Suboxone = 90 film strips/month	+	+ (generic only) • PA required for Vivitrol
Harvard Pilgrim Health Care	+	+	+
Tufts Health Plan	• PA required for Suboxone, Zubsolv, buprenorphine/naloxone with 12-month limit on coverage	• PA required (max dose = 24 mg/day) with 12-month limit on coverage • Quantity limits = 90-120 units per 30 days based on medication strength	+

+: coverage policy identified; ○: no coverage policy identified

PA: prior authorization

5. Clinical Guidelines and Policy Statements

5.1 Methadone

American Society of Addiction Medicine (2010)
http://www.asam.org/docs/publicy-policy-statements/1obot-treatment-7-04.pdf?sfvrsn=0

ASAM considers methadone to be a significantly underutilized treatment and recommends expansion of its use to office-based settings. While OTPs provide some of the necessary structure and intensity needed for many patients who are new to treatment, ancillary services such as counseling that clinics typically provide can be offered in other treatment settings. Expanding methadone to office-based settings would give physicians the flexibility to "graduate" patients to less structured environments without having to change the type of medication that is best suited to their needs.

American Association for the Treatment of Opioid Dependence (2011)
http://www.aatod.org/policies/policy-statements/793-2/

AATOD recommends an outcomes-based approach for legislators and physicians to improve access to methadone-assisted treatment for opioid dependence. AATOD suggests that there has historically been a widespread problem of suboptimal methadone dosing in OTPs that leads to continued substance abuse. Efforts are needed to further educate state officials and raise awareness of the value of methadone in the treatment of opioid dependency, particularly for those in the criminal justice system.

Academy of Managed Care Pharmacy (2010)
http://www.amcp.org/data/jmcp/S14-S21.pdf

AMCP recommends methadone for maintenance treatment, followed by a gradual taper, for patients who have had a history of dependence of at least one year. AMCP also warns against the use of co-administering enzyme-inducing medications such as carbamazepine and St. John's Wort because they could precipitate withdrawal symptoms in methadone-maintained patients.

American Psychiatric Association (2010)
http://psychiatryonline.org/pdfaccess.ashx?ResourceID=243188&PDFSource=6

The APA clinical guidelines suggest that methadone is safe and effective for use in MAT for opioid dependence and higher doses of methadone are generally associated with better retention in treatment and lower rates of illicit opioid use. Methadone-related side effects are limited, and many patients that do exhibit such symptoms develop a tolerance to them over time. The APA

recommends methadone-based maintenance treatment for patients with opioid dependence of ≥1 year.

National Institute on Drug Abuse (2012)
http://www.drugabuse.gov/sites/default/files/podat_1.pdf

NIDA states that methadone maintenance treatment increases patient participation in behavioral therapy and decreases drug use and criminal behavior, which are essential to recovery. NIDA guidelines suggest that patients receive methadone maintenance treatment for one year at a minimum, though treatment duration can potentially be indefinite for patients who require continued maintenance.

Substance Abuse and Mental Health Services Administration
http://buprenorphine.samhsa.gov/Bup_Guidelines.pdf (2004)
http://adaiclearinghouse.org/downloads/TIP-43-Medication-Assisted-Treatment-for-Opioid-Addiction-in-Opioid-Treatment-Programs-51.pdf (2006)

SAMHSA's clinical guidelines state that methadone has the greatest potential for abuse of all the drugs used in MAT, and clinicians should therefore correlate dosing with the patient's level of physical dependence on opioids. SAMHSA notes that patients desiring to be abstinent from all opioids, including MAT, have had a higher rate of success (fewer opioid-positive urines) with a longer taper (30 weeks, decreased at 3%/week) than a shorter taper (10 weeks, decreased at 10%/week). The guidelines also state that physicians should avoid involuntary tapering, if possible. SAMHSA states that patients receiving methadone may be good candidates for buprenorphine-containing medications if they can be maintained on a dose of 30mg/day. However, the guidelines recognize that achieving this transition is difficult given that opioid withdrawal symptoms typically emerge at or below 30mg/day.

5.2 Buprenorphine or buprenorphine/naloxone (Suboxone)

American Society of Addiction Medicine (2011)
http://www.addictioninstituteny.org/html/Buprenorphine%20in%20Opioid%20Addiction.pdf

Buprenorphine efficacy is comparable to methadone, and patients can safely transfer from methadone treatment by gradually reducing their dose to 30-40mg before initiating buprenorphine/naloxone induction. ASAM acknowledges that while maintenance with buprenorphine/naloxone has been shown to improve outcomes for patients under 18, further research is needed to determine its long-term efficacy for this population. ASAM states that though buprenorphine is not recommended for patients with liver function abnormalities, it appears to be subject to fewer drug/drug interactions than methadone.

Academy of Managed Care Pharmacy (2010)

http://www.amcp.org/data/jmcp/S14-S21.pdf

AMCP considers office-based treatment programs a breakthrough model for the management of opioid dependence since buprenorphine and buprenorphine/naloxone have lower risks of overdose and are well tolerated in less-than-daily doses compared to methadone. AMCP suggests, however, that there is a "ceiling effect" for buprenorphine, in which there is no additional benefit by increasing the dose beyond a certain point (16-32mg depending on level of illicit opioid use).

American Psychiatric Association (2010)

http://psychiatryonline.org/pdfaccess.ashx?ResourceID=243188&PDFSource=6

The APA clinical guidelines recommend that buprenorphine can be effective on a less-than-daily schedule and as a bridging agent to naltrexone. Physicians should therefore administer higher, less frequent doses accordingly. Buprenorphine may be best suited for patients with less severe physical dependence. Although the overdose rate is generally low compared to methadone, death is more likely if a combination of buprenorphine and a benzodiazepine is used.

National Institute on Drug Abuse (2012)

http://www.drugabuse.gov/sites/default/files/podat_1.pdf
http://www.drugabuse.gov/sites/default/files/tib_mat_opioid.pdf

NIDA states that the availability of buprenorphine in office-based settings increases access to treatment for opioid-dependent individuals. NIDA supports further research on a long-acting (injectable) form of buprenorphine.

Substance Abuse and Mental Health Services Administration

http://buprenorphine.samhsa.gov/Bup_Guidelines.pdf (2004)
http://adaiclearinghouse.org/downloads/TIP-43-Medication-Assisted-Treatment-for-Opioid-Addiction-in-Opioid-Treatment-Programs-51.pdf (2006)

SAMHSA guidelines suggest that sublingual buprenorphine/naloxone seems to have comparable effectiveness to buprenorphine alone, but that buprenorphine/naloxone has less potential for abuse. If physicians use buprenorphine to initiate withdrawal or discontinue opioid-agonist treatment, naltrexone must also be administered to prevent relapse (this method is used primarily for adolescents or patients with shorter histories of abuse). SAMHSA cautions that switching from methadone to buprenorphine is complex and may not be appropriate for all patients. Typical candidates for buprenorphine maintenance include patients with a history of opioid addiction that have tried other treatment methods but are not physically dependent, those who were previously in a controlled environment, and those who have been addicted for less than one year.

5.3 Naltrexone and Vivitrol (injectable naltrexone)

American Association for the Treatment of Opioid Dependence (2013)
http://www.aatod.org/policies/policy-statements/aatod-guidelines-for-using-naltrexone-vivitrol-in-otps/

AATOD recommends that patients be completely opioid free for 7-10 days before starting Vivitrol treatment to prevent withdrawal. The policy statement cautions that Vivitrol should not be regarded as a type of cure for opioid addiction; rather, conventional modalities, including drug rehabilitation and counseling, should always supplement MAT. Due to Vivitrol's hypertoxicity, AATOD recommends regular clinical evaluations with serial liver function studies.

Academy of Managed Care Pharmacy (2010)
http://www.amcp.org/data/jmcp/S14-S21.pdf

AMCP recommends naltrexone for the treatment of opioid intoxication once acute symptoms have been resolved. Patients must be monitored closely throughout the withdrawal process, particularly in the first few hours, as there is a high risk of severe withdrawal symptoms and hypotension.

American Psychiatric Association (2010)
http://psychiatryonline.org/pdfaccess.ashx?ResourceID=243188&PDFSource=6

The APA clinical guidelines recommend naltrexone as a maintenance agent as it is highly effective in blocking heroin and other short-acting opioids. Retention in treatment is generally poor and has a high risk of relapse. As such, the APA states that though naltrexone is typically underutilized, the treatment option has higher efficacy with motivated patients who are participating in ancillary substance abuse services such as counseling. Voucher incentives in particular appear to improve adherence to naltrexone treatment.

National Institute on Drug Abuse (2012)
http://www.drugabuse.gov/sites/default/files/podat_1.pdf

NIDA considers naltrexone typically to be associated with poor patient compliance, and therefore has limited effectiveness in the treatment of opioid dependency. However, the guidelines suggest that Vivitrol appears to be an effective alternative for those unable to or undecided on whether to use agonist treatment.

Substance Abuse and Mental Health Services Administration
http://buprenorphine.samhsa.gov/Bup_Guidelines.pdf (2004)
http://adaiclearinghouse.org/downloads/TIP-43-Medication-Assisted-Treatment-for-Opioid-Addiction-in-Opioid-Treatment-Programs-51.pdf (2006)

Patients must be fully withdrawn for up to two weeks before beginning naltrexone maintenance treatment. Naltrexone is particularly effective among subgroups with strong psychosocial supports, including health care professionals, business executives, younger patients, and patients involved in the criminal justice system.

5.4 Other Treatment Requirements/Interventions

American Society of Addiction Medicine
http://www.asam.org/docs/publicy-policy-statements/1obot-treatment-7-04.pdf?sfvrsn=0 (2010)
http://www.asam.org/docs/default-source/public-policy-statements/pharmacological-therapies-for-opioid-use-disorder-2013-04-24.pdf?sfvrsn=4 (2013)

ASAM recommends collaboration between addiction medicine and addiction psychiatry organizations to provide the level of care appropriate to address patients' individualized clinical and psychological needs.

American Association for the Treatment of Opioid Dependence (2011)
http://www.aatod.org/policies/policy-statements/793-2/

AATOD suggests the use of prescription monitoring programs (PMPs) as a valuable clinical tool for safely and effectively treating patients, as PMP databases give OTP's access to patient data.

American Psychiatric Association (2010)
http://psychiatryonline.org/pdfaccess.ashx?ResourceID=243188&PDFSource=6

The APA clinical guidelines state that psychosocial treatments, such as behavioral therapies and contingency management, all have varying degrees of effectiveness in reducing opioid-abusing behaviors and retaining patients in treatment, particularly for heroin users. Although psychotherapy alone seems to yield exceptionally high attrition rates, it is particularly effective in aiding in cessation of other substances of abuse.

National Institute on Drug Abuse (2012)
http://www.drugabuse.gov/sites/default/files/podat_1.pdf

NIDA's guidelines suggest that mandatory treatment yields similarly favorable outcomes as voluntary treatment. NIDA considers it best practice to treat comorbidities simultaneously, and to

provide a continuum of services. Guidelines also state that voucher-based incentives are effective in reducing opioid and cocaine use for methadone-maintained patients.

Substance Abuse and Mental Health Services Administration
http://buprenorphine.samhsa.gov/Bup_Guidelines.pdf (2004)
http://adaiclearinghouse.org/downloads/TIP-43-Medication-Assisted-Treatment-for-Opioid-Addiction-in-Opioid-Treatment-Programs-51.pdf (2006)

SAMHSA's clinical guidelines suggest individualizing patient treatment to the extent possible with the resources available, screening for co-morbidities and mental disorders, and addressing the distinct needs of patients with different backgrounds. SAMHSA notes that to determine the appropriateness of office-based or other opioid-agonist treatment, a comprehensive patient assessment is crucial. SAMHSA requires psychosocial treatments to be part of any MAT plan in order to determine if a present psychiatric disorder is a primary disorder or substance-induced. The maintenance treatment model is not one-directional; relapses to drug use happen and patients should always be encouraged to remain in treatment.

6. Evidence Review

The goal of the evidence review was to evaluate the comparative effectiveness and value of MAT for the treatment of opioid dependence. The sections that follow are organized around five "framing" questions of primary interest for this review. These include (1) the comparative effectiveness of maintenance versus short-term opioid withdrawal management approaches; (2) the comparative effectiveness of different pharmacologic treatment options for opioid dependence; (3) the evidence on different protocols for medication dosing and duration; (4) identification of important components of medication-assisted treatment and their correlation with treatment success; and (5) discussion of the available evidence on alternative delivery models for opioid dependence treatment.

Given the very broad scope of this review, we did not conduct a detailed and comprehensive systematic review. Rather, we first identified several prior systematic reviews of relevant RCTs published by the Cochrane Collaboration, as listed below:

- Methadone maintenance versus no opioid replacement therapy (opioid withdrawal management) (Mattick, 2009)
- Buprenorphine versus methadone maintenance (Mattick, 2014)
- Oral naltrexone abstinence treatment (Minozzi, 2011)
- Maintenance/opioid withdrawal management for adolescents (Minozzi, 2009a&2009b)
- Psychosocial and pharmacological treatments for opioid dependence (Amato, 2011a&2011b)

To supplement these reviews, we also identified any additional RCTs, comparative cohort studies, or case series relevant to the framing questions that were published between January 2003 (the year following Suboxone approval in the U.S.) and April 2014. Case series were limited to those involving 100 or more patients; no other restrictions were placed on study selection. The focus of attention for the comparative effectiveness questions (i.e., maintenance versus short-term opioid withdrawal management, methadone versus buprenorphine versus naltrexone) was primarily on comparative studies; we nevertheless abstracted large case series relevant to these questions in order to provide additional context.

We sought published studies and systematic reviews of substance abuse treatment among all patients with dependence on prescription or illicit opioids. We further explored the evidence on adolescents as a subpopulation deemed to be of critical interest by CEPAC. We did not evaluate studies conducted specifically in pregnant women, as not all of the treatment options of interest are available to this subgroup. Interventions of interest included maintenance opioid replacement treatment with methadone or buprenorphine-containing agents (including Suboxone), dose-

tapering strategies for methadone or Suboxone resulting in opioid abstinence with or without naltrexone, use of naltrexone alone without prior stabilization on methadone or buprenorphine, and drug-free opioid withdrawal management. For the purposes of framing question 1, opioid withdrawal managagement was considered to be any program of treatment with opioid abstinence as a goal that was less than 30 days in duration.

Outcomes of primary interest included retention in treatment, use of illicit opioids or other drugs, relapse, and mortality. We also collected information on employment, criminal activity, and health-related quality of life where available. Further details on the literature search strategy for each framing question can be found in Appendix A.

6.1 Maintenance versus Opioid Withdrawal Management

A 2009 Cochrane systematic review of clinical trials comparing maintenance to opioid withdrawal management and other drug-free treatment for opioid dependence found consistently superior outcomes for maintenance approaches. Maintenance was associated with better treatment retention and lower rates of illicit drug use compared to patients who received short-term opioid withdrawal management as their primary course of therapy. Other studies not included in the Cochrane review have produced similar findings. While maintenance treatment appears to be effective for most opioid-dependent patients, there may be a meaningful subset of individuals who are good candidates for opioid withdrawal management. The characteristics of these potential subsets are described below.
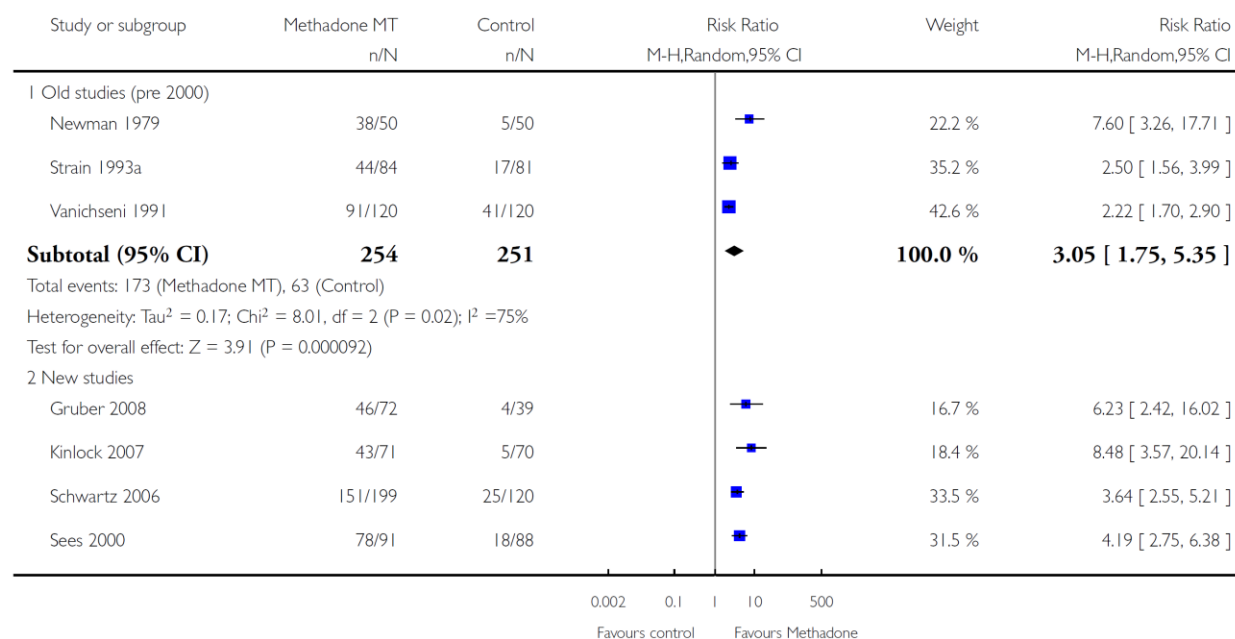
Some case series looking at opioid withdrawal management with or without use of medication have shown high completion rates of the short-term withdrawal phase. One study (Smyth, 2005) reported an 81% completion rate when methadone tapering was used over a 10-day period, while similar results were reported using Suboxone, with 68% of 234 participants successfully completing a 13-day taper (Amass, 2004). However, in this study even patients who completed managed withdrawal had poor outcomes at follow-up. Relapse to heroin use, either by urinalysis or self-reports, was identified in nearly half of participants. Another opioid withdrawal management study (Gandhi, 2003) observed that 74% of participants were using heroin 30 days after successful program completion, and <20% were retained in some form of aftercare at six months of follow-up.

However, prior studies as well as findings from a recent RCT (Sigmon, 2013) suggest that there might be a subset of patients who are more likely to have successful outcomes with short-term opioid withdrawal approaches, including those who are younger, employed, had higher levels of

education, had less severe opioid and other drug use, had fewer medical or psychiatric problems, and were not injecting drugs users.

Nevertheless, in comparing longer-term patient outcomes between opioid withdrawl management approaches and maintenance therapy, the published literature has clearly favored maintenance therapy. A 2009 Cochrane review found that methadone maintenance therapy was superior to drug-free treatment, including drug-assisted and drug-free opioid withdrawal, placebo, and wait-list control (Mattick, 2009). Although there was no statistically significant difference found in mortality between treatment approaches, maintenance therapy was found to retain a higher percentage of patients in treatment over 3-12 months of follow-up (68.1% vs. 25.1%; rate ratio [RR] 3.1; 95% CI 1.8, 5.4; p<.001) and had lower rates of heroin use (45.7% vs. 66.5% positive urine/hair analysis; RR 0.7; 95% CI 0.6, 0.8; p<.001). A forest plot of individual study results is presented in Figure 3 below. Inclusion of studies published both before and after the year 2000 yielded similar findings. It should be noted that, while both outcomes favored maintenance therapy, results were still less than optimal for maintenance approaches (i.e., nearly 50% of patients testing positive for heroin use).

Figure 3. Forest plot of methadone maintenance versus control.

Study or subgroup	Methadone MT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Old studies (pre 2000)					
Newman 1979	38/50	5/50		22.2 %	7.60 [3.26, 17.71]
Strain 1993a	44/84	17/81		35.2 %	2.50 [1.56, 3.99]
Vanichseni 1991	91/120	41/120		42.6 %	2.22 [1.70, 2.90]
Subtotal (95% CI)	**254**	**251**		**100.0 %**	**3.05 [1.75, 5.35]**
Total events: 173 (Methadone MT), 63 (Control)					
Heterogeneity: Tau² = 0.17; Chi² = 8.01, df = 2 (P = 0.02); I² =75%					
Test for overall effect: Z = 3.91 (P = 0.000092)					
2 New studies					
Gruber 2008	46/72	4/39		16.7 %	6.23 [2.42, 16.02]
Kinlock 2007	43/71	5/70		18.4 %	8.48 [3.57, 20.14]
Schwartz 2006	151/199	25/120		33.5 %	3.64 [2.55, 5.21]
Sees 2000	78/91	18/88		31.5 %	4.19 [2.75, 6.38]

Heterogeneity: Tau² = 0.17; Chi² = 8.01, df = 2 (P = 0.02); I² =75%

0.002   0.1   1   10   500

Favours control   Favours Methadone

Source: Mattick RP et al. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev*. 2009;3:CD002209.

These findings are consistent with results from buprenorphine studies identified in our search. For example, a comparative cohort study evaluating buprenorphine for maintenance or opioid withdrawal management in 60 patients who were in a three-month treatment program found that

time in treatment was significantly shorter in the detoxification group (mean: 0.4 weeks vs. 8.5 weeks, p=.001) (Caldiero, 2006).

In addition, although not a direct comparison of "pure" opioid withdrawal management to maintenance therapy, the effectiveness of shorter versus longer maintenance treatment duration was evaluated in the Prescription Opioid Addiction Treatment Study (POATS) (Weiss, 2011). A total of 653 patients were treated in a two-phase study; in the first phase, patients received stabilization with Suboxone for two weeks followed by a two-week taper. Patients with evidence of illicit opioid use were invited to continue in the study's second phase, which included three months of maintenance treatment with Suboxone followed by a four-week taper. Of those completing phase 1, the majority (93.4%) had unsuccessful opioid-use outcomes and were therefore included in the maintenance phase, which showed a program success rate of 49.2% at the completion of treatment (Weiss, 2011).

Certain factors have been found to be significantly associated with positive outcomes for patients in MAT, including absence of a family history of substance abuse, older age, and having a spouse or partner engaged in the patient's rehabilitation (Mattick, 2009). Conversely, factors that are associated with negative treatment outcomes include heroin use (versus prescription opioid use), polydrug use (particularly cocaine and injectable drugs), participation in criminal activity, and a history of psychological problems.

We did not identify any studies comparing short-term opioid withdrawal management approaches with versus without naltrexone. We identified four case series (Bartu, 2002; Chaudhry, 2012; De Jong, 2007; Dijkstra, 2010) evaluating use of oral naltrexone after short-term opioid withdrawal management. Although the completion rates of the opioid withdrawal management phase were comparable to those in case series evaluating opioid withdrawal management without naltrexone (see above), the addition of oral naltrexone does not appear to substantially improve retention rates, which ranged between 24-30% at 2-10 months of follow-up.

Short-term opioid withdrawal management versus maintenance therapy for adolescents

The treatment of opioid dependence in adolescents represents a unique challenge to clinicians. While treatment approaches include short-term detoxification and psychosocial interventions, the risk of relapse remains high (Woody, 2008). Two systematic reviews evaluated opioid withdrawal management and/or maintenance therapy in patients age 18 years or younger (Minozzi, 2009a; Minozzi, 2009b), but found insufficient evidence to distinguish these approaches in the small set of three trials available (n=190). Only one of these studies directly compared maintenance versus opioid withdrawal management, an RCT (n=152) that compared the short-term, tapered use of Suboxone (14 days) in a managed withdrawal framework to extended maintenance use over 12

weeks of follow-up (Woody, 2008). At 12 weeks, treatment retention was significantly higher in the maintenance cohort (70% versus 21%, p<.001), and patients undergoing opioid withdrawal management reported significantly more illicit opioid, cocaine, and marijuana use compared to maintenance patients. A separate non-comparative case series of 100 adolescents treated with methadone maintenance found that 50% remained in treatment for more than 12 months with a drop-out rate of 32%, and 39% of patients eventually transitioned to adult clinic services (Smyth, 2012).

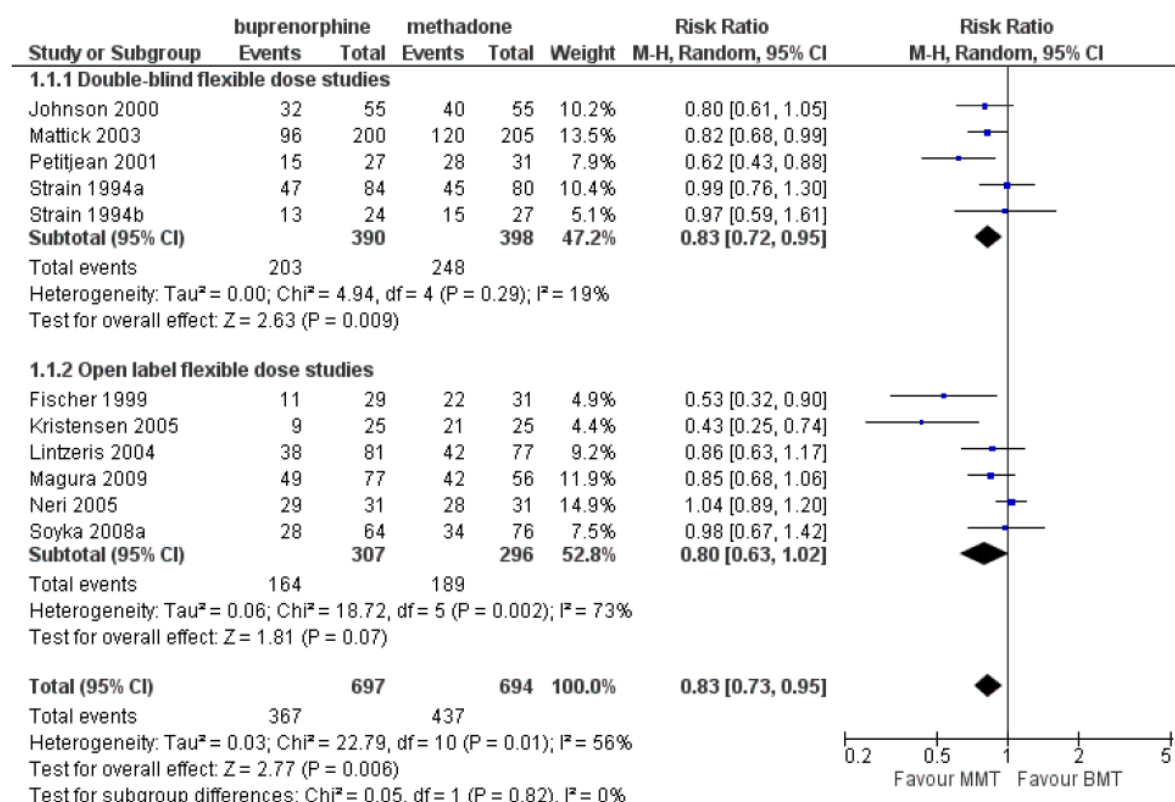## 6.2 Comparative Effectiveness of Methadone, Buprenorphine, and Naltrexone

Both a recent Cochrane review as well as additional studies of maintenance treatment options consistently found that there are no major differences in mortality or illicit drug use achieved with methadone versus Suboxone or buprenorphine (in any form). However, methadone appears to be associated with greater retention in treatment compared to buprenorphine in either flexible or low, fixed doses. In contrast, naltrexone appears to be no better than placebo at retaining patients in treatment, although limited data suggest that long-acting forms (injectable or implantable) may have advantages over oral naltrexone in this regard.

Methadone versus Suboxone/buprenorphine for maintenance therapy

Findings from a recent Cochrane review comparing methadone- to buprenorphine-based maintenance treatment found no statistically-significant differences in illicit drug use, criminal activity, or mortality between treatment approaches (Mattick, 2014). Long-term follow-up from one of the RCTs included in the Cochrane review suggested that mortality rates remained comparable for methadone and buprenorphine after a mean of 8.3 years of follow-up (Gibson, 2008). Finally, while a recent RCT of 80 patients not included in the Cochrane review found a small but statistically-significant difference between methadone and Suboxone in illicit opioid use (1.5% vs. .2% for Suboxone, p=.03), there were no differences in opioid craving and injecting risk behaviors over five months of follow-up (Otiashvili, 2013).

Methadone maintenance does appear, however, to be associated with higher rates of treatment retention relative to buprenorphine. Findings from the Cochrane review of studies utilizing flexible doses of methadone or buprenorphine showed lower rates of treatment retention for buprenorphine (pooled rate 52.3% vs. 63.0%; rate ratio 0.83; 95% CI: 0.72, 0.95) over 3-12 months of follow-up (Mattick, 2014). Study-specific results are shown in Figure 4 on the following page. Findings were similar when maintenance treatments featuring fixed, low doses of buprenorphine (2-6 mg) and methadone (≤40 mg) were compared.

Figure 4. Forest plot of treatment retention in randomized controlled trials comparing methadone to buprenorphine.

Study or Subgroup	buprenorphine Events	Total	methadone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.1.1 Double-blind flexible dose studies							
Johnson 2000	32	55	40	55	10.2%	0.80 [0.61, 1.05]	
Mattick 2003	96	200	120	205	13.5%	0.82 [0.68, 0.99]	
Petitjean 2001	15	27	28	31	7.9%	0.62 [0.43, 0.88]	
Strain 1994a	47	84	45	80	10.4%	0.99 [0.76, 1.30]	
Strain 1994b	13	24	15	27	5.1%	0.97 [0.59, 1.61]	
Subtotal (95% CI)		390		398	47.2%	0.83 [0.72, 0.95]	
Total events	203		248				
Heterogeneity: Tau² = 0.00; Chi² = 4.94, df = 4 (P = 0.29); I² = 19%							
Test for overall effect: Z = 2.63 (P = 0.009)							
1.1.2 Open label flexible dose studies							
Fischer 1999	11	29	22	31	4.9%	0.53 [0.32, 0.90]	
Kristensen 2005	9	25	21	25	4.4%	0.43 [0.25, 0.74]	
Lintzeris 2004	38	81	42	77	9.2%	0.86 [0.63, 1.17]	
Magura 2009	49	77	42	56	11.9%	0.85 [0.68, 1.06]	
Neri 2005	29	31	28	31	14.9%	1.04 [0.89, 1.20]	
Soyka 2008a	28	64	34	76	7.5%	0.98 [0.67, 1.42]	
Subtotal (95% CI)		307		296	52.8%	0.80 [0.63, 1.02]	
Total events	164		189				
Heterogeneity: Tau² = 0.06; Chi² = 18.72, df = 5 (P = 0.002); I² = 73%							
Test for overall effect: Z = 1.81 (P = 0.07)							
Total (95% CI)		697		694	100.0%	0.83 [0.73, 0.95]	
Total events	367		437				
Heterogeneity: Tau² = 0.03; Chi² = 22.79, df = 10 (P = 0.01); I² = 56%							
Test for overall effect: Z = 2.77 (P = 0.006)							
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%							

0.2 0.5 1 2 5
Favour MMT   Favour BMT

Source: Mattick RP et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2014;6(2):CD002207

We identified an additional RCT of 60 patients receiving low-dose buprenorphine or flexible-dose methadone who were followed for 24 weeks (Jagsch, 2005). This RCT was not included in the Cochrane review, for unknown reasons (possibly the fixed versus flexible dose comparison). Retention in treatment at the end of the study was twice as high for methadone (71% vs. 38%, p=.01).

Naltrexone versus buprenorphine or methadone

We identified no head-to-head clinical studies of naltrexone versus methadone. We identified a single RCT comparing naltrexone, buprenorphine, or placebo in 126 detoxified patients (Schottenfeld, 2008) who were followed for up to 24 weeks. Buprenorphine was found to be superior to naltrexone in terms of mean days in treatment (117 vs. 84, p=.022), as well as mean days without heroin use (51 vs. 24, p=.028). In contrast, none of the key study measures statistically differed between naltrexone and placebo.

<u>Buprenorphine versus Suboxone</u>

We identified only two studies that assessed the comparative effectiveness of different forms of buprenorphine. One study (Lintzeris, 2013) compared the sublingual tablet and the film forms of Suboxone and found comparable drug plasma levels, clinical outcomes, and adverse-event rates, although the film version generated higher patient satisfaction scores and dissolved more quickly. Another study (Comer, 2010) found that both Suboxone and buprenorphine alone had abuse potential, but patients' self-reported desire for intravenous drug use and perception of street value was lower with Suboxone.

<u>Long-acting naltrexone versus oral naltrexone versus placebo</u>

A separate Cochrane review assessing six RCTs of maintenance treatment with oral naltrexone versus placebo found that retention and opioid abstinence rates were low with naltrexone (<30%) and not statistically different from rates with placebo (Minozzi, 2011). A single RCT analyzed the effectiveness of a long-acting naltrexone implant among 306 intravenous heroin users over 24 weeks of follow-up and found that the implant had significantly better treatment outcomes than oral naltrexone, including treatment retention (52.9% vs. 15.7% for oral naltrexone, p<.001) and negative urine tests (63.6% vs. 42.7%, p<.001) (Krupitsky, 2012). The implant is not currently approved for use in the U.S., however. Another placebo-controlled RCT (n=250) found that injectable extended-release naltrexone (Vivitrol) retained patients in treatment longer (median 168 vs. 96 days, p=.004), reduced rates of relapse (0.8% vs. 13.7%, p<.0001), and increased total abstinence rates (35.7% vs. 22.6%, p=.022) relative to placebo (Krupitsky, 2011). To date, however, Vivitrol has not been compared to other forms of naltrexone in any comparative study.

Methadone, buprenorphine, and naltrexone for adolescents

Limited research exists comparing opioid replacement therapies in adolescent patient populations. In a single retrospective comparative study of 61 patients aged 14-17 years, treatment with methadone resulted in significantly longer program retention compared to treatment with buprenorphine (mean days: 354 vs. 58, p<.01) (Bell, 2006). The use of methadone was also associated with fewer treatment drop-outs, although statistical testing was not performed.

6.3 Dosing and Duration Protocols

Studies examining dosing and duration of maintenance treatment have found both methadone (~100 mg/day) and Suboxone (16-32 mg/day) have clear dose thresholds at which clinical outcomes no longer improve. In terms of dosing frequency, daily methadone appears to produce better

outcomes than less frequent dosing, while the dosing frequency of buprenorphine appears to make little difference in outcomes. Data suggest that dose tapering regimens with either methadone or Suboxone have limited success, but that longer tapers are superior to shorter-duration tapers.

Dosage Level

Methadone

We identified nine studies, of which two were RCTs, comparing different dosing levels of methadone. One RCT (Epstein, 2009) compared the effectiveness of 70 mg/day versus 100 mg/day of methadone and concluded that 100mg was more effective at reducing illicit opioid use (42% vs. 20% for 70 mg, p=.01), though treatment retention did not differ. The other RCT (Kennedy, 2013) examined whether daily fixed dosing of 100 mg or daily flexible dosing over 100 mg had any impacts on treatment outcomes and determined that the flexible, high-dose group was *less* likely to produce drug-free urines; however, there were no differences in retention. Both studies found that higher doses do not reduce cocaine use, and that other treatment interventions may be required to address polydrug abusers.

Findings from selected case series also found that higher, daily doses of methadone (up to but not exceeding 100 mg) were associated with reductions in illicit opioid use and improved retention in treatment (Dunn, 2003; Fonseca, 2011; Gerra 2003). A large retrospective case series (Nosyk, 2010) evaluated 31,724 treatment "episodes" over an 11-year period from a provincial drug dispensation database and found that a higher daily maintenance dose (over 60mg/day) was positively associated with long-term retention in treatment (>3 years). Another large retrospective case series (N=301) examining a prescription database found a significant positive correlation between dose level and retention in treatment, with the best relationship found at 96mg/day (Dickinson, 2003).

Buprenorphine/Suboxone

While higher doses of buprenorphine are associated with better treatment outcomes, there may be certain thresholds at which buprenorphine reaches its maximum effectiveness. One RCT (Montoya, 2004) concluded that 16mg of buprenorphine appears to be the optimal dose for the discontinuation of illicit drug use, particularly for those who are dually dependent on opioids and cocaine. In terms of frequency of dosing, two RCTs found that less-than-daily doses of burprenorphine appear to be as effective as daily doses in preventing the use of illicit opioids and retaining patients in treatment (Marsch, 2005; Montoya, 2004).

A comparative cohort study (Fareed, 2012) examined daily dosing levels of buprenorphine greater than 16mg vs. 8-16 mg in 56 patients and found that doses higher than 32mg/day did not have any added benefits in reducing the number of positive urinalyses. Another large case series (N=979) found that maintenance doses between 12-32mg and less-than daily dosing appear to have a positive effect on treatment outcomes, including higher rates of treatment compliance, lower rates of relapse, and reduction of illicit drug use (Leonardi, 2008).

Treatment Duration Protocols

Methadone

There were no RCTs evaluating the use of tapering protocols for methadone maintenance. A large retrospective analysis of nearly 15,000 attempts at dose tapering found that rates of "sustained success"—defined as no treatment re-entry, opioid-related hospitalization, or mortality within 18 months following taper completion—were low overall (5.3%) (Nosyk, 2010). Subsequent stratification of episodes by shorter (<12 weeks) vs. longer (≥12 weeks) taper duration indicated that longer tapers were over three times as likely to result in sustained success, but absolute rates were low for _both_ strata (18.6% vs. 4.6%, p<.05).

Buprenorphine/Suboxone

One RCT (Ling, 2009) found that a shorter Suboxone taper was better for patients when the goal is to discontinue treatment, with nearly half of patients in a 7-day taper group supplying opioid-free urines at the end of treatment versus 30% in a 28-day taper group. Another RCT (Weiss, 2011) evaluated a two-phase tapering regimen after maintenance on Suboxone. The study found that only 6.6% of patients assigned to a two-week taper during a 12-week initial study phase achieved self-reported opioid use of no more than four days in a month, absence of two consecutive opioid-positive urinalyses, and no more than one missing sample taken, whereas 49% of patients achieved this composite successful outcome on a longer tapering course of 12 weeks in a 24-week second study phase.

Finally, a small (n=70) RCT (Sigmon, 2013) examined prescription opioid abusers stabilized on Suboxone, then randomized to a one-, two- or four-week Suboxone taper, followed by subsequent treatment with oral naltrexone. The four-week taper group had a higher proportion of participants successfully maintained on naltrexone (50%) compared to 21% for both 1- and 2-week tapers (p=.04), as well as the highest rate of opioid abstinence (50% vs. 16% vs. 20%, p=.03) at the end of the 12-week study. The authors noted that, while this study did not involve a direct comparison with indefinite maintenance treatment, rates of retention and abstinence were similar to those seen with maintenance studies. It was also noted that these rates of success were observed in a

primarily educated and white population with dependence only on prescription opioids (heroin abusers were excluded from the study).

Adolescents

No studies of alternative dosing or duration protocols conducted specifically in adolescents were identified that included information on the outcomes of interest for this review.

6.4 Important Components of Treatment

Available evidence suggests that several types of positive incentives (e.g., contingency vouchers and rewards), as well as negative incentives (e.g., mandatory medication tapers for missed appointments), appear to improve patient retention in treatment. Evidence on the effectiveness of active, goal-oriented therapy such as cognitive-behavioral and interpersonal therapy is mixed; however, interventions to improve counseling adherence and the use of visual aids for goal-setting and tracking may improve treatment compliance. Supervised medication consumption and more frequent dispensing do not appear to improve adherence to treatment, in part because these interventions tend to be reserved for individuals with existing non-adherence patterns.

Patient compliance with opioid dependence treatment remains a significant obstacle to recovery (Brooner, 2004). Several measures have been employed to improve retention in maintenance treatment programs. The most consistent body of evidence examines the use of positive and negative reinforcement measures. For example, we identified several studies examining the impact of contingency vouchers – monetary rewards for remaining in treatment – on treatment retention and illicit drug use. In these studies, patients received vouchers that increased in monetary value with consecutive drug-free urinalyses. In an RCT of 388 patients enrolled in methadone maintenance programs across the U.S., the use of low-cost abstinence incentives (values ranged from $0 - $20) compared to usual care resulted in significantly more frequent submission of negative urinalyses and consecutive weeks of drug abstinence (Peirce, 2006). Schottenfeld et al. (2005) found similar results among patients receiving methadone or buprenorphine during three months of increasing voucher value; once the escalation of rewards stopped, however, benefits of incentives were not sustained. In studies examining the combined use of contingency vouchers and counseling techniques, patients receiving vouchers during the active study period were more likely to complete treatment; however, the impact was not sustained following the return of patients to standard care conditions (Brooner, 2007).

The evidence base also includes findings on the use of negative incentives, such as mandatory tapers of methadone dose with or without increased counseling following drug-positive urinalyses

and/or missed appointments. In an RCT of adaptive stepped care versus standard treatment in 127 patients, those enrolled in the adaptive stepped care treatment arm (i.e., less convenient dosing times and mandatory dose taper for missed counseling or positive urine tests) attended counseling appointments at a significantly higher rate than patients receiving standard care (83% versus 44%, p<.001), and had fewer poor treatment responses (46% versus 79%, p<.001) (Brooner, 2004). Unlike positive incentives, however, negative interventions appear to be less likely to reduce illicit drug use.

The inclusion of active, goal-oriented psychosocial approaches to counseling in the treatment of opioid dependence is legally mandated in methadone treatment (see Section 3), and has been extensively studied. Evidence on the effectiveness of these approaches is mixed, however. For example, in a systematic review of multiple counseling approaches, the impact of additional psychosocial therapy (beyond standard, mandated counseling) was not found to impact treatment retention or rates of abstinence (Amato, 2011b). In two randomized trials of cognitive behavioral therapy or specialized opioid dependence counseling in place of standard counseling and physician care, no significant differences were found in the rates of opioid abstinence or treatment retention, and outcomes were no better than for brief, clinician-provided counseling (Weiss, 2011; Fiellin, 2013). However, there is some evidence of a "dose-response" with counseling, as patients with higher rates of counseling attendance remain in treatment longer and reduce their illicit drug use (Moore, 2012; Brooner, 2007; Montoya, 2005).

Use of other therapeutic approaches, such as addressing patient fears of withdrawal through Acceptance and Commitment Therapy (ACT), may increase abstinence rates, while innovative behavioral algorithms like the Paced Auditory Serial Addition Task (PASAT) may assist in early identification of patients at higher risk of relapse. There is limited information regarding the incremental effects of peer-to-peer sober networks on treatment outcomes, in part because these programs have historically not accepted individuals receiving opioid replacement therapy; the data that do exist suggest that 12-step programs have limited impact when compared to standard methadone maintenance with other forms of counseling (Hayes, 2004).

Other innovative approaches to opioid dependence treatment include visual treatment guides and maps designed to aid in treatment planning and progress tracking, which have been shown to improve attendance at counseling sessions and retention in treatment (Newbern, 2005). These interventions may be particularly appropriate for patients with attention deficits. An example of one of these treatment guides can be found in Figure 5 below.

Intensity of treatment for opioid dependent patients is an important consideration in care delivery. While methadone is generally dosed daily in a clinic setting, Suboxone is available for up to one month as a take-home medication, depending on patient stability. We evaluated several studies

examining the impact of different dosing approaches on treatment retention. Comparisons of outcomes for supervised and observed versus unobserved dosing yielded no significant differences in retention; however, the use of supervised dosing in patients who had already demonstrated non-adherence to treatment at baseline may have influenced these findings (Dunn, 2009). In contrast, utilization of contingency-based, take-home dosing (one week of medication provided based on demonstrated clinical stability with drug-free urine screens) appears to result in greater treatment retention and lower rates of program drop-out (Gerra, 2011).

Figure 5. Example of a visual treatment guide.
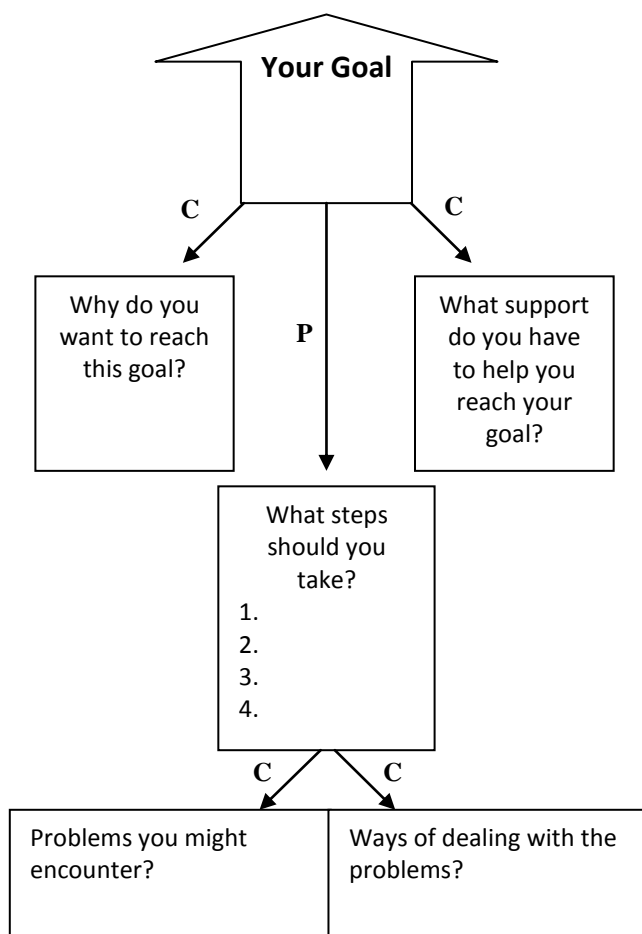
C: characteristic (counseling goal); P: part (action steps)
Source: Czuchry M, et al. Visual representation tools for improving addiction treatment outcomes. *J Psychoactive Drugs*. 2009;41(2):181-187.

6.5 Delivery Models

Alternative delivery mechanisms for counseling in opioid dependence management (e.g., telephonic coaching, group therapy by videoconference) appear to produce similar rates of treatment retention and illicit drug use relative to in-person counseling. Wait-list maintenance interventions and pilot, office-based methadone programs appear to produce outcomes comparable to clinic-based care. Provision of opioid dependence management in alternative settings (e.g., primary care, office-based clinics) with adjunct services appears to retain patients at comparable or better rates relative to standard treatment approaches.

As noted in Section 6.4, evidence is mixed on the benefits of psychosocial therapy in the management of opioid dependence. However, such counseling remains a standard component of medication-assisted treatment. Patient compliance with ongoing counseling is a major challenge, as the frequency, duration, and timing of required sessions may interfere with other treatment-related and unrelated activities (King, 2009). To address this, several studies have evaluated innovative counseling approaches such as Internet-based videoconferencing, telephonic patient support, and stepped-care approaches (Ruetsch, 2012; King, 2009; King, 2006). In these studies rates of drug-positive urinalyses and treatment adherence were comparable to those reported with the use of standard, in-person counseling at up to 12 months of follow-up, and another study reported 93% patient employment (in patients previously unemployed) following one year of treatment (Kidorf, 2004). Alternative counseling approaches appeared to work best in patients with less severe addiction and less concurrent drug use.

Incorporation of job skills training as an integral part of opioid dependence treatment addresses a crucial deficit in this patient population, as rates of employment are generally low (Magura, 2007), and employment is correlated with improved patient outcomes including treatment retention (Kidorf, 2004). Studies comparing vocational interventions such as training in job-seeking, interviewing, and problem-solving skills, demonstrated modest increases in mean days worked and significantly more paid employment (Magura, 2007; Lidz, 2004).

A central challenge for patients seeking treatment for opioid dependence is access. Extensive waiting lists further complicate already-limited access to effective treatment options (Schwartz, 2006). The impact of "bridging" approaches among patients waiting to enroll in methadone maintenance programs has been evaluated in an RCT (Schwartz, 2006). Provision of up to four months of methadone and emergency counseling (all free of charge to the patient) compared with waitlist control resulted in significantly greater patient enrollment in formal, full-scale methadone treatment programs (76% versus 21%, p<.001) (Schwartz, 2006). Patients in this bridging arm of the study also reported fewer days of heroin and cocaine use and fewer arrests at six months of follow-up.

Several pilot studies have investigated the use of methadone in an office-based environment with take-home dosing provided for up to one month, in contrast to the federally-mandated approach of daily observed dosing in a clinic setting. In two studies evaluating patients with demonstrated stability (no illicit drug use in prior 1-3 years, full-time employment), treatment retention was high (79-98% at 12-60 months), and illicit drug use was low (0.4-2.3%) among all patient groups (Harris, 2006; King, 2006). In the King RCT, patients receiving one month of take-home dosing initiated significantly more new vocational or social activities over a 12-month period as compared to standard treatment (81-97% versus 46%, p<.001). Rates of treatment retention in other pilot studies of office-based methadone are summarized by location, sample size, and retention rates in Table 6 below.

Table 6. Published studies of office-based methadone medical management.

Author, Year	Study Location	Number of Enrolled Patients	Patients Retained in Treatment (duration of observation period)
Senay, 1994	Chicago, IL	130	69% (1 year)
Schwartz, 1999	Baltimore, MD	21	71% (12 years)
Salsitz, 2000	New York, NY	158	84% (15 years)
Merrill, 2005	Seattle, WA	30	93% (1 year)

Source: Harris KA et al. A 5-year evaluation of a methadone medical maintenance program. *J Subst Abuse Treat*. 2006;31(4):433-438.

In studies of patients who were _not_ clinically stable and currently using illicit drugs, treatment retention in programs featuring take-home doses appears to be comparable to or better than that in standard methadone programs, but other outcomes are inferior. For example, one study found that newly enrolled patients with unrestricted take-home methadone doses had significantly increased risks of positive urine screens, criminal activity, and self-diversion; however, in a separate group with contingency restrictions (demonstrated clinical stability and negative urinalysis) on take-home doses, rates of these outcomes were similar to standard methadone dosing (Gerra, 2011).

Other studies have evaluated alternative treatment settings for delivery of medication-assisted treatment (with Suboxone/buprenorphine), including hospital-based clinics, community-based clinics, and primary care offices. Findings from these studies suggest that flexible treatment settings may provide benefits in terms of treatment retention. In one RCT, patients (n=94) were assigned to Suboxone treatment within an opioid-treatment program (OTP), a primary care office [psychiatrist's private practice (PCS)], and a group-based cognitive behavioral therapy program

known as the manualized Matrix Model (MMM) (Miotto, 2012). Among patients remaining in treatment beyond nine weeks, OTP participants had statistically-significantly higher drop-out rates compared to PCS and MMM patients (79% vs. 67% and 48% for PCS and MMM respectively, p=.05). However, the number of weeks that patients were retained did not differ statistically between groups, as shown in Table 7 below.

Table 7. Treatment retention among patients receiving opioid dependence treatment in alternate settings.

	OTP (n=28)	PCS (n=33)	MMM (n=33)	p-value
Retention				
Week 9	53.6%	39.3%	54.6%	0.39
Week 20	21.4%	33.3%	51.5%	0.05
Mean # weeks retained	14	19	25	0.11

MMM: manualized Matrix Model; OTP: opioid-treatment program; PCS: psychiatrist's private practice
Source: Miotto K et al. Comparison of buprenorphine treatment for opioid dependence in three settings. *J Addict Med*. 2012;6(1):68-76.

An additional RCT examined integration of opioid dependence treatment into HIV care at a specialty clinic (Lucas, 2010). Ninety-three HIV patients were randomized to a buprenorphine-based induction and maintenance program at the clinic or to standard case management and referral to a traditional OTP. Enrollment and retention in opioid agonist treatment at 12 months of follow-up was significantly greater for those patients receiving integrated care at the clinic compared to those referred to external opioid dependence treatment (74% versus 41%, p<.001) (Lucas, 2010).

Adjunct services such as education on drug risk behavior, HIV/AIDS prevention education, and family counseling improved treatment outcomes in some but not all studies. For example, in an analysis of structural-level factors correlated with success among 28 methadone maintenance programs treating a total of 560 patients, provision of at least two kinds of comprehensive services (including individual, group, and/or family counseling and skills training) was significantly but modestly associated with higher treatment retention rates (58% versus 50%, p<.01) (Lin, 2010); in contrast, an evaluation of individual- and group-based methadone education and skills training provided by health educators failed to reduce illicit drug use at nine months of follow-up relative to standard treatment (Li, 2013).

7. Economic Evaluation

The economic impact of treatment for opioid dependence has been evaluated across multiple settings and perspectives. While the published economic literature is too substantial to describe in detail here, findings from these studies have followed two very consistent themes. One is that MAT, whether with methadone or buprenorphine-containing agents, is highly cost-effective or cost-saving to society, particularly in analyses that incorporate costs of criminal justice, victimization, and lost productivity (Schackman, 2014; Zarkin, 2005; Zaric, 2000; Doran, 2008; Bell, 2007; Barnett, 2010; Barnett, 2001). The other is that MAT has consistently been shown to be cost-effective or cost-saving in relation to treatment _without_ drug therapy (i.e., short-term opioid withdrawal management) (Polsky, 2010; McCarty, 2010; Baser, 2011; Masson, 2004).

In contrast, analyses comparing different methods of MAT have generally found very little to distinguish these approaches. For example, a comprehensive systematic review and economic evaluation conducted by the UK's University of Birmingham Health Services Management Centre (Connock, 2007) found no major differences in clinical effectiveness between methadone and buprenorphine maintenance programs other than better retention in methadone maintenance as previously described (see Section 6). Findings from the economic evaluation indicated differences in quality-adjusted life expectancy of <5 days between methadone and buprenorphine as well as minimal differences in cost.

While the findings described above have been quite consistent, we nevertheless felt it important to assess the comparative value of different approaches to treating opioid dependence with a focus on the realities of treatment in the U.S. setting, as well as to document the costs of opioid dependence in New England and the potential budgetary impact of expanding access to MAT in the region. Methods and results for the comparative value analyses are described in detail in the sections that follow. Our approach for the budgetary impact analysis is described beginning on page 70.

7.1 Cohort Model: Methods

Overview

We developed a simulation model to evaluate the comparative value of different approaches to treating opioid dependence among 1,000 hypothetical patients entering treatment. Model outcomes and costs were calculated over a two-year time horizon; consistent with methods for economic evaluation, outcomes and costs occurring in the second year were discounted using a 3% rate (Gold, 1996). Each patient could have one of four possible outcomes of treatment, as listed on the following page:

- In treatment
- Out of treatment, drug-free
- Out of treatment, relapsed
- Deceased

We adopted a societal perspective for this analysis given the potential for significant impacts of opioid dependence outside of the health care system. Costs therefore included not only those of substance abuse drug therapy and related services as well as other health care expenditures, but also "social costs" of law enforcement, victimization, and productivity loss (see "Costs" below). Cost-effectiveness was calculated alternatively as the cost per relapse averted and the cost per death averted respectively. All key model inputs can be found in Table 8 on page 62.

Treatment Strategies

We considered multiple treatment strategies for this evaluation. These included maintenance treatment with either methadone or Suboxone, stabilization with Suboxone followed by a 4-week taper to either oral naltrexone or Vivitrol, and use of oral naltrexone or Vivitrol alone for opioid withdrawal management.

Clinical Outcomes

Rates of retention in treatment for methadone, Suboxone, and oral naltrexone alone (63%, 52%, and 28%, respectively) were estimated using pooled rates of retention reported in recent Cochrane reviews (Mattick, 2014; Minozzi, 2011). We calculated retention with Vivitrol alone to be 50% greater than that of oral naltrexone based on findings from a recent placebo-controlled RCT (Krupitsky, 2011). Finally, we estimated retention with the tapering strategies based on findings from an RCT of a Suboxone-oral naltrexone approach (Sigmon, 2013). There are no published data on the use of Vivitrol as part of a tapering strategy. Because this long-acting formulation has potential adherence advantages over oral naltrexone, however, we conservatively assumed a 5% improvement in overall retention if Vivitrol was used as the opioid antagonist.

We assumed the proportion of patients "out of treatment" who were drug-free versus relapsed to be equal, based on data from a three-year cohort study of maintenance treatment outcomes (Comiskey, 2010). Importantly, we applied this to methadone as the treatment with the highest reported rate of retention. Given that 63% of patients receiving methadone were retained in treatment, we estimated that 18.5% of patients each would be drug-free and relapsed respectively (i.e., an equal division of the 37% not still in treatment at two years). However, we could not apply these proportions directly to other treatment strategies with inferior retention rates, as this would have resulted in counterintuitively higher proportions of drug-free individuals. Instead, we set the

universal "drug-free" rate based on the methadone rate (18.5%) which was reduced for each strategy by differential rates of mortality (see below). The rate of relapse for all other strategies was calculated as the proportion remaining after accounting for rates of retention in treatment, out of treatment and drug-free, and mortality.

Mortality for relapsed patients was estimated to be 1.4% annually, based on a long-term follow-up study (mean: 8.3 years) of an RCT of methadone versus buprenorphine maintenance (Gibson, 2008). We estimated annual rates of death among patients in methadone and buprenorphine maintenance treatment to be 0.2% and 0.02% based on drug overdose death rates reported among treatment enrollees in France (Auriacombe, 2004). We assumed that patients out of treatment and drug-free to be "recovered" and therefore would have no excess risk of substance-abuse related death. We assumed the same for patients in treatment with oral naltrexone or Vivitrol, given the low potential for abuse or diversion and no risk of fatal overdose with this agent.

Costs

Costs included those of drug therapy for opioid dependence, other substance abuse services, other health care services (i.e., other than for routine substance abuse treatment), and "social costs" of law enforcement, victimization, and productivity loss. We obtained costs of drug therapy and other substance abuse services for each strategy of interest from a retrospective analysis of health care claims from commercial payers and managed Medicaid plans (Baser, 2011). Costs of other health care services among relapsed patients as well as those who died were estimated to total approximately $20,000 annually based on an assessment of the attributable costs of opioid abuse (White, 2005); we assumed these would be reduced by approximately 50% for patients in treatment based on data on drug-treated versus untreated patients in the Baser study (Baser, 2011). Patients who were out of treatment and drug-free were assumed to incur treatment costs only in the first year; health care costs in the second year were estimated using World Health Organization (WHO) figures for per-capita health care costs (WHO, 2013).

We estimated social costs of opioid dependence to total $106,000 annually, based on an analysis of crime frequency and severity as well as employment impacts on both perpetrators and victims among 114 opioid abusers in Canada (Wall, 2000). We further assumed that law enforcement and victimization costs would be reduced by 75% among patients in treatment, consistent with reported reductions in arrest frequency and severity in a two-year follow-up study of methadone maintenance treatment (Schwartz, 2009). For all treatment strategies other than methadone, we assumed a 50% reduction in productivity loss costs, based on data on increased employment among patients enrolled in MATs (SAMHSA, 2006). We assumed no benefit for methadone in this regard given the requirements for daily in-person dosing and intensive counseling in U.S. settings.

Table 8. Key model inputs.

Parameter	Estimate	Source(s)
Retention in treatment (%):		
MMT	63.0	Mattick, 2014
BMT	52.3	Mattick, 2014
Suboxone 4 wks, oral NTX taper	50.0	Sigmon, 2013
Suboxone 4 wks, Vivitrol taper	55.0	Assumption
Oral NTX alone	27.7	Minozzi, 2011
Vivitrol alone	41.6	Krupitsky, 2011
Out of treatment, relapsed (%):		
MMT	18.5	Mattick, 2014; Comiskey, 2010
BMT	29.2	Mattick, 2014
Suboxone 4 wks, oral NTX taper	31.5	Sigmon, 2013
Suboxone 4 wks, Vivitrol taper	26.5	Assumption
Oral NTX alone	53.8	Minozzi, 2011
Vivitrol alone	40.0	Krupitsky, 2011
Out of treatment, drug-free (%)*:	16.9-17.7	Comiskey, 2010
Annual mortality (%):		
Out of treatment, relapsed	1.4	Gibson, 2008
In treatment, MMT	0.2	Auriacombe, 2004
In treatment, BMT	0.02	Auriacombe, 2004
Annual treatment costs (Drug therapy/ Other substance abuse services, 2013$):		Baser, 2011
MMT	493/9,884	
BMT	3,030/5,838	
Suboxone 4 wks, oral NTX taper	1,181/3,904	
Suboxone 4 wks, Vivitrol taper	6,890/3,493	
Oral NTX alone	930/3,420	
Vivitrol alone	6,639/3,009	
Annual costs of other health care services (2013$):		
In treatment	10,391	White, 2005; Baser, 2011
Out of treatment, relapsed	20,111	White, 2005
Out of treatment, drug-free	9,007	WHO, 2013
Annual social costs of opioid dependence (2013$):		Wall, 2000
Law enforcement	47,984	
Victimization	50,471	
Productivity loss	7,878	

*Proportion of patients out of treatment and drug free set as constant (18.5%) based on proportion equal to relapse for methadone; reduced for each treatment strategy by rate of mortality
MMT: methadone maintenance treatment; BMT: buprenorphine maintenance treatment; NTX: naltrexone

Costs expressed in other currencies were converted to U.S. dollar amounts using prevailing exchange rates in the year in which they were reported. All costs are presented as 2013 U.S. dollar amounts; we adjusted these when necessary using the medical care component of the U.S. Consumer Price Index (Bureau of Labor Statistics, 2014).

Key Model Assumptions

Major assumptions made for this analysis, including those previously described, are noted in Table 9 below. Importantly, we assumed that all clinical outcomes were associated with the initial treatment strategy only; we did not assume switching between strategies (other than in the tapering strategy, which by definition involves a change in treatment modality), nor did we model the impact of readmission to treatment for patients who had relapsed. Both of these approaches would have necessitated complex "time-to-event" analyses for which detailed observational data are unavailable. We also did not include any information on competing mortality risks given the short-term nature of the model. Finally, we did not include any estimate of other "social" costs, such as caregiver burden, in our calculations of overall costs. Nonetheless, the components of cost included in this analysis are consistent with those of other major economic evaluations in the field.

Table 9. Key assumptions for cohort model of opioid dependence treatment.

Assumption	Rationale
Outcomes driven by initial treatment strategy only	*Lack of detailed, time-dependent data on therapy switch and/or readmission to treatment*
Competing mortality risks (beyond those related to in- vs. out-of-treatment status)	*Unlikely to affect outcomes in short-term model*
Certain social costs (e.g., caregiver burden) not included	*Cost components consistent with other published economic evaluations*
Absolute increase in retention of 5% for taper to Vivitrol vs. oral naltrexone	*Assumption; no available data*
Rate of "drug-free" patients constant (modifiable only by differential rate of death)	*Counterintuitive to assume that higher rates of treatment "drop out" would translate to higher rates of drug-free individuals*
No benefit of methadone in reducing productivity loss	*Assumption that need for daily in-person dosing and intensive treatment would counteract any potential for improved employment*

7.2 Cohort Model: Results

Two-year outcomes and costs among 1,000 hypothetical individuals entering treatment can be found in Table 10 on the following page. Model results are first presented for maintenance treatment with methadone and Suboxone as the two most common approaches, followed by alternative strategies in descending order of effectiveness.

The model results suggest that, of 1,000 initial patients, approximately 630 receiving methadone maintenance would be retained in treatment after two years versus approximately 520 for Suboxone maintenance. The naltrexone tapering strategies would retain 500-550 of the 1,000 patients. Use of Vivitrol or oral naltrexone alone produced the lowest retention rates of approximately 420 and 280 per 1,000 respectively. Consistent with the relative rankings of treatment retention outcomes, methadone maintenance produced the lowest relapse rate (~190 per 1,000), while oral naltrexone produced the highest (540 per 1,000). Rates of death were <1% for all strategies except Vivitrol and oral naltrexone alone (12-16 per 1,000), reflecting higher mortality rates associated with relapse.

Two-year costs of methadone drug therapy (~$700) were much lower than drug costs for all other strategies except oral naltrexone alone. In contrast, costs of other substance abuse services for methadone maintenance (~$14,000) were 2-7 times higher than costs of maintenance with other strategies, reflecting the regulated intensity of methadone-based care. This difference was counteracted somewhat by lower costs of other health care services for methadone versus all other strategies, due to greater levels of treatment retention (the costs of other health care services among patients in opioid dependence treatment are 50% lower than the costs among those out of treatment).

Putting together drug therapy costs, the costs for other substance abuse services, and the costs of all other health care services, the sum of all two-year health care costs did not substantially differ across maintenance treatment strategies (range: $32,000 - $39,000). Health care costs were lowest for the Suboxone-oral naltrexone taper, due to the generic availability of naltrexone, the short-term duration of Suboxone treatment, and lower intensity of other substance abuse services for patients receiving naltrexone versus continued maintenance treatment. Health care costs were highest for methadone, as reductions in the costs of other health care services only offset a portion of the higher costs of more intensive substance abuse treatment. While not reflected in the table, the two-year health care costs for relapsed or dead patients were nearly $40,000, meaning that costs of substance abuse treatment were entirely offset with _any_ form of treatment.

When social costs were considered as well, maintenance therapy options appeared to produce significant overall cost-savings. The two-year social costs associated with opioid dependence are estimated to be over $200,000, 4-5 times greater than the cost of health care services for each strategy. All versions of opioid dependence treatment reduced social costs substantially compared

to no treatment, but methadone stands out with 10-35% reductions in social costs over all alternative approaches due to its higher retention rates. As a result, total (health care plus social) costs were lower for methadone maintenance ($131,000) than for any other treatment strategy. Total costs were similar among the maintenance and tapering strategies, but were substantially higher for Vivitrol ($157,000) and oral naltrexone ($175,000) alone because they were the least effective. It should be noted again, however, that the total cost figures for all treatment strategies are lower than the total costs estimated for an individual with opioid dependence who is not initiated on _any_ form of treatment.

Table 10. Two-year outcomes and costs among 1,000 hypothetical patients treated for opioid dependence.

Outcome/Cost	MMT	BMT	SUB/VIV Taper	SUB/Oral NTX Taper	Vivitrol Alone	Oral NTX Alone
Treatment outcome (per 1,000):						
In treatment	630	523	550	500	416	277
Relapsed	185	292	265	315	400	538
Drug –free	177	176	177	176	173	169
Died	8	9	8	9	12	16
Cost ($, per patient):						
Drug therapy	699	3,655	8,553	1,249	6,585	665
Other SA services	14,017	7,043	4,146	4,297	2,985	2,446
Other health care	23,926	25,993	25,454	26,441	28,109	30,844
**SUBTOTAL**	_**38,642**_	_**36,691**_	_**38,153**_	_**31,988**_	_**37,679**_	_**33,954**_
Social costs	92,068	102,337	98,033	105,917	119,239	141,076
**TOTAL**	_**130,710**_	_**139,028**_	_**136,187**_	_**137,905**_	_**156,918**_	_**175,030**_

MMT: methadone maintenance treatment; BMT: buprenorphine maintenance treatment; NTX: naltrexone; SUB: Suboxone; VIV: Vivitrol

Table 11 on the following page summarizes our assessment of the cost-effectiveness of these opioid dependence treatment strategies, focusing on both the cost per additional relapse averted and the cost per additional death averted. The universal referent treatment was oral naltrexone alone as the alternative with the lowest retention rate; other comparisons of interest (e.g., methadone versus Suboxone maintenance) were conducted if feasible. Note that the available ratios are based on health care costs only; when total costs are considered, the most effective strategies are also the least costly, which precludes calculation of cost-effectiveness ratios.

Cost-effectiveness of different maintenance options (considering health care costs only)

Comparisons of each treatment strategy to oral naltrexone alone yielded relatively similar estimates of the cost per additional relapse averted for methadone maintenance ($13,000), Suboxone

maintenance ($11,000), and Suboxone stabilization followed by a taper to Vivitrol ($15,000). The oral naltrexone taper strategy was both less costly and more effective than oral naltrexone alone. Finally, the cost per relapse averted for Vivitrol alone was approximately $27,000, as it was approximately $4,000 more costly and prevented fewer relapses than the maintenance and taper strategies.

Table 11. Comparative cost-effectiveness of opioid dependence treatments (selected comparisons).

Outcome/Cost	MMT	BMT	SUB/VIV Taper	SUB/Oral NTX Taper	Vivitrol Alone
Health Care Costs Only					
vs. oral NTX alone:					
$ per relapse averted	$13,000	$11,000	$15,000	Less costly, more effective	$27,000
$ per death averted	$608,000	$395,000	$531,000	Less costly, more effective	$927,000
MMT vs. BMT:					
$ per relapse averted	$18,000	---	---	---	---
$ per death averted	$2.5 m	---	---	---	---
VIV vs. oral NTX Taper:					
$ per relapse averted	---	---	$123,000	---	---
$ per death averted	---	---	$4.3 m	---	---
Total Costs					
vs. oral NTX alone:					
$ per relapse averted	Less costly, more effective	Less costly, more effective	Less costly, more effective	Less costly, more effective	Less costly, more effective
$ per death averted	Less costly, more effective	Less costly, more effective	Less costly, more effective	Less costly, more effective	Less costly, more effective
MMT vs. BMT:					
$ per relapse averted	Less costly, more effective	---	---	---	---
$ per death averted	Less costly, more effective	---	---	---	---
VIV vs. oral NTX Taper:					
$ per relapse averted	---	---	Less costly, more effective	---	---
$ per death averted	---	---	Less costly, more effective	---	---

 MMT: methadone maintenance treatment; BMT: buprenorphine maintenance treatment; NTX: naltrexone; SUB: Suboxone; VIV: Vivitrol

Estimates of the cost per death averted were much higher ($400,000 - $900,000), as absolute differences in mortality were very small across the strategies. It is worth noting again that mortality estimates in this study were restricted to deaths related to substance abuse for those out of treatment and to treatment-related deaths (overdoses) for those in maintenance treatment. In addition, no excess mortality was assumed while patients were on oral naltrexone or Vivitrol.

Comparisons of methadone to Suboxone maintenance yielded estimates of $18,000 per relapse averted and $2.5 million per death averted, as health care costs with methadone were $2,000 greater and relapse rates differed by ~10% in favor of methadone. Comparisons of tapering strategies with Vivitrol versus oral naltrexone yielded cost-effectiveness estimates of $123,000 per relapse averted and $4.3 million per death averted.

Cost-effectiveness of different maintenance options (considering total costs)

As mentioned previously, inclusion of social costs in a total cost calculation changes the picture of these comparisons. When all costs are considered, _all_ other treatment strategies prevent more relapses, result in fewer deaths, and have lower costs than oral naltrexone alone. Methadone maintenance is also somewhat more effective and less expensive than Suboxone maintenance, and a tapering strategy using Vivitrol has better clinical results and slightly lower costs than an oral naltrexone tapering strategy.

While adolescents are clearly an important subpopulation, data were too scarce to populate a complete model focusing only on this group. Nevertheless, it seems reasonable to conclude that the economic benefits seen in this model would be increased in adolescents given that crime-based costs and long-term productivity losses may be even greater in teenagers not receiving adequate treatment.

7.3 Budget Impact Analysis: Methods

The budget impact analysis was also conducted over a two-year period. The population under consideration was limited to those individuals with opioid dependence who are either receiving treatment or who need but are _not_ receiving any treatment (i.e., patients out of treatment but drug-free were not considered). We generated estimates of the numbers of treated and untreated patients for each New England state based on data collected in the 2009-2012 rounds of the National Survey of Drug Use and Health (NSDUH) (SAMHSA, 2013c). Information was collected for both adolescents (age 12-17) and adults (18+).

At baseline, we assumed that treated patients would receive maintenance with either methadone or Suboxone, and weighted the proportion receiving each based on 2012 data from SAMHSA's National Survey of Substance Abuse Treatment Services (N-SSATS) (SAMHSA, 2013b). Costs for treated patients were identical to those generated for the cohort model (including social costs) and were also weighted by the proportion of methadone versus Suboxone recipients. We assumed that the costs for untreated patients would be equal to cohort model costs for relapsed patients.

We also generated estimates of the number of deaths that would occur for patients in and out of treatment based on the sources used in the cohort model. Mortality rates for patients in treatment were also weighted by the maintenance modality received.

We then assessed the effects that moving untreated patients into treatment would have on deaths and total costs in the region over a two-year period. All newly-treated patients were assumed to be treated with Suboxone, as we felt that expanded access to Suboxone was more realistic than methadone expansion in the current regulatory environment. Consistent with estimates from the cohort model, slightly more than 50% of these newly treated patients would be expected to remain in treatment after two years. Rates of increase in the proportion of individuals receiving treatment ranged from 5-50%.

7.4 Budget Impact Analysis: Results

Currently, it is estimated that, of the 133,000 New Englanders with opioid dependence, 40,000 receive maintenance treatment. Moving 10% of untreated patients into treatment would increase the size of the population retained in treatment by 12%, to 45,000. Moving 50% into treatment would increase the treated population by over 60%, to 64,000.

Estimates of the numbers of substance abuse-related deaths for New England are presented in Figure 6 on the following page for adolescents, adults, and in total. At baseline, approximately 2,800 deaths would be expected to occur in a two-year period, 450 of which would be among adolescents. Expanding treatment access by 10% would reduce the death count by nearly 150 (30 of whom would be adolescents). Aggressive expansion would produce more substantial results. For example, a 50% expansion would be expected to save nearly 700 lives in two years, including over 100 adolescents.

Figure 6. Impact of expanding access to maintenance treatment on substance-abuse related deaths in New England, over a two-year timeframe.
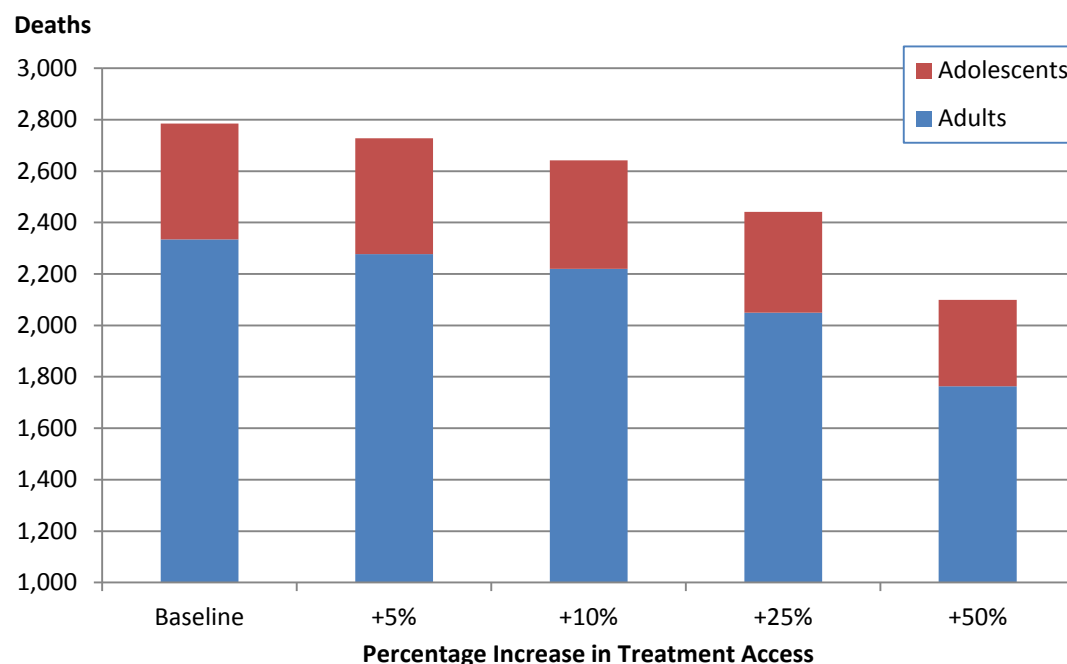

When considering health care costs alone, the additional costs associated with expanding access to maintenance treatment are essentially fully offset by savings in the cost of other health care services. Current health care costs for all individuals with opioid dependence are estimated to total approximately $5.2 billion for the region ($1.5 and $3.7 billion for treated and untreated individuals, respectively). Moving 5% of untreated individuals into treatment would increase treatment expenditures by $73 million, but result in reductions in the cost of other health care services by about $80 million. Greater levels of expansion would result in greater net cost savings. For example, a 10% expansion would increase treatment costs by $183 million, but reductions in the cost of other health care services of nearly $200 million would result in net cost savings of $15 million. A 25% expansion would more than double net cost savings to approximately $35 million.

The effects of expanded access to maintenance treatment on _total_ (health care plus social) costs are more dramatic, as presented in Figure 7 on the following page. At baseline, total costs of opioid dependence in the region are estimated to be approximately $29 billion over two years, 81% of which is generated by dependent individuals not currently in treatment. At each level of treatment expansion, net savings are substantial, given that costs of health care services are already offset by treatment and reductions in social costs are pronounced. For example, expanding treatment by as little as 5% would decrease total costs for the entire population of individuals with opioid dependence by approximately $220 million. A 25% expansion would decrease overall population costs by approximately $1.3 billion, and a 50% expansion would decrease overall costs by $2.6

billion. Put another way, each additional health care dollar spent on expanding maintenance treatment would return approximately $1.80 in savings. Importantly, all of these savings are realized even under the assumption that only slightly more than 50% of individuals newly-accessing Suboxone treatment would remain in treatment after two years.

While the budget impact of expanding treatment was not estimated separately for adolescents versus adults, patients aged 12-17 are estimated to represent approximately 20% of the treated population in the NSDUH survey data (SAMHSA, 2013c). If cost levels are assumed to be similar for both subpopulations, a 5% expansion in the number of adolescents treated would produce approximately $44 million in savings for these patients.

Figure 7. Total costs (health care plus social costs of opioid dependence) of persons with opioid dependence in New England, assuming different levels of increase in percentage of individuals brought into treatment. Total costs go down with each incremental increase in the percentage of patients in medication-assisted treatment programs.

Total Cost (Billions)

Increase in Percentage of All Individuals with Opioid Dependence in Treatment
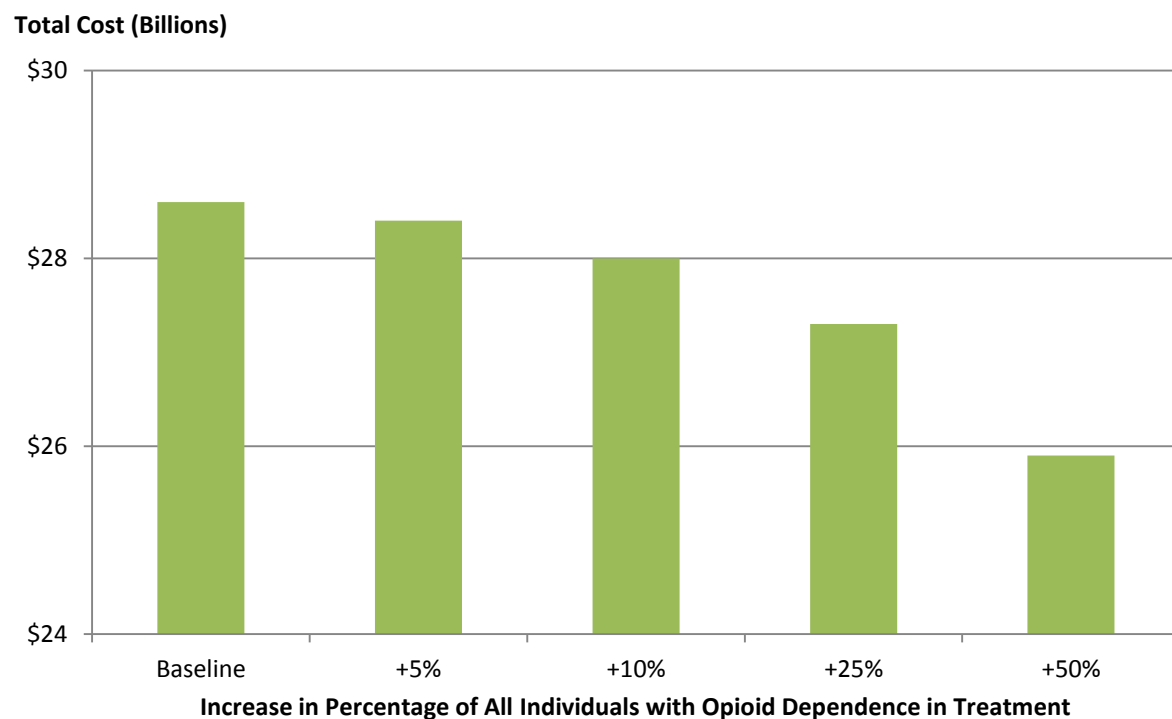
7.5 Summary

The findings of the simulation model suggest that maintenance treatment with either methadone or Suboxone retains more patients in treatment over a two-year period in comparison to use of either oral or injectable naltrexone for abstinence treatment alone. Methadone and Suboxone maintenance have very similar outcomes and overall health care costs. Compared to use of oral

naltrexone alone, maintenance treatment increases the cost of health care services (i.e., substance abuse and other health care services) by $3,000-$5,000, but estimates of the cost per additional relapse averted are relatively low: <$15,000 in our analysis. As a benchmark, published estimates of the cost per relapse in other mental health conditions (e.g., depression, schizophrenia) have considered estimates <$50,000 per relapse averted to be a cost-effective use of resources (Scott, 2003; Citrome, 2014; Mihalopoulos, 2004).

When the "social" costs of law enforcement, crime victimization, and lost productivity were included in our estimates, maintenance treatment becomes both more effective and less costly than abstinence treatment with oral naltrexone. For example, methadone would still be cost-saving overall versus oral naltrexone on a societal basis even if substance abuse services were provided *free of charge*.

Our findings for strategies involving stabilization with short-term Suboxone followed by a taper to either oral naltrexone or Vivitrol are also intriguing, as these strategies are estimated to produce retention figures comparable to methadone maintenance but without requirements for continued opioid replacement. These findings should be interpreted with great caution, however, as our estimate of the effectiveness of oral naltrexone was based on a single, small (n=70) RCT (Sigmon, 2013), and Vivitrol's retention benefits were assumed in the absence of published data on its use in a tapering strategy. However, it is important to note that treatment with <u>any</u> of these strategies reduces costs in comparison to no treatment. The two-year costs of untreated opioid dependence are estimated to total nearly $250,000 per untreated individual; these costs are reduced by nearly half with maintenance treatment strategies and even by 30% with the least effective strategy considered (oral naltrexone alone).

The impact of moving untreated individuals into treatment was further confirmed by our budgetary impact analysis. The total health care plus social costs of opioid dependence are estimated to total $29 billion annually in the region, 81% of which is generated by untreated patients. In addition, nearly 3,000 substance abuse-related deaths occur over a two-year period. Any expansion of the treated population will produce cost reductions for the region of approximately $1.80 for every dollar invested over a two-year period. If 50% of currently untreated patients had treatment available to them, cost savings for the region would be nearly $3 billion and nearly 700 lives would be saved, 100 of which would be adolescents. It is important to remember that estimated reductions in both the number of substance abuse-related deaths and costs occurred even with an assumed treatment retention rate for Suboxone of only slightly more than 50%.

We note some limitations of our analysis. First, we assumed that all outcomes would be driven by initial treatment; in reality, some patients experiencing relapse would re-enter treatment within the two-year period and be treated successfully. There are insufficient data on the success of retreatment for all of the strategies of interest, so any estimate would involve significant conjecture

on our part. Nonetheless, our estimates of the long-term outcomes of initial maintenance treatment are consistent with those of other cohort studies in the literature (Comiskey, 2010).

Also, as noted earlier in the report, the estimates of retention in treatment for methadone and Suboxone were obtained from a meta-analysis of RCTs that involved provision of both medications in the same treatment setting and with identical levels of available support services. This does not reflect current practice in the U.S., where methadone is delivered in a tightly-controlled environment with substantial oversight and support services available, and Suboxone is typically provided in an office-based setting with fewer controls and inconsistent levels of support. Retention in typical practice may therefore vary significantly, and treatment setting may influence this result as much or more than the medication delivered.

Our estimates of health care and social costs come from disparate sources that may not be fully generalizable to the region. For example, social costs were obtained from a landmark study, but one nevertheless conducted in Canada; this study also included an estimate of health care costs, but we chose to exclude it and focus on a U.S.-based study for that component. However, our results are robust to changes in all cost estimates. For example, reducing the social cost estimates by half does not change the order of findings for each treatment strategy, and still produces net cost savings of nearly $900 million if treatment is expanded to 50% of currently untreated persons in New England.

8. CEPAC Votes and Deliberation

During CEPAC public meetings, the Council deliberates and votes on key questions related to the review of the evidence produced by the Institute for Clinical and Economic Review (ICER). At the June 20, 2014 meeting, CEPAC discussed and placed votes assessing the comparative clinical effectiveness and value of various treatment approaches addressed in this evidence review. The key questions are developed by ICER for each appraisal, with input from the CEPAC Advisory Board to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice and medical policy decisions. Ex-officio CEPAC members participate fully in the discussion of the evidence but do not vote. The voting results are presented below, as well as key comments reflecting the considerations mentioned by CEPAC during the voting process.

When voting on comparative value, CEPAC was asked to assume the perspective of a state Medicaid program that must make resource decisions within a relatively fixed budget for care. For each question on value, CEPAC placed two separate votes: one considering only the direct medical costs associated with each intervention, and one considering both the societal and medical costs associated with each intervention. CEPAC is not given prescribed boundaries or thresholds for budget impact or incremental cost-effectiveness ratios to guide its judgment of low, reasonable, or high value. However, CEPAC did make use of a series of value categories designed by ICER to assist the Council in assigning an overall value rating (see Figure 8 below). CEPAC members who vote "no" on comparative clinical effectiveness are designated to a special "low" value vote category for lack of evidence to demonstrate comparative clinical effectiveness.

Figure 8: Value Categories for CEPAC's votes

Low Value	Reasonable/Comparable Value	High Value
Worse outcomes; Higher or equivalent cost	Worse outcomes; Lower cost	Comparable outcomes; Lower cost
Comparable outcomes; Higher costs	Comparable outcomes; Comparable cost	Promising but inconclusive evidence of better outcomes; Lower cost
Promising but inconclusive evidence of better outcomes; Higher cost	Promising but inconclusive evidence of better outcomes; Comparable cost	Better outcomes; Lower or comparable cost
Better outcomes; Too high a cost	Better outcomes; Reasonable higher cost	Better outcomes; Slightly higher cost

Comparative Clinical Effectiveness and Value: Medication-assisted Maintenance Therapy vs. Detoxification[1]

1. Is the evidence adequate to demonstrate that long-term maintenance therapy with any medication is superior to short-term detoxification for most patients with opioid dependence?

   CEPAC Vote:

   12 yes (92%)   1 no (8%)

   Comments: CEPAC members who voted "yes" cited the strong quality of evidence for maintenance therapy supported by the Cochrane review, as well as testimony from clinical experts that reinforced the conclusions of the research. The CEPAC member who voted "no" stated that while there is overwhelming evidence regarding the efficacy of long-term maintenance therapy, there is uncertainty of its superiority for "most" patients. The Council member noted that the existing evidence primarily looked at relatively short taper periods, and it may be that longer periods are needed for patient success than those examined. Additionally, the Council member argued that the existing evidence does not adequately identify subpopulations that might respond differently to the various treatment protocols.

2. From the perspective of a state Medicaid program, would you judge the value of long-term maintenance therapy with any medication compared to detoxification to be high, reasonable, or low?

   CEPAC Vote:

   Considering only direct medical costs:

   10 high (77%)   1 reasonable (8%)   1 low (8%)   1 abstain (8%)

   Considering medical costs and societal costs together:

   11 high (85%)   1 reasonable (8%)   1 low (8%)

---

[1] The terminology "detoxification" has been replaced with short-term "opioid withdrawal management" elsewhere in this document based on feedback received from the American Society of Addiction Medicine that this terminology is more clinically accurate. We retained the use of "detoxification" in this section since this was the exact wording presented to CEPAC at the time of voting.

Comments: CEPAC members who voted that long-term maintenance therapy has "high" comparative value agreed that compared to detoxification, maintenance therapy demonstrates "better outcomes at a low or comparable cost". Council members provided the same rationale when considering only health care costs and when considering both medical and societal costs together.

3. From the perspective of a state Medicaid program, would you judge the value of expanded access to maintenance therapy with any medication versus the status quo to be high, reasonable, or low?

   CEPAC Vote:

   Considering only direct medical costs:

   9 high (69%)   3 reasonable (23%)   1 low (8%)

   Considering medical and societal costs together:

   12 high (85%)   1 low (8%)

   Comments: CEPAC members who voted that expanded access to maintenance therapy has "high" comparative value also categorized their vote as "better outcomes at a low or comparable cost," both when considering medical costs alone and together with societal costs.

Comparative Clinical Effectiveness and Value: Methadone vs. Suboxone

4. Is the evidence adequate to demonstrate that maintenance therapy with methadone is at least functionally equivalent to maintenance with Suboxone in treating patients with opioid dependence?

   CEPAC Vote:

   12 yes (92%)   1 no (8%)

   Comments: The Council member who voted "no" cited concerns that the appropriate dosing levels may not have been achieved in the available studies, as well as potential differences in treatment setting that may have confounded results.

5. From the perspective of a state Medicaid program, would you judge the value of methadone treatment compared to Suboxone treatment to be high, reasonable, or low?

Considering only direct medical costs:

2 high (15%) | **8 reasonable (62%)** | 2 low (15%) | 1 abstain (8%)

Considering medical and societal costs together:

3 high (23%) | **8 reasonable (62%)** | 1 low (8%) | 1 abstain (8%)

Comments: The majority of CEPAC members who voted that methadone has "reasonable" value indicated that it has "comparable outcomes and comparable costs" when compared to Suboxone, both when considering medical costs alone or medical and societal costs combined. The CEPAC member who voted that methadone is at least functionally equivalent to Suboxone but has low value reasoned that the costs of generic Suboxone will likely drop overtime, impacting the overall budget impact for this treatment.

Comparative Clinical Effectiveness: Vivitrol vs. Oral Naltrexone

6. Among patients who can be successfully tapered from maintenance therapy with any medication (e.g. Suboxone, methadone.) to opioid antagonist treatment, is the evidence adequate to demonstrate that Vivitrol is as good as or superior to oral naltrexone for patients with opioid dependence?

   CEPAC Vote:

   1 yes (8%) | **12 no (92%)**

   Comments: CEPAC emphasized that this vote of inadequate evidence does not imply that Vivitrol is an ineffective treatment option, or that access to it should therefore be restricted. Rather, the strength of evidence is inadequate to determine the effectiveness of Vivitrol relative to oral naltrexone, and additional research is needed to better establish its role in the management of patients with opioid dependence.

   Note: CEPAC did not place a vote comparing the value of Vivitrol to oral naltrexone since a majority of the Council did not deem the evidence adequate to demonstrate the comparative clinical effectiveness between these two options.

Broader Considerations for Equity

7. Are there any considerations related to public health, equity, disparities in access or outcomes for specific patient populations, or other social values that should also be considered in medical policies related to the use of methadone, Suboxone, Vivitrol, or oral naltrexone?

   Comments: Council members emphasized that concerns for public health, equity, and disparities are major issues within this topic and policy solutions must address system capacity and access in order to better connect patients to effective treatment. Council members suggested that future research attempt to capture how patients perform with treatment over time, since it often takes individuals with addiction multiple attempts at treatment to succeed. CEPAC also cited the need for more research assessing outcomes of maintenance therapy for adolescents to determine whether or for which young adults MAT is the best choice. Council members also noted the challenge of voting on the comparative value and effectiveness of different approaches when for so many patients treatment choice is based on regulation and availability rather than evidence-based policies or decision-making.

9. Recommendations to Guide Practice and Policy in New England

Before the CEPAC public meeting, ICER staff conducted unstructured interviews with 15 policy experts to explore real world perspectives on recent practice and delivery system innovations, potential policy changes, and other opportunities to improve how patients utilize and access treatment for opioid addiction in New England. Interviewees came from each New England state and leading national organizations, with positions in OTPs, patient advocacy organizations, state agencies, clinical societies, academic institutions, and office-based addiction treatment centers.

The results from these interviews were used to frame a set of policy and practice recommendations that informed a moderated Policy Expert Roundtable discussion during the CEPAC meeting between Council members and a panel of regional policy experts. Panelists included clinical experts, health insurers, state agency representatives, and a patient advocate who discussed with CEPAC members various policy options for addressing treatment quality, health system capacity, and access to care in New England. The participants in the Roundtable discussion are shown below:

Rebecca Boss, MA	Rhode Island	Deputy Director, Department of Behavioral Healthcare, Developmental Disabilities and Hospitals (BHDDH), State of Rhode Island
John Brooklyn, MD	Vermont	Physician, Community Health Centers of Burlington
Barbara Cimaglio	Vermont	Deputy Commissioner, Alcohol and Drug Abuse Programs, State of Vermont
TJ Donovan, JD	Vermont	State Attorney for Chittenden County, State of Vermont
Kevin Flanigan, MD	Maine	Medical Director, MaineCare Services, State of Maine
John Hammel, MD	New Hampshire & Vermont	Director, Substance Abuse Services, White River Junction VA
Lisa Muré, MEd, CPS	New Hampshire	Director for Prevention, New Hampshire Center for Excellence Senior Consultant, Community Health Institute
Stacey Sigmon, PhD	Vermont	Associate Professor of Psychiatry, University of Vermont Director, The Chittenden Clinic
Jeff Simmons, MD	Massachusetts	Medical Director for Behavioral Health, Blue Cross Blue Shield of Massachusetts
Tom Simpatico, MD	Vermont	Chief Medical Officer, Vermont Department of Health Access
Jacquelyn Starer, MD, FACOG, FASAM	Massachusetts	Associate Attending Physician, Faulkner Hospital Associate Director, Physician Health Services, Inc. President, Massachusetts Chapter of ASAM
Joycelyn Woods, MA, CMA	National	Executive Director, National Alliance for Medication Assisted Recovery

Combining the insights gained from the earlier policy expert interviews with the votes on the evidence by CEPAC and the ensuing Policy Expert Roundtable discussion, the following set of recommendations are presented to guide the application of evidence to improve opioid dependence management practice and policy in New England. The discussion reflected multiple perspectives and opinions and therefore none of the recommendations should be taken as a consensus view held by all participants.

1. Coordinated efforts are needed across New England to improve access to opioid dependence treatment for the large number of individuals who lack adequate access to high quality care options.

There was sentiment among the stakeholders interviewed that restrictions in the area of addiction medicine are disproportionate to regulations in all other fields of medicine and serve to reinforce stigma and prevent the provision of high quality, responsive treatment. Experts felt strongly that regulations that isolate treatment with methadone from the rest of clinical care and place restrictions on the number of patients served with buprenorphine-containing medications must be relaxed to address the overwhelming need for opioid addiction services in New England.

Some clinical experts suggested extending methadone treatment to office-based use, as described in the King and Harris 2006 pilot studies in Section 6, as a means of expanding access to care. Some Roundtable panelists feared that the diversion risks associated with methadone made office-based methadone programs too risky politically because if implementation went poorly it could potentially discredit the progress that has been made elsewhere to expand access to this treatment. The patient advocate representative on the Roundtable emphasized, however, the importance for long-term stable patients to be able to access treatment in private settings where there is less interaction with other patients with addiction. Clinical experts on the Roundtable also stated that the vast majority of patients in treatment use medication responsibly, and that concerns for prescription abuse are secondary to concerns for access.

CEPAC and Roundtable panelists also underscored the need for more resources to develop the skills and expertise of DATA 2000 waivered physicians in order to increase their capacity and willingness to serve more patients with addiction. Even with excess demand, many DATA 2000 waivered physicians are not prescribing to capacity or at all. According to the experts interviewed, some practices abstain from treating more patients with addiction due to insufficient resources to address the full scope of behavioral and psychosocial needs associated with substance abuse disorder, where others fear risk of diversion and potential abuse of medications. Primary care providers in particular often feel undertrained or unsupported to take on new patients with addiction. Further dissemination of standardized guidelines and protocols is therefore needed to help physicians make use of evidence-based

practices and reduce practice variation. CEPAC members agreed with Roundtable panelists that provider organizations and clinical societies should develop stronger peer networks to help organizations and specialties treating patients with addiction manage care more effectively.

To expand access to Suboxone and buprenorphine, policy experts and CEPAC also agreed that limits on the number of patients that can be treated by qualified clinical teams should be relaxed in appropriate clinical settings. Experts acknowledged, however, that if clinical practices are allowed to increase the volume of patients receiving buprenorphine medications that measures should be taken to ensure that these practices are part of well-organized group settings that can provide adequate structure and support for physicians and other clinicians. Some clinical experts on the Roundtable also recommended that the scope of DATA 2000 be broadened to allow qualified nurse practitioners to prescribe buprenorphine-containing medications. Clinical experts interviewed for this review argued that current prescribing restrictions serve to reinforce the need for a black market for Suboxone where patients can self-medicate or at least replace the use of heroin and other long-acting drugs.

Policy experts also recognized that the highly restrictive entry criteria for some MAT programs that add another barrier to entry for patients should be revised to improve access to pharmacotherapy options. For example, in Maine some federally-qualified health centers (FQHCs) impose rules that prohibit practices from treating patients that do not already receive care within the FQHC, greatly limiting the number of providers available to patients with opioid dependence.

CEPAC agreed with policy experts that individuals should be screened for opioid addiction in primary care settings in order to support early interventions for recovery. Primary care providers should be encouraged and trained to screen for addiction during general exams, particularly when screening or diagnosing psychiatric disorders, which often present as co-morbidities of substance abuse.

> ***Policy/Practice Option: Utilizing physician assistants and nurse practitioners to increase physician-prescribing capacity***
>
> In Massachusetts, a network of office-based addiction treatment programs called Clean Slate Centers has attempted to increase the number of DATA 2000 waivered physicians prescribing at capacity. According to this model, licensed prescribers work as part-time physicians who treat patients with Vivitrol or Suboxone. In addition to prescribing treatment, these physicians review patient charts, conduct group medical visits, and answer questions from staff regarding patient management. The model also utilizes full-time clinical and supportive staff to manage all other aspects of care, allowing physicians to increase their prescribing capacity beyond their main clinic. The goal of this approach is to "remove treatment from busy, over-stretched primary care settings, and provide the infrastructure necessary for primary care physicians and psychiatrists to collaborate with behavioral health providers and experienced full-time clinicians so that patients are able to receive the comprehensive care necessary to achieve recovery."

> ***Policy/Practice Option: Use of technology and telemedicine to expand access to treatment***
>
> Researchers in Vermont have recently received National Institutes of Health (NIH) funding to make use of a new computerized device called the Med-O-Wheel to help patients on treatment waiting lists access some level of medication-assisted treatment. The device is for take-home use and dispenses a single dose of buprenorphine for a limited two-hour window each day, making it difficult for patients to abuse medication. The transparent back to the device also allows physicians to monitor diversion. Patients receiving buprenorphine through the Med-O-Wheel will also receive telephone-based monitoring and support that provides daily check-ins, documents patient cravings, and refers patients to other needed resources. The goal of this model is to expand patient access by offering an alternative safe delivery option for medication, thereby increasing the willingness of physicians with concerns for diversion to provide treatment.

2. Develop innovative strategies that connect individuals in the criminal justice system to treatment for their addiction.

Clinical and policy experts discussed at length during the in-person meeting the need for more efficient referral pathways for connecting individuals with non-violent addiction-related crimes to treatment. Roundtable panelists noted the challenges for patients leaving the correction system who are wait-listed for treatment at OTPs and are unable to find a primary care physician to provide treatment for their addiction, increasing the risk for recidivism. Stakeholders involved in the criminal justice system emphasized that solutions to addiction cannot be achieved in penal institutions alone and therefore stronger integration between the

criminal justice and clinical systems is required. CEPAC and Roundtable panelists recommended that policymakers establish jail diversion programs in which non-violent offenders are assessed for addiction and referred to appropriate treatment in lieu of incarceration. Some states in New England, like Vermont, Massachusetts, and Connecticut, have developed similar models and pilot programs for jail diversion.

Policy experts on the Roundtable also suggested expanding treatment to incarcerated individuals by providing Suboxone or buprenorphine to individuals who will be in prison for more than a short period and making MAT available to individuals who are waiting for sentencing. Clinical experts and patient advocates on the Roundtable noted that even though naltrexone has been recognized as an opportunity to support opioid-dependent individuals at risk for relapse who are exiting the controlled environment of the corrections system, that it should not be used indiscriminately in this population. Many individuals who are believed to be opiate-free are not, and some individuals that exit incarceration with Vivitrol are likely to never return to treatment and will be at higher risk for overdose.

Policy/Practice Option: Jail diversion for low-level drug offenses
The LEAD Model is a pilot program in Seattle, WA that diverts low-level drug offenders that meet certain thresholds into community-based support services and treatment programs instead of prison. The LEAD model is unique to other jail diversion programs in that diversion is established at the "pre-booking" stage, or prior to when offenses are charged to avoid the legal costs associated with court trials, etc. Individuals participating in the program are connected with case management and counseling services immediately. Addiction services for LEAD participants are provided through a formal contract with a community-based organization that specialized in outreach services to chronically homeless and dependent adults. The LEAD program is the result of multi-stakeholder collaborative between representatives from the criminal justice system, the legal system, local and state governments, and community organizations. The pilot is fully funded through foundation and grant support and the model for the pilot is based off of similar programs in the United Kingdom that have been employed broadly throughout the country.

---

3. Clinicians should individualize treatment, including decisions about medication choice, counseling, and supportive social services, according to an initial assessment of a patient's baseline severity and unique health care needs. For most patients, MAT will be more effective than attempts at short-term managed withdrawal. However, short-term managed withdrawal may be a reasonable consideration for a subset of patients with relatively short-term histories of addiction and less intravenous opioid use.

Experts and CEPAC members agreed that the treatment needs for each patient with opioid dependence are different, and therefore clinicians must adequately assess patients to determine the level, intensity, and modality of treatment most appropriate for his or her unique circumstances. A comprehensive assessment that determines a patient's overall health risk; presence of co-morbid disorders or conditions, including chronic pain or co-occurring substance abuse; social and behavioral challenges; and extent of dependence is considered crucial to adequately refer patients to necessary services and develop a treatment plan individualized to meet the patient's needs. Clinicians providing the initial assessment should be qualified and adequately trained in addiction disorders.

Given how broadly patient expectations and treatment objectives vary, some experts suggested that treatment plans involve short-term goal setting with the patient using a structured treatment protocol designed to achieve those objectives. Experts noted that treatment plans should evolve based on a patient's level of engagement and stage of change, and therefore flexibility with treatment goals is essential.

Since opioid dependence is a chronic relapsing condition, it requires a long-term treatment approach. CEPAC agreed with clinical and policy experts that maintenance therapy is an integral component of treatment and patients rarely succeed with short-term opioid withdrawal management alone. Clinical experts on the Roundtable emphasized the danger of policies that require individuals to attempt opioid withdrawal first before receiving MAT, as patients are at very high risk of overdose once their tolerance has decreased. However, short-term managed withdrawal may be a reasonable consideration for a subset of patients with relatively short-term histories of addiction and less intravenous opioid use.

CEPAC and Roundtable panelists agreed that the results of a patient's initial assessment and evaluation should determine the medication selected for treatment. Advocates and providers noted that patients with higher opioid tolerance, longer histories of use, and unstable living situations might benefit from a more structured program with methadone. Conversely, individuals with mild-to-moderate levels of dependence and greater life stability who require less treatment oversight may be considered for first-line treatment with buprenorphine-containing medications. Some clinical experts also suggested that naltrexone may be an effective first-line treatment option for individuals with short histories of opioid use who access treatment early. CEPAC members and Policy Roundtable panelists recommended that specialty societies, states, and other stakeholders work collaboratively to develop evidence-based screening tools, questionnaires, or algorithms to help identify the most appropriate treatment based on individual patients' unique factors. Unfortunately, significant treatment capacity constraints make matching patients to medication a major challenge; instead, the treatment choice is often dictated by availability of the limited options.

A majority of Roundtable panelists and CEPAC members expressed concern that a strict time limit on treatment for all patients is not consistent with the evidence. However in Maine, where doing so is required, the state Medicaid program (MaineCare) has adopted new authorization criteria for success designed to support individualized treatment. State regulation mandates that MaineCare only cover Suboxone for a period of 24 months, after which patients must demonstrate "medical necessity," or that a patient has had some measure of "success" with treatment, to remain on medication. Under this model, patients determine goals for treatment individually with their physician, and it is to each physician's clinical discretion whether Suboxone is effective after the initial 24-month period in achieving treatment objectives. Criteria for medical necessity may include improvements in living stability, active employment seeking, or regained social relationships, and patients need not achieve all criteria for treatment to be authorized. According to stakeholders in Maine tasked with implementing this model, for some patients this requirement has created a positive incentive and has improved patient engagement in their treatment plan.

4. Develop systems to triage patients entering treatment to the level of care more appropriate for their individual needs in order to support patient-centered treatment and allow for more capacity in the system.

Policymakers and treatment centers in New England are considering ways to allocate resources more effectively to manage the growing numbers of opioid-dependent patients. CEPAC and Roundtable panelists discussed the importance for states and provider groups to develop coordinated care networks in which patients receive short-term intensive outpatient care until stabilized, and then are referred outward to other outpatient practices for lower levels of ongoing care and MAT in primary care settings or community-based practices. Vermont is one of the states in New England implementing this model on a state-wide basis, as described on the following page.

> ***Policy/Practice Option: Vermont "Hub and Spoke" Model***
>
> Vermont is employing a coordinated system-wide model for triaging patients with opioid dependence to appropriate levels of care. The goal for this model is to support patient-centered treatment while more effectively distributing resources to allow for greater capacity in the system. Called the "Hub and Spoke" model, this system makes use of specialty treatment centers ("hubs"), as well as federally-qualified health centers, patient-centered medical homes, and other practices with physicians licensed to prescribe Suboxone ("spokes"). Patients begin treatment for opioid dependence centrally at the "hub," where they receive a period of intense treatment composed of comprehensive assessment, MAT, and other supportive services for an initial stabilization period. Once stabilized, patients are referred outward to a "spoke" for ongoing care and maintenance with Suboxone. Clinically complex patients may continue to receive care at the "hub," or are referred elsewhere for inpatient or rehabilitation services if more intensive care is deemed appropriate. Stable patients receive ongoing care at the "spoke," which typically involves a prescribing physician, nurse, case manager, and counselor-led care team that monitors treatment adherence, provides counseling, supports contingency management, and coordinates patient access to other recovery supports as needed. This model is being implemented in stages and is not working perfectly yet, as the average spoke maintains a small number of patients and not all licensed physicians are prescribing to capacity.

5. Mandatory requirements for certain kinds of counseling can have unintended consequences and should be reconsidered to ensure that they are not negatively affecting patient outcomes.

State and health insurer medical policy often require that treatment plans meet certain criteria for counseling in order for patients to receive MAT. Though CEPAC members recognized the importance of social support and counseling for many patients, the Council and Roundtable panelists agreed that the decision for counseling should be individual rather than a blanket requirement, and therefore policies of this kind should be reconsidered. Moreover, since there are not enough counselors to serve every patient with addiction, these policies may potentially "bottleneck treatment" and serve as an additional barrier to care.

Roundtable panelists also noted that many counselors are not specifically trained in addiction and that individuals with dependence may be better served through peer-led recovery support that addresses techniques for relapse prevention from a patient's perspective.

6. Provide treatment for opioid dependence through comprehensive, team-based care with collaboration across health care providers.

Experts agreed that patients with opioid dependence should have access to comprehensive health care services that address the full range of co-occurring clinical, social, and environmental factors surrounding dependence. Housing support, wellness services, substance abuse education, occupational rehabilitation, transportation, reproductive counseling, parenting support, and legal support are among the social services most important for patient success.

Physician-led, team-based care allows treatment centers to provide a range of services among a shared network of providers, often within the same facility, which experts noted helps improve patient retention. The multi-disciplinary care team may be composed of addiction-certified physicians, psychologists, counselors, social workers, and other complementary practitioners that coordinate care and integrate with other medical and psychiatric services, as necessary. Treatment programs that are unable to provide the full of spectrum of services that opioid-dependent patients require on-site should maintain a strong referral network with local mental health providers and other social agencies, as well as a robust case management system that tracks patients' progress and helps coordinate services for them as they access treatment.

Treatment programs across New England have adopted innovative approaches to foster collaboration and integration across providers. For example, some practices require patients to sign HIPAA release forms upon admission so that practitioners can openly communicate and discuss treatment progress for shared patients. Other programs have developed a system of communication across all treating providers, requesting that primary care physicians and pain management specialists prescribing benzodiazepines fill out information sheets that notify the addiction specialist. Finally, some practices hold weekly meetings for all care team members that discuss each patient's progress, how to prevent patient dropouts, and how services can be better integrated.

Clinical experts noted that coordinating care for patients with dependence can be difficult given how isolated this patient population is in some states, and how different treatment systems tend to function in silos. Experts also noted that the regulatory environment for substance abuse services makes it a challenge to adequately monitor and transition patients between different care systems. For example, policy experts participating on the Roundtable noted that existing federal regulations on confidentiality that are stricter than HIPAA make it difficult to share data between providers, posing a challenge at times to full care integration.

> ***Policy/Practice Option: Use of medical homes to foster collaboration across health care providers and expand access to comprehensive, team-based services***
>
> Rhode Island is using a patient-centered medical home (PCMH) approach to provide comprehensive, team-based care to patients receiving MAT. Under this model, OTPs act as health home providers and assign participating patients to a health team, which may be specialized to meet their specific health care needs. Each patient is assigned a nurse and case manager to provide ongoing monitoring, assistance with referrals, development of care plans, recovery support, and support for transition between levels of care. The goal of this model is to support stronger, formalized relationships between OTPs, which have daily contact with patients, with community health care providers in order to provide comprehensive treatment for patients with dependence using MAT.

7. Clinical strategies for dosing and tapering of MAT should adopt an individualized approach that engages the patient in setting goals.

Experts emphasized that for patients receiving MAT, no standardized approach for dosing and tapering will work for all patients, and therefore the level at which patients receive medication must be individualized. Experts acknowledged that though clinicians generally do not want to keep patients on medication indefinitely, there is little consensus on whether or how best to taper patients off maintenance therapy. Standardized treatment cut-offs are often regarded as counterproductive and even dangerous, and experts reported that even when patients taper and attempt to withdraw from MAT, many ultimately go back on medication or relapse to illicit drug-seeking behaviors.

Patient engagement is critical to assess whether a patient is motivated and has the supports necessary to attempt tapering. Stakeholders in Maine, where treatment programs are required to attempt to wean patients on Suboxone to a lower dose within two years as a condition for reimbursement, have found tapering boosts patients' self-confidence and engagement in their treatment plan. Under this model, patients that cannot tolerate a lower dose are allowed to return to a higher dose for as long as clinically appropriate. Several Roundtable panelists cautioned, however, that mandatory tapers may have unintended results and run contrary to some existing clinical guidelines.

With patient engagement, some programs have had success implementing a gradual tapering strategy that slowly weans patients off medication over the course of several months. Ongoing re-assessment is necessary, with flexibility to halt or reverse the taper as needed. Experts shared anecdotally that tapers tend to be most successful in patients with less severe dependency who have a supportive environment (e.g., stable relationships and living

environment, active employment). Other programs have suggested that keeping patients unaware of where they are in dosing can also be helpful. Some clinical experts also highlighted naltrexone as a crucial tool for preventing relapse after a successful taper, as it blocks the patient's ability to feel "high." However, providers recognized that only a limited number of patients are good candidates for naltrexone given the requirements to be opioid-free for at least seven days and the motivation necessary to avoid the "high." Ideal candidates for taper with this therapy tend to be patients that have lower severity baseline dependence, higher psychosocial stability, and a non-using social network.

8. Evidence-based insurance coverage policies for opioid dependence services should support efficient clinical practice and provide enough flexibility to help clinicians appropriately support the care needs of a diverse group of patients.

Strict prior authorization criteria establish an additional layer of regulation that many stakeholders feel create another barrier to treatment. Clinicians interviewed underscored the need for insurers to attempt to institute more efficient prior authorization processes for Suboxone and Vivitrol to achieve the intended policy goals while minimizing the burden for patients, pharmacists, and physicians. At present, some payers require prescribing physicians to call in patient information and answer a series of questions that some clinicians interviewed feel could easily be addressed through fax. Though some experts agreed that prior authorization requirements have validity to ensure quality prescribing, many felt that they ultimately serve as another obstacle to providing high quality treatment. Many patients wait until they are down to one or two pills before refilling their prescription, and prior authorization requirements mean that some patients are unable to receive their medication when needed. Physicians suggested that payers provide "fast-track" prior authorization processes for reliable prescribers. Doing so would maintain protections against physicians that are not prescribing in good faith, but allow those with a demonstrated high quality prescribing record to treat patients as efficiently as possible. Health insurers on the Roundtable noted that prior authorization is not intended to reduce access to treatment, but rather to avoid standardized requirements or protocols that will not work for many people.

Insurers and providers share the burden of balancing concerns for diversion with the desire to provide a dose high enough to ensure a patient does not experience withdrawal and drop out of treatment. No standardized approach for dosing (or tapering) will work for all patients, and therefore the level at which patients receive medications must be individualized. Mechanisms to facilitate rapid consideration of requests for dosing beyond established limits should be instituted.

Clinicians also mentioned the need to relax other coverage criteria that serve as deterrents to care, such as regular urine testing for patients with long histories of successful maintenance therapy. Experts emphasized that strict protocols and regular testing are important in the initial phases of treatment, but they reinforce the stigmatization of opioid-dependent patients by requiring ongoing monthly testing of individuals who have been stable on treatment for many years. Payers should therefore consider exemptions for some patients from specific coverage criteria.

Given concerns for patient safety when taking MAT, many clinicians interviewed support policies for compliance monitoring and random "call backs" to prevent abuse and diversion. ("Call backs" refers to the practice of randomly selecting patients with take-home medication privileges to return to clinic and present the medication dose in its original bottle.) Though such approaches may be reasonable, as with other policies there should be some mechanism for consideration of exempting some patients demonstrating long-term adherence to treatment. Some clinicians cautioned that strict policies for MAT may serve to reinforce stigma that individuals with dependence lack self-will and are criminals.

Clinical and policy experts on the Roundtable also noted that increases to reimbursement rates for addiction treatment to bring them on par with payment for other clinical services should be considered to reduce the stigma that still affects addiction medicine specialists.

9. Policymakers should develop long-term solutions to recruit, train, and retain qualified physicians to the field of addiction medicine in addition to fostering greater awareness and skills for recognizing opioid addiction among primary care clinicians.

Recruiting and retaining enough qualified physicians to meet the demand for opioid dependence services remains one of the most significant challenges confronting New England states. According to the policy experts, federal legislation limiting the number of patients that physicians can treat with buprenorphine-containing medications, strict licensing regulations for OTPs, and public hostility to establishing new treatment centers have significantly contributed to the shortage of providers offering addiction treatment. Stakeholders emphasized the need for more targeted efforts to recruit physicians to addiction medicine. Experts suggested that medical schools require physicians in training receive more exposure to addiction medicine and that treatment of substance abuse be incorporated as a standard part of residency training to help recruit more professionals to the field.

Clinical experts and CEPAC members also recommended implementing greater efforts to train and support primary care physicians in recognizing addiction disorder, leveraging training and physician mentorship programs from ASAM and AAAP that assist primary care providers to incorporate screening, brief interventions, and referrals to substance abuse treatment centers as a standard part of care.

10. Funders and the clinical research community should focus future study on key areas where further evidence is needed to appropriately manage patients with opioid dependence.

Although there is a large body of evidence supporting the use of MAT in patients with opioid dependence, significant research gaps exist. CEPAC and Policy Roundtable panelists recognized that existing evidence demonstrates high relapse rates with short-term opioid withdrawal management, but that more research is needed to identify those patients for whom abstinence may be an appropriate short, medium, or long-term goal, and how best to achieve and maintain abstinence in this population. The Council also called for additional RCTs testing the comparative effectiveness of different dosing and tapering protocols. In particular, significant questions remain in the clinical community on how best to identify patients for potential tapers who have been on treatment for many years. CEPAC and Roundtable panelists also agreed that additional research is needed assessing the effectiveness of MAT for adolescent populations with short-term addiction histories, as well as the comparative effectiveness of Vivitrol compared to oral naltrexone.

References

Aetna. Medication search. https://pbm.aetna.com/wps/portal/FRAMED_UNAUTH_MEDICATION_SEARCH_TOOL?businessSectorCode=CM%3fwt.ac=IFPharmPlanSelector. Accessed April, 2014.

Aetna. Pharmacy clinical policy bulletins, Aetna non-Medicare prescription drug plan: narcotic partial agonists. http://www.aetna.com/products/rxnonmedicare/data/2014/CNS/narc_partial_agonists.html. Accessed April, 2014.

Alford DP, LaBelle CT, Kretsch N, et al. Five year experience with collaborative care of opioid addicted patients using buprenorphine in primary care. *Arch Intern Med*. 2011;171(5):425-431.

Amass L, Ling W, Freese TE, et al. Bringing buprenorphine-naloxone detoxification to community treatment providers: the NIDA Clinical Trials Network field experience. *Am J Addict*. 2004;13(Suppl 1):S42-S66.

Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database Syst Rev*. 2011a;9:CD005031.

Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *Cochrane Database Syst Rev*. 2011b;10:CD004147.

American Society of Addiction Medicine (ASAM). Advancing access to addiction medicines (2013). http://www.asam.org/docs/advocacy/Implications-for-Opioid-Addiction-Treatment. Accessed March, 2014.

American Society of Addiction Medicine (ASAM). Office-based Opioid Agonist Treatment (OBOT) (2004). http://www.asam.org/advocacy/find-a-policy-statement/view-policy-statement/public-policy-statements/2011/12/15/office-based-opioid-agonist-treatment-(obot). Accessed April, 2014.

Anson P. FDA Approves New Opioid Addiction Treatment. National Pain Report. June 9, 2014: http://americannewsreport.com/nationalpainreport/fda-approves-new-opioid-addiction-treatment-8824003.html

Anthem. Clinical UM guideline. Naltrexone (Vivitrol®) injections for the treatment of alcohol and opioid dependence. http://www.anthem.com/medicalpolicies/guidelines/gl_pw_a053720.htm. Accessed April, 2014.

Anthem. National drug list 3 tier. https://www.anthem.com/health-insurance/customer-care/forms-library. Accessed May, 2014.

Auriacombe M, Fatséas M, Dubernet J, Daulouède JP, Tignol J. French field experience with buprenorphine. *Am J Addict*. 2004;13(Suppl 1):S17-S28.

Ball SA, Nich C, Rounsaville BJ, Eagan D, Carroll KM. Million Clinical Multiaxial Inventory-III subtypes of opioid dependence: validity and matching to behavioral techniques. *J Consult Clin Psychol*. 2004;72(4):698-711.

Bargagli AM, Schifano P, Davoli M, Faggiano F, Perucci CA. Determinants of methadone treatment assignment among heroin addicts on first admission to public treatment centres in Italy. *Drug Alcohol Depend.* 2005;79(2):191-199.

Barnett PG, Masson CL, Sorensen JL, Wong W, Hall S. Linking opioid-dependent hospital patients to drug treatment: health care use and costs 6 months after randomization. *Addiction*. 2006;101(12):1797-1804.

Barnett PG, Trafton JA, Humphreys K. The cost of concordance with opiate substitution treatment guidelines. *J Subst Abuse Treat*. 2010;39(2):141-149.

Barnett PG, Zaric GS, Brandeau ML. The cost–effectiveness of buprenorphine maintenance therapy for opiate addiction in the United States. *Addiction*. 2001;96(9):1267-1278.

Bartu A, Freeman NC, Gawthorne GS, Allsop SJ, Quigley AJ. Characteristics, retention and readmissions of opioid-dependent clients treated with oral naltrexone. *Drug Alcohol Rev*. 2002;21(4):335-340.

Baser O, Chalk M, Fiellin DA, Gastfriend DR. Cost and utilization outcomes of opioid-dependence treatments. *Am J Manag Care*. 2011;17(Suppl 8):S235-S248.

Bell J, Mutch C. Treatment retention in adolescent patients treated with methadone or buprenorphine for opioid dependence: a file review. *Drug Alcohol Rev*. 2006;25(2):167-171.

Bell J, Shanahan M, Mutch C, et al. A randomized trial of effectiveness and cost-effectiveness of observed versus unobserved administration of buprenorphine-naloxone for heroin dependence. *Addiction*. 2007;102(12):1899-1907.

Bell JR, Ryan A, Mutch C, Batey R, Rea F. Optimising the benefits of unobserved dose administration for stable opioid maintenance patients: follow-up of a randomised trial. *Drug Alcohol Depend*. 2008;96(1-2):183-186.

Bickel WK, Jones BA, Landes RD, Christensen DR, Jackson L, Mancino M. Hypothetical intertemporal choice and real economic behavior: delay discounting predicts voucher redemptions during contingency-management procedures. *Exp Clin Psychopharmacol*. 2010;18(6):546-552.

Bickel WK, Marsch LA, Buchhalter AR, Badger GJ. Computerized behavior therapy for opioid dependent outpatients: a randomized controlled trial. *Exp Clin Psychopharmacol*. 2008;16(2):132-143.

Bisaga A, Sullivan MA, Cheng WY, et al. A placebo controlled trial of memantine as an adjunct to oral naltrexone for opioid dependence. *Drug Alcohol Depend*. 2011;119(1-2):e23-e29.

Blondell, RD, Ashrafioun, L, Dambra, CM, Foschio, EM, Zielinski, AL, Salcedo, DM. A clinical trial comparing tapering doses of buprenorphine with steady doses for chronic pain and coexistent opioid addiction. *J Addict Med*. 2010;4(3):140-146.

Blue Cross Blue Shield of Massachusetts. Behavioral health policy: methadone treatment and intensive detoxification or ultra-rapid detoxification for opiate addiction. http://www.bluecrossma.com/common/en_US/medical_policies/274%20Methadone%20Treatment%20and%20Intensive%20Detoxification%20or%20Ultra-Rapid%20Detoxification%20for%20Opiate%20Addiction%20prn.pdf. Accessed April, 2014.

Blue Cross Blue Shield of Massachusetts. Pharmacy medical policy: quality care dosing (QCD) guidelines. http://www.bluecrossma.com/common/en_US/medical_policies/621%20Quality%20Care%20Dosing%20-%20QCD%20-%20Guidelines%20prn.pdf. Accessed April, 2014.

Blue Cross Blue Shield of Massachusetts. Pharmacy medical policy: Suboxone® and buprenorphine containing products for the treatment of opioid dependence. http://www.bluecrossma.com/common/en_US/medical_policies/094_Suboxone_and_Buprenorphine_Containing_Products_for_the_Treatment_of_Opioid_Dependence_prn.pdf. Accessed April, 2014.

Blue Cross Blue Shield of Rhode Island. Commercial formulary. https://www.bcbsri.com/providers/formulary-drug-information/commercial-formulary. Accessed April, 2014.

Blue Cross Blue Shield of Rhode Island. Medical coverage policy: treatment of opioid dependence. https://www.bcbsri.com/sites/default/files/polices/Treatment_Opioid_Dependence.pdf. Accessed April, 2014.

Blue Cross Blue Shield of Vermont. Rx management programs for Vermonters. http://www.bcbsvt.com/provider/eligibility-benefits/rx-management-programs/!ut/p/a1/jdBBDsIgEAXQs_QEfECQLrFqYSMxBq1sDKuGRKsL4_ltXRmq1dlN8n5-ZkggDQldfKQ23tO1i-dhD_JEqQJIilkYN4dda8P3mnI40YPjO3B-u4TdGDBuKGqJ__L4MjrPr0TV5yvBy4XmtUXePwY_-g8kTFbsZiNASzkAZirlASdz8OEHLzBx5O3ifYNkW10UT91mQPM!/dl5/d5/L2dJQSEvUUt3QS80SmlFL1o2XzExODAxMjgySThENTEwSVY4QUtSRTMxME4w/. Accessed April, 2014.

Bovasso G, Cacciola J. The long-term outcomes of drug use by methadone maintenance patients. *J Behav Health Serv Res.* 2003;30(3):290-303.

Brooner RK, Kidorf MS, King VL, Stoller KB, Neufeld KJ, Kolodner K. Comparing adaptive stepped care and monetary-based voucher interventions for opioid dependence. *Drug Alcohol Depend.* 2007;88(Suppl 2):S14-S23.

Brooner RK, Kidorf MS, King VL, et al. Behavioral contingencies improve counseling attendance in an adaptive treatment model. *J Subst Abuse Treat*. 2004;27(3):223-232.

Buhl L, Saelan H, Sørensen TM. Adverse events due to change in organization of problem drug users' treatment? *Scand J Public Health*. 2004;32(2):130-135.

Bureau of Labor Statistics. United States Department of Labor. Economic news release: Consumer Price Index summary. http://www.bls.gov/news.release/cpi.nr0.htm. Accessed April, 2014.

Caldiero RM, Parran TV Jr, Adelman CL, Piche B. Inpatient initiation of buprenorphine maintenance vs. detoxification: can retention of opioid-dependent patients in outpatient counseling be improved? *Am J Addict*. 2006;15(1):1-7.

Campbell CI, Alexander JA, Lemak CH. Organizational determinants of outpatient substance abuse treatment duration in women. *J Subst Abuse Treat*. 2009;37(1):64-72.

Carpenter KM, Smith JL, Aharonovich E, Nunes EV. Developing therapies for depression in drug dependence: results of a stage 1 therapy study. *Am J Drug Alcohol Abuse*. 2008;34(5):642-652.

Carreno JE, Alvarez CE, Narciso GI, Bascaran MT, Diaz M, Bobes J. Maintenance treatment with depot opioid antagonists in subcutaneous implants: an alternative in the treatment of opioid dependence. *Addict Biol*. 2003;8(4):429-438.

Carrieri, MP, Rey, D, Loundou, A, Lepeu, G, Sobel, A, Obadia, Y. Evaluation of buprenorphine maintenance treatment in a French cohort of HIV-infected injecting drug users. *Drug Alcohol Depend*. 2003;72(1):13-21.

Carroll J. Updated: FDA steamrolls over panel vote, spurns Titan's addiction drug Probuphine. FierceBiotech. May 1, 2013: http://www.fiercebiotech.com/story/fda-steamrolls-over-panel-vote-spurns-titans-addiction-drug-probuphine/2013-05-01.

Center for Substance Abuse Treatment. *Clinical Guidelines for the use of Buprenorphine in the Treatment of Opioid Addiction*. Treatment Improvement Protocol (TIP) Series 40. DHHS publication no. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration (SAMHSA); 2004.

Center for Substance Abuse Treatment. *Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs*. Treatment Improvement Protocol (TIP) Series 43. DHHS publication no. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration (SAMHSA); 2005.

Centers for Disease Control and Prevention (CDC). Compressed mortality data: underlying cause-of-death (2013a). http://wonder.cdc.gov/mortsql.html. Accessed April, 2014.

Centers for Disease Control and Prevention (CDC). Injury Center. Saving lives and protecting people: preventing prescription painkiller overdoses (2013b). http://www.cdc.gov/injury/about/focus-rx.html. Accessed April, 2014.

Centers for Disease Control and Prevention (CDC). Prescription painkiller overdoses in the US (2011). http://www.cdc.gov/vitalsigns/PainkillerOverdoses/index.html. Accessed April, 2014.

Chakrabarti A, Woody GE, Griffin ML, Subramaniam G, Weiss RD. Predictors of buprenorphine-naloxone dosing in a 12-week treatment trial for opioid-dependent youth: secondary analyses from a NIDA Clinical Trials Network study. *Drug Alcohol Depend*. 2010;107(2-3):253-256.

Chawarski MC, Mazlan M, Schottenfeld RS. Behavioral drug and HIV risk reduction counseling (BDRC) with abstinence contingent take-home buprenorphine: a pilot randomized clinical trial. *Drug Alcohol Depend*. 2008;94(1-3):281-284.

Chawarski MC, Zhou W, Schottenfeld. Behavioral drug and HIV risk reduction counseling (BDRC) in MMT programs in Wuhan, China: a pilot randomized clinical trial. *Drug Alcohol Depend*. 2011;115(3):237-239.

Chopra MP, Landes RD, Gatchalian KM, et al. Buprenorphine medication versus voucher contingencies in promoting abstinence from opioids and cocaine. *Exp Clin Psychopharmacol*. 2009;17(4):226-236.

Cigna. Pharmacy Resources. https://cignaforhcp.cigna.com/web/public/resourcesGuest/!ut/p/b1/hY7LboJAGIWfxQcw8xOL4JJbuY6Cw-DAxpBI2qEqUCk48_Qdm25tz-4k37mgCjFUXeuJv9Uj7671-

eGr9XHnm2stIBD4UfoKYQpOqBGyAhMUUCoAnsiC__IHxODlSFqzx2JkiXSmvJWZwDJbbdsGsBvOeMPSU7GntmUvl4PhqUz1U_vH6 jboLg0qFWY8X9cRm3gzo_z3g-jj_LRLC5d2kt-jpCg1gvUwOVta7HWj5OZIPgxN0HkgXAx3281ieMf5hgb1TY8T7- sGzhQm4jNS_Xsi5KGVOZUG7Yo5s3Tp18G8WKD- QqfexNk3QjnD0A!!/dl4/d5/L0lDU0lKSmdwcGlRb0tVUm0vb0dvZ0FFSVFoakVDVUlnQUlBSXlGQU1od1VoUzRKUkVBUlBwGQU1od1VoUzRKUkVBTHAEBISEvNEczYUQyZ2p2eWhEVXdwTWhSTlVJZyEhL1o3X09HODYxSFMwSEdKUEYwSVAwQ0kxU1MzMDg1LzAvMjYxNzM3MjI4NzQwLyUwc2l0ZXMlMGNoY3AlMHJlc291cmNllTGlicmFyeeSUwcGhhcm1IdWJMYW5kaW5nLnBoZ2U!/. Accessed April, 2014.

Citrome L, Kamat SA, Sapin C, et al. Cost-effectiveness of aripiprazole once-monthly compared with paliperidone palmitate once-monthly injectable for the treatment of schizophrenia in the United States. *J Med Econ*. 2014;12:1-10.

Comer SD, Sullivan MA, Vosburg SK, et al. Abuse liability of intravenous buprenorphine/naloxone and buprenorphine alone in buprenorphine-maintained intravenous heroin abusers. *Addiction*. 2010;105(4):709-718.

Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry*. 2006;63(2):210-218.

Comiskey CM, Stapleton R. Longitudinal outcomes for treated opiate use and the use of ancillary medical and social services. *Subst Use Misuse*. 2010;45(4):628-641.

ConnectiCare. Pharmacy center. http://www.connecticare.com/pharmacy.aspx. Accessed April, 2014.

Connecticut Department of Social Services. Connecticut Medicaid preferred drug list (PDL). https://www.ctdssmap.com/CTPortal/Portals/0/StaticContent/Publications/CT_PDL_medicaid.pdf. Accessed April, 2014.

Connecticut General Assembly. An act concerning various revisions to the Department of Mental Health and Addiction Services' statutes (2014). Substitute Bill No. 5145 (HB05145APP__041614). http://www.cga.ct.gov/2014/TOB/H/2014HB-05145-R02-HB.htm. Accessed April, 2014.

Connock M, Juarez-Garcia A, Jowett S, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technol Assess.* 2007;11(9):1-171,iii-iv.

Crist RC, Clarke TK, Ang A, et al. An intronic variant in OPRD I predicts treatment outcome for opioid dependence in African-Americans. *Neuropsychopharmacology*. 2013;38(10):2003-2010.

Czuchry M, Newbern-McFarland D, Dansereau DF. Visual representation tools for improving addiction treatment outcomes. *J Psychoactive Drugs*. 2009;41(2):181-187.

Deck D, Carlson MJ. Retention in publicly funded methadone maintenance treatment in two Western states. *J Behav Health Serv Res*. 2005;32(1):43-60.

DeFulio A, Everly JJ, Leoutsakos JMS, et al. Employment-based reinforcement of adherence to an FDA approved extended release formulation of naltrexone in opioid-dependent adults: a randomized controlled trial. *Drug Alcohol Depend*. 2012;120(1-3):48-54.

De Jong CA, Roozen HG, van Rossum LG, Krabbe PF, Kerkhof AJ. High abstinence rates in heroin addicts by a new comprehensive treatment approach. *Am J Addict*. 2007;16(2):124-130.

Deck D, Carlson MJ. Retention in publicly funded methadone maintenance treatment in two Western States. *J Behav Health Serv Res*. 2005;32(1):43-60.

Dickinson GL, Rostami-Hodjegan A, Lagundoye O, Seivewright N, Pratt P, Lennard MS. A six-year evaluation of methadone prescribing practices at a substance misuse treatment centre in the UK. *J Clin Pharm Ther*. 2006;31(5):477-484.

Digiusto E, Shakeshaft A, Ritter A, O'Brien S, Mattick RP. Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD). *Addiction*. 2004;99(4):450-460.

Dijkstra BA, De Jong CA, Bluschke SM, Krabbe PF, van der Staak CP. Does naltrexone affect craving in abstinent opioid-dependent patients? *Addict Biol.* 2007;12(2):176-182.

Dijkstra BA, De Jong CA, Wensing M, Krabbe PF, van der Staak CP. Opioid detoxification: from controlled clinical trial to clinical practice. *Am J Addict*. 2010;19(3):283-290.

Donovan DM, Knox PC, Skytta JA, Blayney JA, DiCenzo J. Buprenorphine from detox and beyond: preliminary evaluation of a pilot program to increase heroin dependent individuals' engagement in a full continuum of care. *J Subst Abuse Treat*. 2013;44(4):426-432

Doolittle B, Becker W. A case series of buprenorphine/naloxone treatment in a primary care practice. *Subst Abus*. 2011;32(4):262-265.

Doran CM. Economic evaluation of interventions to treat opiate dependence. Pharmacoeconomics. 2008;26(5):371-393.

Dunn, J. A survey of methadone prescribing at an inner-city drug service and a comparison with national data. *Psychiatric Bulletin*. 2003;27:167-170.

Dunn J, Haskew M, Pant A. Adherence to substitute opioid prescribing: survey of inner-London drug services. *Psychiatr Bull R Coll Psychiatr*. 2009;33(9):336-340.

Dunn KE, Defulio A, Everly JJ, et al. Employment-based reinforcement of adherence to oral naltrexone treatment in unemployed injection drug users. *Exp Clin Psychopharmacol*. 2013;21(1):74-83.

Epstein DH, Hawkins WE, Covi L, Umbricht A, Preston KL. Cognitive-behavioral therapy plus contingency management for cocaine use: findings during treatment and across 12-month follow-up. *Psychol Addict Behav*. 2003;17(1):73-82.

Epstein DH, Schmittner J, Umbricht A, Schroeder JR, Moolchan ET, Preston KL. Promoting abstinence from cocaine and heroin with a methadone dose increase and a novel contingency. *Drug Alcohol Depend*. 2009;101(1-2):92-100.

Everly JJ, DeFulio A, Koffarnus MN, et al. Employment-based reinforcement of adherence to depot naltrexone in unemployed opioid-dependent adults: a randomized controlled trial. *Addiction*. 2011;106(7):1309-1318.

Executive Office of Health and Human Services, State of Rhode Island. Pharmacy: medical coverage policies. http://www.eohhs.ri.gov/ProvidersPartners/ProviderManualsGuidelines/MedicaidProviderManual/Pharmacy.aspx. Accessed June, 2014.

Fals-Stewart W, O'Farrell TJ. Behavioral family counseling and naltrexone for male opioid-dependent patients. *J Consult Clin Psychol*. 2003;71(3):432-442.

Fareed A, Vayalapalli S, Casarella J, Drexler K. Treatment outcome for flexible dosing buprenorphine maintenance treatment. *Am J Drug Alcohol Abuse*. 2012;38(2):155-160.

Fiellin DA, Barry DT, Sullivan LE, et al. A randomized trial of cognitive behavioral therapy in primary care-based buprenorphine. *Am J Med*. 2013;126(1):74.e11-17.

Fiellin DA, Pantalon MV, Chawarski, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. *N Engl J Med*. 2006;355(4):365-374.

Flynn PM, Joe GW, Broome KM, Simpson DD, Brown BS. Recovery from opioid addiction in DATOS. *J Subst Abuse Treat*. 2003;25(3):177-186.

Fonseca, F, de la Torre, R, Diaz, L, et al. Contribution of cytochrome P450 and ABCB1 genetic variability on methadone pharmacokinetics, dose requirements, and response. *PLoS One*. 2011;6(5):e19527.

Gandhi DH, Jaffe JH, McNary S, Kavanagh GJ, Hayes M, Currens M. Short-term outcomes after brief ambulatory opioid detoxification with buprenorphine in young heroin users. *Addiction*. 2003;98(4):453-462.

Gerra G, Ferri M, Polidori E, Santoro G, Zaimovic A, Sternieri E. Long-term methadone maintenance effectiveness: psychosocial and pharmacological variables. *J Subst Abuse Treat*. 2003;25(1):1-8.

Gerra G, Saenz E, Busse A, et al. Supervised daily consumption, contingent take-home incentive and non-contingent take-home in methadone maintenance. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(2):483-489.

Giacomuzzi S, Kemmler G, Ertl M, Riemer Y. Opioid addicts at admission vs. slow-release oral morphine, methadone, and sublingual buprenorphine maintenance treatment participants. *Subst Use Misuse*. 2006;41(2):223-244.

Gibson A, Degenhardt L, Mattick RP, Ali R, White J, O'Brien S. Exposure to opioid maintenance treatment reduces long-term mortality. *Addiction*. 2008;103(3):462-468.

Gibson AE, Doran CM, Bell JR, Ryan A, Lintzeris N. A comparison of buprenorphine treatment in clinic and primary care settings: a randomised trial. *Med J Aust*. 2003;179(1):38-42.

Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. Cost-Effectiveness in Health and Medicine. New York, NY: Oxford University Press; 1996.

Gossop M, Marsden J, Stewart D. Remission of psychiatric symptoms among drug misusers after drug dependence treatment. *J Nerv Ment Dis*. 2006;194(11):826-832.

Gossop M, Marsden J, Stewart D, Kidd T. The National Treatment Outcome Research Study (NTORS): 4-5 year follow-up results. *Addiction*. 2003;98(3):291-303.

Gossop M, Stewart D, Browne N, Marsden J. Methadone treatment for opiate dependent patients in general practice and specialist clinic settings: outcomes at 2-year follow-up. *J Subst Abuse Treat*. 2003;24(4):313-321.

Gossop M, Stewart D, Marsden J. Treatment process components and heroin use outcome among methadone patients. *Drug Alcohol Depend*. 2003;71(1):93-102.

Grabowski J, Rhoades H, Stotts A, et al. Agonist-like or antagonist-like treatment for cocaine dependence with methadone for heroin dependence: two double-blind randomized clinical trial. *Neuropsychopharmacology.* 2004;29(5):969-981.

Greenwald MK. Opioid abstinence reinforcement delays heroin lapse during buprenorphine dose tapering. *J Appl Behav Anal*. 2008;41(4):603-607.

Groß A, Marsch LA, Badger GJ, Bickel WK. A comparison between low-magnitude voucher and buprenorphine medication contingencies in promoting abstinence from opioids and cocaine. *Exp Clin Psychopharmacol*. 2006;14(2):148-156.

Gruber VA, Delucchi KL, Kielstein A, Batki SL. A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug Alcohol Depend*. 2008;94(1-3):199-206

Gunderson EW, Wang XQ, Fiellin DA, Bryan B, Levin FR. Unobserved versus observed office buprenorphine/naloxone induction: a pilot randomized clinical trial. *Addict Behav*. 2010;35(5):537-540.

Haddad MS, Zelenev A, Altice FL. Integrating buprenorphine maintenance therapy into federally qualified health centers: real-world substance abuse treatment outcomes. *Drug Alcohol Depend*. 2013;131(1-2):127-135.

Hall W, Doran C, Degenhardt L, Shepard D. Illicit opiate abuse*.* In: Jamison DT, Breman JG, Measham AR, et al, eds*. Disease Control Priorities in Developing Countries*. 2nd ed. Washington (DC): World Bank; 2006. Chapter 48.

Harris EE, Jacapraro JS, Rastegar DA. Criminal charges prior to and after initiation of office-based buprenorphine treatment. *Subst Abuse Treat Prev Policy*. 2012;7:10.

Harris KA Jr., Arnsten JH, Joseph H, et al. A 5-year evaluation of a methadone medical maintenance program. *J Subst Abuse Treat*. 2006;31(4):433-438.

Harvard Pilgrim Health Care. 3-tier prescription drug program. https://www.harvardpilgrim.org/portal/page?_pageid=253,360877&_dad=portal&_schema=PORTAL. Accessed April, 2014.

Hayes SC, Wilson KG, Gifford EV, et al. A preliminary trial of twelve-step facilitation and acceptance and commitment therapy with polysubstance-abusing methadone-maintained opiate addicts. *Behav Ther*. 2004;35(4):667-688.

Hill KP, Bennett HE, Griffin ML, et al. Association of cannabis use with opioid outcomes among opioid-dependent youth. *Drug Alcohol Depend*. 2013;132(1-2):342-345.

Hillhouse M, Canamar CP, Ling W. Predictors of outcome after short-term stabilization with buprenorphine. *J Subst Abuse Treat*. 2013;44(3):336-432.

Hillhouse M, Domier CP, Chim D, Ling W. Provision of ancillary medications during buprenorphine detoxification does not improve treatment outcomes. *J Addict Dis*. 2010;29(1):23-29.

Holland R, Matheson C, Anthony G, et al. A pilot randomised controlled trial of brief versus twice weekly versus standard supervised consumption in patients on opiate maintenance treatment. *Drug Alcohol Rev*. 2012;31(4):483-491.

Hser YI, Li J, Jiang H, et al. Effects of a randomized contingency management intervention on opiate abstinence and retention in methadone maintenance treatment in China. *Addiction.* 2011;106(10):1801-1809.

Hser YI, Saxon AJ, Huang D, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction*. 2014;109(1):79-87.

Jagsch R, Gombas W, Schindler SD, Eder H, Moody DE, Fischer G. Opioid plasma concentrations in methadone-and buprenorphine-maintained patients. *Addict Biol*. 2005;10(4):365-371.

Judson G, Bird R, O'Connor P, et al. Drug injecting in patients in New Zealand Methadone Maintenance Treatment programs: an anonymous survey. *Drug Alcohol Rev*. 2010;29(1):41-46.

Kamal F, Flavin S, Campbell F, Behan C, Fagan J, Smyth R. Factors affecting the outcome of methadone maintenance treatment in opiate dependence. *Ir Med J*. 2007;100(3):393-397.

Kennedy, AP, Phillips, KA, Epstein, DH, Reamer, DA, Schmittner, J, Preston, KL. A randomized investigation of methadone doses at or over 100mg/day, combined with contingency management. *Drug Alcohol Depend.* 2013;130(1-3):77-84.

Kidorf M, Brooner RK, Gandotra N, et al. Reinforcing integrated psychiatric service attendance in an opioid-agonist program: a randomized and controlled trial. *Drug Alcohol Depend*. 2013;133(1):30-36.

Kidorf M, Neufeld K, Brooner RK. Combining stepped-care approaches with behavioral reinforcement to motivate employment in opioid-dependent outpatients. *Subst Use Misuse*. 2004;39(13-14):2215-2238.

King VL, Kidorf MS, Stoller KB, Schwartz R, Kolodner K, Brooner RK. A 12-month controlled trial of methadone medical maintenance integrated into an adaptive treatment model. *J Subst Abuse Treat*. 2006;31(4):385-393.

King VL, Stoller KB, Kidorf M, et al. Assessing the effectiveness of an Internet-based videoconferencing platform for delivering intensified substance abuse counseling. *J Subst Abuse Treat*. 2009;36(3):331-338.

Krabbe PF, Koning JP, Heinen N, Laheij RJ, van Cauter RM, De Jong CA. Rapid detoxification from opioid dependence under general anaesthesia versus standard methadone tapering: abstinence rates and withdrawal distress experiences. *Addict Biol*. 2003;8(3):351-358.

Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet*. 2011;377(9776):1506-1513.

Krupitsky E, Zvartau E, Blokhina E, et al. Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. *Arch Gen Psychiatry*. 2012;69(9):973-981.

Krupitsky E, Zvartau E, Blokhina E, et al. Naltrexone with or without guanfacine for preventing relapse to opiate addiction in St.-Petersburg, Russia. *Drug Alcohol Depend*. 2013;132(3):674-680.

Lee JD, Grossman E, DiRocco D, Gourevitch MN. Home buprenorphine/naloxone induction in primary care. *J Gen Intern Med*. 2009;24(2):226-232.

Leonardi C, Hanna N, Laurenzi P, Fagetti R. Multi-centre observational study of buprenorphine use in 32 Italian drug addiction centres. *Drug Alcohol Depend*. 2008;94(1-3):125-132.

Li L, Sangthong R, Chongsuvivatwong V, McNeil E, Li J. Multiple substance use among heroin-dependent patients before and during attendance at methadone maintenance treatment program, Yunnan, China. *Drug Alcohol Depend*. 2011;116(1-3):246-249.

Li L, Wu Z, Liang LJ, et al. An intervention targeting service providers and clients for methadone maintenance treatment in China: a cluster-randomized trial. *Addiction*. 2013;108(2):356-366.

Liao, D. Chen, PC, Chen, CH, et al. Higher methadone doses are associated with lower mortality in patients of opioid dependence in Taiwan. *J Psychiatr Res*. 2013;47(10):1530-1534.

Lidz V, Sorrentino DM, Robison L, Bunce S. Learning from disappointing outcomes: an evaluation of prevocational interventions for methadone maintenance patients. *Subst Use Misuse*. 2004;39(13-14):2287-2308.

Lin C, Wu Z, Rou K, et al. Structural-level factors affecting implementation of the methadone maintenance therapy program in China. *J Subst Abuse Treat*. 2011;38(2):119-127.

Ling W, Hillhouse M, Ang A, Jenkins J, Fahey J. Comparison of behavioral treatment conditions in buprenorphine maintenance. *Addiction*. 2013;108(10):1788-1798.

Ling W, Hillhouse M, Domier C, et al. Buprenorphine tapering schedule and illicit opioid use. *Addiction*. 2009;104(2):256-265.

Lintzeris N, Leung SY, Dunlop AJ, et al. A randomised controlled trial of sublingual buprenorphine-naloxone film versus tablets in the management of opioid dependence. *Drug Alcohol Depend*. 2013;131(1-2):119-126.

Lobmaier PP, Kunøe N, Gossop M, Waal H. Naltrexone depot formulations for opioid and alcohol dependence: a systematic review. *CNS Neurosci Ther*. 2011;17(6):629-636.

Lucas GM, Chaudhry A, Hsu J, et al. Clinic-based treatment for opioid-dependent HIV-infected patients versus referral to an opioid treatment program: a randomized controlled trial. *Ann Intern Med*. 2010;152(11):704-711.

Magura S, Blankertz L, Madison EM, Friedman E, Gomez A. An innovative job placement model for unemployed methadone patients: a randomized clinical trial. *Subst Use Misuse*. 2007;42(5):811-828.

Maine.gov. MaineCare: PA – prior authorization forms. http://www.mainecarepdl.org/pafiles. Accessed April, 2014.

Maine.gov. MaineCare: Preferred drug lists (PDL). http://www.mainecarepdl.org/pdl. Accessed April, 2014.

Mannelli P, Patkar AA, Peindl K, Murray HW, Wu LT, Hubbard R. Effectiveness of low-dose naltrexone in the post-detoxification treatment of opioid dependence. *J Clin Psychopharmacol.* 2007;27(5):468-474.

Marsch LA, Bickel WK, Badger GJ, Jacobs EA. Buprenorphine treatment for opioid dependence: the relative efficacy of daily, twice and thrice weekly dosing. *Drug Alcohol Depend*. 2005;77(2):195-204.

Mass.gov. Health and Human Services: MassHealth drug list. https://masshealthdruglist.ehs.state.ma.us/MHDL/. Accessed April, 2014.

Masson CL, Barnett PG, Sees KL, et al. Cost and cost-effectiveness of standard methadone maintenance treatment compared to enriched 180-day methadone detoxification. *Addiction*. 2004;99(6):718-726.

Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev*. 2009;3:CD002209.

Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2014;2:CD002207.

McCarty D, Perrin NA, Green CA, Polen MR, Leo MC, Lynch F. Methadone maintenance and the cost and utilization of health care among individuals dependent on opioids in a commercial health plan. *Drug Alcohol Depend*. 2010;111(3):235-240.

Meade CS, Lukas SE, McDonald LJ, et al. A randomized trial of transcutaneous electric acupoint stimulation as adjunctive treatment for opioid detoxification. *J Subst Abuse Treat*. 2010;38(1):12-21.

Meade CS, Weiss RD, Fitzmaurice GM, et al. HIV risk behavior in treatment-seeking opioid-dependent youth: results from a NIDA Clinical Trials Network multi-site study. *J Acquir Immune Defic Syndr*. 2010;55(1):65-72.

Merrill JO, Jackson TR, Schulman BA, et al. Methadone medical maintenance in primary care. An implementation evaluation. *J Gen Intern Med*. 2005;20(4):344-349.

Micromedex Healthcare Series. RED BOOK® Online. Greenwood Village, CO: Truven Health Analytics, 2014. http://truvenhealth.com/. Accessed May, 2014.

Mihalopoulos C, Magnus A, Carter R, Vos T. Assessing cost-effectiveness in mental health: family interventions for schizophrenia and related conditions. *Aust N Z J Psychiatry*. 2004;38(7):511-519.

Minozzi S, Amato L, Davoli M. Detoxification treatments for opiate dependent adolescents. *Cochrane Database Syst Rev*. 2009a;4:CD006749.

Minozzi S, Amato L, Davoli M. Maintenance treatments for opiate dependent adolescent. *Cochrane Database Syst Rev*. 2009b;2:CD007210.

Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev*. 2011;4:CD001333.

Mintzer IL, Eisenberg M, Terra M, MacVane C, Himmelstein DU, Woolhandler S. Treating opioid addiction with buprenorphine-naloxone in community-based primary care settings. *Ann Fam Med*. 2007;5(2):146-150.

Miotto K, Hillhouse M, Donovick R, et al. Comparison of buprenorphine treatment for opioid dependence in three settings. *J Addict Med*. 2012;6(1):68-76.

Montoya ID, Gorelick DA, Preston KL, et al. Randomized trial of buprenorphine for treatment of concurrent opiate and cocaine dependence. *Clin Pharmacol Ther*. 2004;75(1):34-48.

Montoya ID, Schroeder JR, Preston KL, et al. Influence of psychotherapy attendance on buprenorphine treatment outcome. *J Subst Abuse Treat*. 2005;28(3):247-254.

Moore BA, Barry DT, Sullivan LE, et al. Counseling and directly observed medication for primary care buprenorphine/naloxone maintenance: a pilot study. *J Addict Med*. 2012;6(3):205-211.

Moore BA, Fiellin DA, Barry DT, et al. Primary care office-based buprenorphine treatment: comparison of heroin and prescription opioid dependent patients. *J Gen Intern Med*. 2007;22(4):527-530.

Mullen L, Barry J, Long J, et al. A national study of the retention of Irish opiate users in methadone substitution treatment. *Am J Drug Alcohol Abuse*. 2012;38(6):551-558.

Mumola CJ, Karberg JC. Bureau of Justice Statistics, US Department of Justice. Drug use and dependence, state and federal prisoners, 2004 (2006). http://www.bjs.gov/index.cfm?ty=pbdetail&iid=778. Accessed April, 2014.

National Institute on Drug Abuse (NIDA). Abuse of prescription pain medications risks heroin use (2014). http://www.drugabuse.gov/related-topics/trends-statistics/infographics/abuse-prescription-pain-medications-risks-heroin-use. Accessed April, 2014.

Nava F, Manzato E, Leonardi C, Lucchini A. Opioid maintenance therapy suppresses alcohol intake in heroin addicts with alcohol dependence: preliminary results of an open randomized study. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32(8):1867-1872.

Neufeld KJ, Kidorf MS, Kolodner K, King VL, Clark M, Brooner RK. A behavioral treatment for opioid dependent patients with antisocial personality. *J Subst Abuse Treat*. 2008;34(1):101-111.

Neumann AM, Blondell RD, Azadfard M, Nathan G, Homish GG. Primary care patient characteristics associated with completion of 6-month buprenorphine treatment. *Addict Behav*. 2013;38(11):2724-2728.

New Hampshire Department of Health and Human Services. Preferred drug list (PDL). http://www.dhhs.nh.gov/ombp/pharmacy/documents/preferred.pdf. Accessed April, 2014.

New Hampshire Department of Health and Human Services. Suboxone®/buprenorphine prior authorization request form. http://www.dhhs.nh.gov/ombp/pharmacy/documents/suboxone.pdf. Accessed April, 2014.

Newbern D, Dansereau DF, Czuchry M, Simpson D. Node-link mapping in individual counseling: treatment impact on clients with ADHD-related behaviors. *J Psychoactive Drugs*. 2005;37(1):93-103.

Nielsen S, Hillhouse M, Thomas C, Hasson A, Ling W. A comparison of buprenorphine taper outcomes between prescription opioid and heroin users. *J Addict Med*. 2013;7(1):33-38.

Nosyk B, Anglin MD, Brissette S, et al. A call for evidence-based medical treatment of opioid dependence in the United States and Canada. *Health Aff (Millwood)*. 2013;32(8):1462-1469.

Nosyk B, Marsh DC, Sun H, Schechter MT, Anis AH. Trends in methadone maintenance treatment participation, retention, and compliance to dosing guidelines in British Columbia, Canada: 1996-2006. *J Subst Abuse Treat*. 2010;39(1):22-31.

Nosyk B, Sun H, Evans E, et al. Defining dosing pattern characteristics of successful tapers following methadone maintenance treatment: results from a population-based retrospective cohort study. *Addiction*. 2012;107(9):1621-1629.

Nunes EV, Rothenberg JL, Sullivan MA, Carpenter KM, Kleber HD. Behavioral therapy to augment oral naltrexone for opioid dependence: a ceiling on effectiveness? *Am J Drug Alcohol Abuse.* 2006;32(4):503-517.

Nyamathi A, Shoptaw S, Cohen A, et al. Effect of motivational interviewing on reduction of alcohol use. *Drug Alcohol Depend*. 2010;107(1):23-30.

Nyamathi AM, Sinha K, Greengold B, et al. Effectiveness of intervention on improvement of drug use among methadone maintained adults. *J Addict Dis*. 2011;30(1):6-16.

Office of National Drug Control Policy. Substance abuse and the affordable care act. http://www.whitehouse.gov/ondcp/healthcare. Accessed April, 2014.

Olsen Y, Sharfstein JM. Confronting the stigma of opioid use disorder – and its treatment. *JAMA*. 2014;311(14):1393-1394.

Otiashvili D, Piralishvili G, Sikharulidze Z, Kamkamidze G, Poole S, Woody GE. Methadone and buprenorphine-naloxone are effective in reducing illicit buprenorphine and other opioid use, and reducing HIV risk behavior--outcomes of a randomized trial. *Drug Alcohol Depend*. 2013;133(2):376-382.

Pade PA, Cardon KE, Hoffman RM, Geppert CM. Prescription opioid abuse, chronic pain, and primary care: a Co-occurring Disorders Clinic in the chronic disease model. *J Subst Abuse Treat*. 2012;43(4):446-550.

Peirce JM, Petry NM, Stitzer ML, et al. Effects of lower-cost incentives on stimulant abstinence in methadone maintenance treatment. *Arch Gen Psychiatry*. 2006;63(2):201-208.

Peles E, Linzy S, Kreek M, Adelson M. One-year and cumulative retention as predictors of success in methadone maintenance treatment: a comparison of two clinics in the United States and Israel. *J Addict Dis*. 2008;27(4):11-25.

Peles E, Schreiber S, Adelson M. 15-Year survival and retention of patients in a general hospital-affiliated methadone maintenance treatment (MMT) center in Israel. *Drug Alcohol Depend*. 2010;107(2-3):141-148.

Pollack MH, Penava SA, Bolton E, et al. A novel cognitive-behavioral approach for treatment-resistant drug dependence. *J Subst Abuse Treat*. 2002;23(4):335-342.

Polsky D, Glick HA, Yang J, Subramaniam GA, Poole SA, Woody GE. Cost-effectiveness of extended buprenorphine-naloxone treatment for opioid-dependent youth: data from a randomized trial. *Addiction*. 2010;105(9):1616-1624.

Potter JS, Marino EN, Hillhouse MP, et al. Buprenorphine/naloxone and methadone maintenance treatment outcomes for opioid analgesic, heroin, and combined users: findings from starting treatment with agonist replacement therapies (START). *J Stud Alcohol Drugs*. 2013;74(4):605-613.

Raby WN, Carpenter KM, Rothenberg J, et al. Intermittent marijuana use is associated with improved retention in naltrexone treatment for opiate-dependence. *Am J Addict*. 2009;18(4):301-308.

Raistrick D, West D, Finnegan O, Thistlethwaite G, Brearley R, Banbery J. A comparison of buprenorphine and lofexidine for community opiate detoxification: results from a randomized controlled trial. *Addiction*. 2005;100(12):1860-1867.

Rea, F, Bell, JR, Young, MR, Mattick, RP. A randomised, controlled trial of low dose naltrexone for the treatment of opioid dependence. *Drug Alcohol Depend*. 2004;75(1):79-88.

Reece AS. Psychosocial and treatment correlates of opiate free success in a clinical review of a naltrexone implant program. *Subst Abuse Treat Prev Policy*. 2007;2:35.

Revia® [package insert]. Pomona, NY: Duramed Pharmaceuticals, Inc.; 2013.

Rhode Island Department of Human Services. Rhode Island Medicaid fee for service preferred drug list. http://www.eohhs.ri.gov/Portals/0/Uploads/Documents/pdl_list.pdf. Accessed June, 2014.

Roux P, Sullivan MA, Cohen J, et al. Buprenorphine/naloxone as a promising therapeutic option for opioid abusing patients with chronic pain: reduction of pain, opioid withdrawal symptoms, and abuse liability of oral oxycodone. *Pain*. 2013;154(8):1442-1448.

Ruetsch C, Cacciola J, Tkacz. A national study of telephone support service for patients receiving office-based buprenorphine medication-assisted treatment: study feasibility and sample description. *J Subst Abuse Treat*. 2010;39(4):307-317.

Ruetsch C, Tkacz, McPherson TL, Cacciola J. The effect of telephonic patient support on treatment for opioid dependence: outcomes at one year follow-up. *Addict Behav*. 2012;37(5):686-689.

Saxon AJ, Ling W, Hillhouse M, et al. Buprenorphine/Naloxone and methadone effects on laboratory indices of liver health: a randomized trial. *Drug Alcohol Depend*. 2013;128(1-2):71-76.

Schlosburg JE, Vendruscolo LF, Bremer PT, et al. Dynamic vaccine blocks relapse to compulsive intake of heroin. *Proc Natl Acad Sci USA*. 2013;110(22):9036-9041.

Schottenfeld RS, Chawarski MC, Mazlan M. Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;371(9631):2192-2200.

Schottenfeld RS, Chawarski MC, Pakes JR, Pantalon MV, Carroll KM, Kosten TR. Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. *Am J Psychiatry*. 2005;162(2):340-349.

Schackman BR, Leff JA, Polsky D, Moore BA, Fiellin DA. Cost-effectiveness of long-term outpatient buprenorphine-naloxone treatment for opioid dependence in primary care. *J Gen Intern Med.* 2012;27(6):669-676.

Schwartz RP, Highfield DA, Jaffe JH, et al. A randomized controlled trial of interim methadone maintenance. *Arch Gen Psychiatry*. 2006;63(1):102-109.

Schwartz RP, Jaffe JH, Highfield DA, Callaman JM, O'Grady KE. A randomized controlled trial of interim methadone maintenance: 10-month follow-up. *Drug Alcohol Depend*. 2007;86(1):30-36.

Schwartz RP, Jaffe JH, O'Grady KE, et al. Interim methadone treatment: impact on arrests. *Drug Alcohol Depend*. 2009;103(3):148-154.

Scott J, Pope M. Cognitive styles in individuals with bipolar disorders. *Psychol Med*. 2003;33(6):1081-1088.

Sigmon SC, Dunn KE, Saulsgiver K, et al. A randomized, double-blind evaluation of buprenorphine taper duration in primary prescription opioid abusers. *JAMA Psychiatry*. 2013;70(12):1347-1354.

Silverman K, Robles E, Mudric T, Bigelow GE, Stitzer ML. A randomized trial of long-term reinforcement of cocaine abstinence in methadone-maintained patients who inject drugs. *J Consult Clin Psychol*. 2004;72(5):839-854.

Smyth BP, Fagan J, Kernan K. Outcome of heroin-dependent adolescents presenting for opiate substitution treatment. *J Subst Abuse Treat*. 2012;42(1):35-44.

Soeffing JM, Martin LD, Fingerhood MI, Jasinski DR, Rastegar DA. Buprenorphine maintenance treatment in a primary care setting: outcomes at 1 year. *J Subst Abuse Treat*. 2009;37(4):426-430.

Somers CJ, O'Connor J. Retrospective study of outcomes, for patients admitted to a drug treatment centre board. *Ir Med J*. 2012;105(9):295-298.

Sontag D. The double-edged drug: addiction treatment with a dark side. New York Times. November 16, 2013: http://www.nytimes.com/2013/11/17/health/in-demand-in-clinics-and-on-the-street-bupe-can-be-savior-or-menace.html?_r=0.

Sorensen JL, Andrews S, Delucchi KL, et al. Methadone patients in the therapeutic community: a test of equivalency. *Drug Alcohol Depend*. 2009;100(1-2):100-106.

Sorensen JL, Masson CL, Delucchi K, et al. Randomized trial of drug abuse treatment-linkage strategies. *J Consult Clin Psychol*. 2005;73(6):1026-1035.

Staines GL, Blankertz L, Magura S, et al. Efficacy of the Customized Employment Supports (CES) model of vocational rehabilitation for unemployed methadone patients: preliminary results. *Subst Use Misuse*. 2004;39(13-14):2261-2285.

Stein MD, Herman DS, Kettavong M, et al. Antidepressant treatment does not improve buprenorphine retention among opioid-dependent persons. *J Subst Abuse Treat*. 2010;39(2):157-166.

Stitzer ML, Peirce J, Petry NM, et al. Abstinence-based incentives in methadone maintenance: interaction with intake stimulant test results. *Exp Clin Psychopharmacol*. 2007;15(4):344-350.

Stotts AL, Green C, Masuda A, et al. A stage I pilot study of acceptance and commitment therapy for methadone detoxification. *Drug Alcohol Depend*. 2012;125(3):215-222.

Strang, John, McCambridge, Jim, Best, David, et al. Loss of tolerance and overdose mortality after inpatient opiate detoxification: Follow up study. *BMJ*. 2003;326(7396):959-960.

Strong DR, Brown RA, Sims M, Herman DS, Anderson BJ, Stein MD. Persistence during stress-challenge associated with lapse to opioid use during buprenorphine treatment. *J Addict Med*. 2012;6(3):219-225.

Suboxone® [package insert]. Richmond, VA: Reckitt Benckiser Pharmaceuticals Inc.; 2011.

Subramaniam GA, Warden D, Minhajuddin A, et al. Predictors of abstinence: National Institute of Drug Abuse multisite buprenorphine/naloxone treatment trial in opioid-dependent youth. *J Am Acad Child Adolesc Psychiatry*. 2011;50(11):1120-1128.

Substance Abuse and Mental Health Services Administration (SAMHSA). Buprenorphine physician & treatment program locator. http://buprenorphine.samhsa.gov/bwns_locator/. Accessed April, 2014.

Substance Abuse and Mental Health Services Administration (SAMHSA). Einstein expert panel: medication-assisted treatment and the criminal justice system (2013a). [See Appendix: DEA and substance abuse treatment in the criminal justice system (Miller LT, 2011).] http://www.samhsa.gov/traumajustice/pdf/Final%20MAT_031014.pdf. Accessed April, 2014.

Substance Abuse and Mental Health Services Administration (SAMHSA). *National Survey of Substance Abuse Treatment Services (N-SSATS): 2012. Data on Substance Abuse Treatment Facilities*. BHSIS Series S-66, HHS Publication No. (SMA) 14-4809. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013b. http://www.samhsa.gov/data/DASIS/NSSATS2012_Web.pdf. Accessed April, 2014.

Substance Abuse and Mental Health Services Administration (SAMHSA). *Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings*. NSDUH Series H-46, HHS publication no. (SMA) 13-4795. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013c. http://www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/NationalFindings/NSDUHresults2012.htm. Accessed April, 2014.

Substance Abuse and Mental Health Services Administration (SAMHSA). The SAMHSA evaluation of the impact of the DATA waiver program: summary report (2006). http://buprenorphine.samhsa.gov/FOR_FINAL_summaryreport_colorized.pdf. Accessed April, 2014.

Sullivan MA, Bisaga A, Mariani JJ, et al. Naltrexone treatment for opioid dependence: Does its effectiveness depend on testing the blockade? *Drug Alcohol Depend*. 2013;133(1):80-85.

Sullivan LE, Moore BA, Chawarski MC, et al. Buprenorphine/naloxone treatment in primary care is associated with decreased human immunodeficiency virus risk behaviors. *J Subst Abuse Treat*. 2008;35(1):87-92.

Teesson M, Ross J, Darke S, et al. One year outcomes for heroin dependence: findings from the Australian Treatment Outcome Study (ATOS). *Drug Alcohol Depend*. 2006;83(2):174-180.

Tetrault JM, Fiellin DA. Current and potential pharmacological treatment options for maintenance therapy in opioid-dependent individuals. *Drugs*. 2012;72(2):217-228.

Tetrault JM, Moore BA, Barry DT, et al. Brief versus extended counseling along with buprenorphine/naloxone for HIV-infected opioid dependent patients. *J Subst Abuse Treat*. 2012;43(4):433-439.

The Commonwealth of Massachusetts, the 188th General Court. An act to provide Addiction/Sobriety Solutions through Increased Substance Treatment (ASSIST) (2014). Bill H.3825. https://malegislature.gov/Bills/188/House/H3825. Accessed April, 2014.

Thomas CP, Fullerton CA, Kim M, et al. Medication-assisted treatment with buprenorphine: assessing the evidence. *Psychiatr Serv*. 2014;65(2):158-170.

Trafton JA, Humphreys K, Harris AHS, Oliva E. Consistent adherence to guidelines improves opioid dependent patients' first year outcomes. *J Behav Health Serv Res*. 2007;34(3):260-271.

Tufts Health Plan. Pharmacy: commercial 3-tier formularies. http://www.tuftshealthplan.com/providers/provider.php?sec=pharmacy&content=pharmacy&WT.mc_id=providers_leftnav_pharmacy&WT.mc_ev=click. Accessed April, 2014.

Tufts Health Plan. Pharmacy medical necessity guidelines: Suboxone® and Zubsolv® (buprenorphine HCl/naloxone HCl). http://www.tuftshealthplan.com/providers/pdf/pharmacy_criteria/suboxone_zubsolv.pdf. Accessed April, 2014.

Tufts Health Plan. Pharmacy medical necessity guidelines: Subutex® (buprenorphine HCl). http://www.tuftshealthplan.com/providers/pdf/pharmacy_criteria/subutex.pdf. Accessed April, 2014.

UnitedHealthcare. UnitedHealthcare clinical pharmacy programs. Suboxone® (buprenorphine HCl and naloxone), Zubsolv and buprenorphine HCl. https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Pharmacy%20Resources/Notification_Suboxone.pdf. Accessed April, 2014.

UnitedHealthcare. UnitedHealthcare – pharmacy benefit. Supply limits per duration. https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Pharmacy%20Resources/Clinical%20Programs/QD_Supply_Limits.pdf. Accessed April, 2014.

U.S. Department of Justice, National Drug Intelligence Center (NDIC). *The Economic Impact of Illicit Drug Use on American Society.* Washington D.C.: United States Department of Justice; 2011. http://www.justice.gov/archive/ndic/pubs44/44731/44731p.pdf. Accessed April, 2014.

Vermont State Legislature. The Vermont Legislative Bill Tracking System. An act relating to pretrial services, risk assessments, and criminal justice programs (2014). Bill S. 295. http://www.leg.state.vt.us/database/status/summary.cfm?Bill=S.0295&Session=2014. Accessed April, 2014.

Vermont.gov. Department of Vermont Health Access (DVHA). Preferred drug list (PDL) & clinical criteria. http://ovha.vermont.gov/for-providers/preferred-drug-list-clinical-criteria. Accessed April, 2014.

Vivitrol® [package insert]. Waltham, MA: Alkermes Inc.; 2010.

Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies – tackling the opioid-overdose epidemic. *N Engl J Med*. 2014;370(22):2063-2066.

Wall R, Rehm J, Fischer B, et al. Social costs of untreated opioid dependence. J Urban Health. 2000;77(4):688-722.

Wang EA, Moore BA, Sullivan LE, Fiellin DA. Effect of incarceration history on outcomes of primary care office-based buprenorphine/naloxone. *J Gen Intern Med*. 2010;25(7):670-674.

Warden D, Subramaniam GA, Carmody T, et al. Predictors of attrition with buprenorphine/naloxone treatment in opioid dependent youth. *Addict Behav*. 2012;37(9):1046-1053.

Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry*. 2011;68(12):1238-1246.

White AG, Birnbaum HG, Mareva MN, et al. Direct costs of opioid abuse in an insured population in the United States. *J Manag Care Pharm*. 2005;11(6):469-479.

Wilcox CE, Bogenschutz MP, Nakazawa M, Woody G. Concordance between self-report and urine drug screen data in adolescent opioid dependent clinical trial participants. *Addict Behav.* 2013;38(10):2568-2574.

Wilcox CE, Bogenschutz MP, Nakazawa M, Woody GE. Compensation effects on clinical trial data collection in opioid-dependent young adults. *Am J Drug Alcohol Abuse.* 2012;38(1):81-86.

Willenbring ML, Hagedorn HJ, Postier AC, Kenny M. Variations in evidence-based clinical practices in nine United State Veterans Administration opioid agonist therapy clinics. *Drug Alcohol Depend*. 2004;75(1):97-106.

Woody, GE, Poole SA, Subramaniam G, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. *JAMA*. 2008;300(17):2003-2011.

WHO Department of Health Statistics and Informatics. Global Health Observatory. World health statistics 2013. http://www.who.int/gho/publications/world_health_statistics/2013/en/. Accessed April, 2014.

Wu LT, Blazer DG, Stitzer ML, Patkar AA, Blaine JD. Infrequent illicit methadone use among stimulant-using patients in methadone maintenance treatment programs: a national drug abuse treatment clinical trials network study. *Am J Addict*. 2008;17(4):304-311.

Zaric GS, Barnett PG, Brandeau ML. HIV transmission and the cost-effectiveness of methadone maintenance. *Am J Public Health*. 2000;90(7):1100-1111.

Zarkin GA, Dunlap LJ, Hicks KA, Mamo D. Benefits and costs of methadone treatment: results from a lifetime simulation model. *Health Econ*. 2005;14(11):1133-1150.

Zhang Z, Friedmann PD, Gerstein DR. Does retention matter? Treatment duration and improvement in drug use. *Addiction*. 2003;98(5):673-684.