



# ADVANCING ACCESS TO ADDICTION MEDICATIONS

A PROJECT OF **THE AMERICAN SOCIETY OF ADDICTION MEDICINE** – THE VOICE OF ADDICTION MEDICINE



Advancing Access to Addiction Medications:  
**Implications for Opioid Addiction Treatment**

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## **Table of Contents**

***Please Note: The following page numbers correspond to the PDF page numbers, not the page numbers within each report.***

### **Report I: Availability Without Accessibility? State Medicaid Coverage and Authorization Requirements for Opioid Dependence Medications, The Avisa Group, 2013.**

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Executive Summary	9
Medicaid Medication-Assisted Treatment Survey Report	12
I: Background: Epidemic of Deaths from Opioid Pain Relievers	12
II: Medicaid Survey Rationale: State Medicaid Programs as Payors for Public Sector Substance Use Disorder Treatment Including Medication-Assisted Treatment with Opioid Dependence Medications and Related Counseling	12
III: FDA-Approved Medications Indicated for the Treatment of Opioid Dependence: Methadone, Buprenorphine and Injectable Naltrexone	18
IV: Initial approvals of SUD Treatment Medications Through Medicaid FFS and Medicaid Managed Care Vendors	21
V: Medicaid Agency Survey Methods and Responses	25
VI: Survey Results	28
VII: Commentary on State Coverage and Utilization/Quality Management Requirements in Medicaid Programs: Injectable Naltrexone and Buprenorphine	41
VIII: Implications of These Findings for Medicaid Enrolled Opioid Dependent Patients and Their Provider and Families	41
IX: State Medicaid Programs That Report Currently Generous, Innovative or Accessible Coverage of MAT for Opioid Dependence	42
Appendices	45
ASAM Medicaid Survey	46
Data	53

## **Report II: Report of Commercial Health Plan Medication Coverage and Benefits Survey, Treatment Research Institute (TRI), 2013.**

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Definitions	72
Executive Summary	73
Methodology	79
Results	82
Discussion	87
References	98
Appendices	100
Additional Results Charts	106

## **Report III: FDA Approved Medications for the Treatment of Opiate Dependence: Literature Reviews on Effectiveness & Cost-Effectiveness, Treatment Research Institute (TRI), 2013.**

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Summary of Review Findings and Implications	
Introduction and Background	115
Findings and Implications	120
Part 1: Systematic Review of Effectiveness Literature	
Executive Summary	123
Introduction and Background	125
Methods	127
Results	129
Discussion and Future Directions	136
Appendices	139
References	161

## Part 2: Systematic Review of Cost-Effectiveness Literature

Executive Summary	177
Introduction and Background	179
Methods	184
Results	186
Discussion	202
Appendices	203
References	211



# **AVAILABILITY WITHOUT ACCESSIBILITY?**

## **State Medicaid Coverage And Authorization Requirements For Opioid Dependence Medications**

FINAL

Report Prepared for the American Society of Addiction Medicine

by

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THE AVISA GROUP

JUNE 2013

# Table of Contents

EXECUTIVE SUMMARY ..... 4

MEDICAID MEDICATION-ASSISTED TREATMENT SURVEY AND STUDY REPORT ..... 7

**I. Background: Epidemic of Deaths from Opioid Pain Relievers ..... 7**

**II. Medicaid Survey Rationale: State Medicaid Programs as Payors for Public Sector Substance Use Disorder Treatment Including Medication-Assisted Treatment with Opioid Dependence Medications and Related Counseling ..... 7**

Coverage for Opioid Medications and Medication Coverage Limitations Are Increasing Simultaneously ..... 9

American Society of Addiction Medicine: Addiction as a Chronic Medical Disorder and Medicaid Coverage ..... 9

Public Policy Concern: Growing Rates of Prescription Opioid Addiction and Uncertain Availability of Medicaid Coverage for Opioid Addiction Pharmacotherapies ..... 10

Brief Overview of Opioid Addiction and the States ..... 11

Distinctive Geographic Characteristics and Differences ..... 12

**III. FDA-Approved Medications Indicated for the Treatment of Opioid Dependence: Methadone, Buprenorphine and Injectable Naltrexone ..... 13**

Methadone..... 13

Buprenorphine ..... 13

Medicaid and Buprenorphine..... 14

Naltrexone: Tablets and Injectable ..... 15

**IV. Initial approvals of SUD Treatment Medications Through Medicaid FFS and Medicaid Managed Care Vendors ..... 16**

Terminology Used Loosely and in Confusing Ways ..... 17

Silos, Silos, Silos: Complicating Integration and MAT ..... 18

Silos within Silos: OTP's and Medicaid ..... 19

Medicaid Managed Care ..... 19

**V. Medicaid Agency Survey Methods and Responses ..... 20**

MAP 1 - Primary Source of Data ..... 22

**VI. Survey Results ..... 23**

Methadone Coverage ..... 23

MAP 2 - Medicaid Funding of Buprenorphine Maintenance ..... 23

Buprenorphine Coverage: Old and New, Brand and Generic Changes Anticipated ..... 24

MAP 3 - Medicaid Coverage Of Buprenorphine/Naloxone ..... 25

Coverage of Injectable Naltrexone (Vivitrol) .....	25
MAP 4 - Medicaid Coverage of Injectable Naltrexone .....	26
Coverage of All Three FDA-Approved Medications .....	27
MAP 5 - Provides Coverage of All Three FDA-Approved Medications.....	27
Prior Authorization Requirements for FDA-Approved Opioid Dependence Medications .....	28
MAP 6 - Prior Authorization Requirements for Buprenorphine / Naloxone.....	28
MAP 7 - Prior Authorization Requirements for Injectable Naltrexone.....	30
Counseling Requirements.....	30
MAP 8 - Counseling Requirements for Approval of Buprenorphine .....	32
MAP 9 - Counseling Requirements for Approval of Injectable Naltrexone .....	33
Time and Dosage and/or Payment Limits: Methadone .....	33
Time and Dosage Limits: Buprenorphine .....	34
MAP 10 - Lifetime Limits on Buprenorphine (Months) .....	34
MAP 11 - Maximum Daily Dose of Buprenorphine .....	35
<b>VII. Commentary on State Coverage and Utilization/Quality Management Requirements in Medicaid Programs: Injectable Naltrexone and Buprenorphine.....</b>	<b>36</b>
<b>VIII. Implications of these findings for Medicaid Enrolled Opioid Dependent Patients and their Providers and Families .....</b>	<b>36</b>
<b>IX. State Medicaid Programs That Report Currently Generous, Innovative or Accessible Coverage of MAT for Opioid Dependence.....</b>	<b>38</b>
APPENDICES.....	40
ASAM MEDICAID SURVEY .....	41
DATA.....	48



## EXECUTIVE SUMMARY

- There is an epidemic of overdose deaths from opioid pain relievers in the United States according to a November 2011 report from the Centers for Disease Control and Prevention. The overdose death rate continues to worsen. It is now comparable to deaths from motor vehicle crashes involving persons under age 65. Overdose death rates have more than tripled since 1990.
- The CDC's report shows that the opioid overdose death rates vary fivefold by state, with higher death rates in states with high rates of poverty, and higher death rates among non-Hispanic whites and native Americans/Alaska Natives. Opioid overdose death rates were highest among persons aged 45-54 years. The overdose rate for this group also saw the biggest increase from 1999 - 2010.
- More rural and more impoverished counties tend to have higher prescription drug overdose death rates. Medicaid populations are at greater risk for overdose.
- According to the CDC report, nonmedical use of opioid pain relievers costs U.S. health insurers approximately \$72.5 billion annually in healthcare costs. These include costs paid by Medicaid, a State-Federal insurance program that will increase in importance under the ACA.
- Dependence on opioid pain relievers, as well as addiction to heroin, is now widely recognized as a chronic disease, not a defect of character. As with other diseases, there are medications approved by the FDA through their science-based approval process as effective for treatment. Today, there are three different FDA-approved medications (as well as several evidence-based counseling therapies used in Medication-Assisted Treatment - MAT) available to treat diagnosed opioid dependence. They could be available to and should be widely used by state Medicaid agencies for treatment of clinically appropriate patients in states and areas most affected by the epidemic in order to stem its death toll. However, these medications must first be covered for and accessible to patients and prescribers under a state's Medicaid benefit rules in order for effective treatment, rather than avoidable overdose, relapse, morbidity and death, to take place for opioid-addicted Medicaid enrollees.
- Because of Medicaid's growing importance as a public payer for addiction treatments and due to the advent of the growing, tragic and avoidable prescription drug addiction and overdose epidemic that is hitting poor urban and rural areas the hardest, the American Society of Addiction Medicine (ASAM) decided to survey and study state Medicaid agencies' coverage of and patient and practitioner access to these critical medication-assisted treatments (MAT). Under the circumstances and based on clinical best practices, ASAM would have liked to see comprehensive Medicaid coverage of and provider access to the three approved opioid dependence medications and associated evidence-based therapies.

- On the contrary, ASAM's 2013 study of Medicaid coverage of and patient and practitioner access to opioid dependence treatment medications demonstrates important coverage and use limitations. These critically needed medications that could help avoid the OPR overdose epidemic are being substantially underutilized by state Medicaid programs (as well as some commercial health insurers surveyed by ASAM under a separate study) just at the time that the U.S. prescription drug epidemic is growing worse and the states themselves are holding prescription drug abuse "summits" that rarely discuss these effective treatments and that are often held without the state Medicaid officials in attendance.
- An independently conducted concurrent national ASAM member survey confirms the results of the ASAM Medicaid survey. ASAM practitioners reported Medicaid coverage, utilization management, financing, reimbursement and regulatory issues as significant obstacles to treatment - the same obstacles that the Medicaid survey finds. This kind of concurrence helps verify the credible findings of both surveys.
- ASAM's Medicaid survey also indicated that there are few Medicaid eligible and enrolled addiction medicine and other prescribers and treatment programs offering MAT. In one Southern state, for example, only one methadone program is obtaining state Medicaid reimbursement. The scarcity of Medicaid eligible and enrolled practitioners and programs that could provide MAT to Medicaid patients limits geographic access for opioid dependent Medicaid enrollees, requiring long commutes and/or Medicaid-paid transportation, whose costs are rising substantially as a result.
- Additional limitations and barriers to real patient and practitioner access are common and risky to the vulnerable addicted patient. Depending on the state Medicaid agency surveyed, they can include the following (See color Maps 1 - 11 in the body of the report that illustrate these findings):
  - No coverage of one or two of the three of the approved medications
  - Limits on dosage prescribed - limits that may not correspond to clinically recommended dosages of the medications
  - Lifetime limits on MAT for methadone and/or buprenorphine, unlike other medications
  - Complex initial prior authorization and reauthorization processes that become more demanding with each reauthorization period
  - Prescription refill limits that do not reflect chronic disease expectations
  - Minimal counseling coverage while using counseling as a preauthorization/reauthorization requirement that requires extensive detail and document submission

- Practitioner limitations (who can prescribe or provide counseling)
- Preauthorization and reauthorization processes specific to MAT for opioid dependence or a particular medication that may take days or weeks while at-risk patients risk relapse, overdose and death
- "Fail first" (or "step therapy") criteria that require documentation that other, possibly less costly therapies have been attempted but were ineffective - all while the opioid-addicted patient waits
- Requirements for submission of extensive documentation of counseling before approval or reauthorization is granted, with rules sometimes including submission of counselors' treatment notes and patient attendance records
- Written utilization management and/or drug utilization review committee notes reported or found on the Internet that show primarily financial, rather than quality management or patient life-saving concerns, as justification for limitations placed on approval of medications for opioid dependence

ASAM's state Medicaid survey also found Medicaid agency respondents working on the medications or associated counseling for MAT who were in separate organizational silos and did not know anything about the coverage or use of other medications or counseling in their agencies or who did not know their own agency's own formulary or utilization management requirements; this lead to intra-agency inconsistency in coverage and access as well as the previously noted inequities in coverage across the state Medicaid agencies.

# MEDICAID MEDICATION-ASSISTED TREATMENT SURVEY AND STUDY REPORT

## I. Background: Epidemic of Deaths from Opioid Pain Relievers

There is an epidemic of overdose deaths from opioid pain relievers in the United States according to a report from the Centers for Disease Control (CDC 2011<sup>1</sup>). The overdose death rate continues to worsen. It is now comparable to deaths from motor vehicle crashes involving persons under age 65. Overdose death rates have more than tripled since 1990<sup>2</sup>. The CDC's report shows that the opioid overdose death rates vary fivefold by state, with higher death rates in states with high rates of poverty, and higher death rates among non-Hispanic whites and native Americans/Alaska Natives. Opioid overdose death rates were highest among persons aged 45-54 years. The overdose rate for this group also saw the biggest increase from 1999 - 2010<sup>3</sup>. More rural and more impoverished counties tend to have higher prescription drug overdose death rates. Medicaid populations are at greater risk for overdose. According to the CDC report, nonmedical use of opioid pain relievers costs U.S. health insurers approximately \$72.5 billion annually in healthcare costs. These include costs paid by Medicaid, a State-Federal insurance program that will increase in importance under the ACA.

## II. Medicaid Survey Rationale: State Medicaid Programs as Payors for Public Sector Substance Use Disorder Treatment Including Medication-Assisted Treatment with Opioid Dependence Medications and Related Counseling

Medicaid was first established via Title XVIII of the Social Security Act of 1965 (PL 89-97) and signed into law by President Lyndon Johnson. It is a means-tested state-Federal matching program. Medicaid is designed to offer enrolled low income persons and families coverage of defined acute, rehabilitative and/or long term health care services and supports, including the state option to provide addiction treatment. Most states have opted to provide addiction treatments under Medicaid. However, typically those addiction benefits have not been updated to reflect current science, including medication-assisted treatment (MAT) using one or more of the opioid dependence medications.

Medicaid coverage of treatment for opioid dependence ranges from very modest to more extensive. Many provide some or all covered services or coverage of patient populations under managed care arrangements, often using multiple regional managed care vendors. Almost all coverage of substance use disorder (SUD) treatments, including opioid dependence treatment medications and associated counseling, are subject to a variety of state Medicaid policies and

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<sup>1</sup> Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report, Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- United States, 1999--2008, November 4, 2011 / 60(43);1487-1492

<sup>2</sup> Centers for Disease Control and Prevention, Policy Impact: Prescription Painkiller Overdoses, November 2011.

<sup>3</sup> Centers for Disease Control and Prevention, Prescription Drug Abuse and Overdose: Public Health Perspective, October 24, 2012

rules. Medicaid rules specify a variety of specific criteria which must be met in order for payment of a service or medication used for the treatment of opioid dependence to be approved for payment. There are special requirements for approval of MAT of opioid dependence, such as documented patient compliance with counseling, that do not apply to other chronic medical diseases such as diabetes or high blood pressure.

With the advent of the Affordable Care Act (ACA), Medicaid has become an even more significant substance use disorder treatment payor for low and limited income persons and families than it was before the passage of the ACA. States that have relied on non-ACA sources of funding to pay for addiction treatment for low income patients will find that they now need to shift those benefits to Medicaid to cover the growing opioid dependent population under health care reform. Certain non-Medicaid funding sources that states have used previously, such as the SAPT block grant, may be reduced nationally as SUD funding for these opioid dependent patients is increasingly offered under Medicaid.

That shift in SAPT block grant funding could be a particular problem for those states that have no Medicaid expansion planned - or for those states whose Medicaid programs currently resist paying for one or all of the opioid medications. In those states, the non-Medicaid funding sources, if any, will likely continue to be even more critical to the opioid dependent patients, even if they access Medicaid funding for their medical care.

Given the complexity of the policies governing Medicaid coverage of opioid dependence medications and practitioner and patient reports that some states were further limiting access to these pharmacotherapies, the American Society of Addiction Medicine (ASAM), a medical professional society representing 3,000 physicians who specialize in the treatment of addiction, commissioned the AVISA Group to survey the state Medicaid programs to gain a clearer understanding of how Medicaid patients can access these therapies. ASAM has long recognized addiction as a chronic disease of the brain that can be treated effectively with evidence-based therapy, including psychosocial treatments and FDA-approved medications as part of medication-assisted treatment (MAT). Currently there are three medications approved and indicated for the treatment of opioid dependence: methadone, buprenorphine/naloxone, and extended-release injectable naltrexone. The ASAM Medicaid survey results focus on coverage, utilization management, and quality management requirements for prescribing or dispensing these FDA-approved medications for opioid dependence.

Despite varied state approaches to the implementation of the Affordable Care Act (ACA) and the expansion of Medicaid, many aspects of the ACA reforms have already been implemented through Federal regulation and statewide Medicaid waivers. These reforms often include substance use disorder benefits but may or may not include coverage of the three FDA-approved opioid dependence medications. Given that many of the remaining provisions of the ACA, including the January 2014 launch of state and/or state-Federally administered health insurance exchanges, understanding the current status of Medicaid coverage for opioid pharmacotherapies and associated psychosocial therapies will be useful in developing future benefit policies.

Much of the original optional state Medicaid coverage of substance use disorder (SUD) treatments focused on traditional acute and ambulatory detoxification and non-medical residential and counseling treatment services, sometimes only for pregnant and post-partum women. Some state Medicaid programs stepped into medication-assisted treatment (MAT) area first by offering coverage for MAT with methadone in OTP's (nationally accredited and SAMHSA regulated and state licensed and regulated outpatient methadone clinics). Methadone was the first medication approved for the treatment of opioid dependence and has been used as for this purpose since 1964<sup>4</sup> but gaining full coverage under Medicaid for methadone has been challenging.

However, as of 2013, according to ASAM survey respondents and secondary sources such as formularies and provider handbooks and reviews of selected public notes from posted Medicaid drug utilization review and pharmacy and therapeutics (P&T) committee meetings, ASAM found that most state Medicaid programs now also offer coverage for buprenorphine treatment that far surpasses the number of Medicaid agencies that cover methadone or naltrexone (tablet or injectable). Medicaid coverage of buprenorphine is usually as a pharmacy benefit, either under Medicaid FFS or via Medicaid managed care plans contracted with the state Medicaid agency.

### **Coverage for Opioid Medications and Medication Coverage Limitations Are Increasing Simultaneously**

An increasing number of state Medicaid programs are now offering some access to brand and generic opioid treatment medications, including both oral and injectable naltrexone. It is clear that as Medicaid becomes a broader coverage and reform vehicle for low and limited income persons and families, it will become an even more major payor for all SUD treatments, including MAT.

In addition, like Medicare, Medicaid is now a plan design bellwether. It is a reference model for state and county coverage reform initiatives, commercial payors, health care organizations, medical and other professional societies and health plans including Medicare and Medicaid accountable care organizations (ACO's). However, as public and private addiction treatment coverage requirements are broadening, Medicaid agencies are looking simultaneously for new ways to spread finite funding across all medical and behavioral health benefits. As a result, increasing numbers of Medicaid programs are imposing limitations on coverage for the opioid pharmacotherapies and counseling that comprise MAT.

### **American Society of Addiction Medicine: Addiction as a Chronic Medical Disorder and Medicaid Coverage**

Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death (ASAM Definition of Addiction). However, addiction can be

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<sup>4</sup> Joseph, PH.D., Herman; Sharon Stancliff, M.D., and John Langrod, PH.D. (October/November 2000). "[Methadone Maintenance Treatment \(MMT\): A Review of Historical and Clinical Issues](#)". *The Mount Sinai Journal of Medicine* 67 (5 and 6): 347

treated effectively and patients can recover if treated with evidence-based interventions such as MAT.

Historically, Medicaid addiction treatment benefits, including MAT, have been more limited than those for medical or surgical health care benefits. With the passage of the 2008 Mental Health Parity and Addiction Equity Act (MHPAEA) and the 2010 Patient Protection and Affordable Care Act (ACA) health care benefits for addiction treatment could become more accessible to more people and could be delivered in a more equitable manner. Given the expansion of benefits for patients who receive SUD coverage in the public and in the private insurance markets, the American Society of Addiction Medicine (ASAM) sought to understand the level of access Medicaid addiction patients have today and how that may impact the ability of public and private health plans and Medicaid to meet their new and expanded addiction treatment coverage demands.

ASAM commissioned two surveys related to coverage and utilization/quality management requirements for the three FDA-approved opioid dependence medications: a survey of state coverage in all 50 state Medicaid programs and a survey of coverage among a sampling of key commercial health plans in the ten most populated states (Report of Commercial Health Plan Medication Coverage and Benefits Survey, Treatment Research Institute, 2013). The results of the Medicaid coverage survey are summarized in this report.

### **Public Policy Concern: Growing Rates of Prescription Opioid Addiction and Uncertain Availability of Medicaid Coverage for Opioid Addiction Pharmacotherapies**

In November 2011, the Centers for Disease Control and Prevention (CDC) declared that the United States was dealing with a prescription drug overdose epidemic. However, at the same time many public and private insurers are creating coverage and utilization management policies that are limiting access to pharmacotherapies approved by the FDA for the treatment of opioid addiction. Due to the deeply-rooted stigma around the disease of addiction and misperceptions about treatment options, efficacy and availability, additional barriers to treatment like coverage limitations put an already undertreated and vulnerable patient population at even greater risk in the midst of the epidemic.

Pharmacotherapies for opioid addiction, used in concert with behavioral therapies and other recovery support services (commonly referred to as “Medication-Assisted Treatment” or “MAT”, have been shown to be highly effective in the treatment of opioid addiction. However, earlier surveys (Avisa, 2008 and others) have shown highly variable and sometimes scanty levels of coverage for MAT for opioid dependence in the public sector, including in Medicaid programs. This ASAM survey sought to better understand the current level of Medicaid coverage for MAT as of May 2013 and expanded on early surveys by exploring Medicaid utilization management and prior authorization requirements not captured in earlier surveys.

While this survey focuses on pharmacotherapies to treat opioid dependence, pharmacotherapies for the treatment of alcohol dependence also exist. Understanding the requirements for covering and approving them under Medicaid and commercial insurance is also important to ASAM and may be the subject of future research. Additionally, since the

majority of Medicaid enrollees are now in managed care programs, including persons with alcohol and drug addictions, it will be important to assess Medicaid managed care vendor coverage and prior authorization policies around the FDA-approved opioid dependence and alcohol medications.

Due to time constraints, this current survey looked largely at the Medicaid fee-for-service program. States using managed care vendors have multiple vendor plans, each of which may have different policies. One mid-Western state Medicaid program told ASAM that it had 9 separate Medicaid managed care vendors to cover the state. Medicaid managed care vendors may or may not adopt the existing state Medicaid formulary and utilization management techniques examined in this survey of opioid dependence MAT. States vary in terms of how closely they manage formulary and other clinical and benefit decisions made by competitively selected managed care vendors. Some states lay out and require use of their own Medicaid policies in RFP's and contracts. Others allow or require clinical discretion and some commonalities in coverage, formulary lists and prior authorization, reauthorization and other utilization and quality management criteria and procedures.

### **Brief Overview of Opioid Addiction and the States**

Opioid addiction today is closely associated with non-medical use of prescription pain relievers (as opposed to primary or initial heroin dependence ). Opioid medications may be legitimately obtained by patients by means of one or more prescriptions. They can also be obtained from illegal transactions ranging from misuse or diversion of legitimately prescribed opioids to outright theft of them, to "loans" of these opioid medications to friends and family members of those with prescriptions. Although addiction to opioids is often associated by the public with use and abuse of heroin, reported illicit use of prescription pain relievers in the U.S. currently far exceeds illegal use of heroin as an increasing public health and public safety concern. According to the National Survey on Drug Use and Health (NSDUH), in 2011, 0.2% of the US population aged twelve and over reported having used heroin in the past year, compared to 4.3% who reported illicit use of pain relievers in that year<sup>5</sup>. Reported illicit use of either prescription opioids or heroin is not equivalent to clinical addiction or dependence, but the magnitude of the difference between reported use and abuse of heroin and the reported use and abuse of prescription opioids reveals far heavier primary or initial use of prescription opioids than of heroin. That changes for some addicted persons as the cost of illegally acquired prescription opioids increases substantially with increased use of these narcotics.

Regular opioid abusers who become seriously dependent often compromise their incomes, or may have low incomes to begin with, and are often forced to turn to cheaper street drugs, especially heroin, to continue dependence. The comparative preponderance of prescription opioid abusers vs. primary or initial heroin users is reflected in the population of those same users who become addicted, some of whom seek and receive coverage and treatment, with and without the of FDA-approved opioid dependence treatment medications and counseling. In any case, the rates of reported use, misuse and addiction to prescription opioids is increasing in many states. It is affecting Medicaid health costs related to that addiction and its consequences,

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<sup>5</sup> SAMHSA, National Survey on Drug Use and Health, 2011



which include heightened morbidity, high utilization of emergency services, overdose and premature mortality, amongst other negative outcomes that afflict those who are not adequately treated for their dependence. At the same time, as noted above, Medicaid as a payor for opioid dependence treatment may or may not have stepped up to meet the challenge of treating these patients with covered, evidence-based medications and counseling.

### **Distinctive Geographic Characteristics and Differences**

The rate of illicit use of prescription pain relievers and heroin differs significantly among the states, which manage their own Medicaid programs. Typically, states have attempted to address their differing and increasing opioid addiction and related treatment issues in low income populations with varying choices and levels of Medicaid funding, Substance Abuse Prevention and Treatment (SAPT) block grant funding, Prescription Drug Monitoring Program (PDMP) program funds and other funding sources, including state and county revenues, child welfare funding, supportive housing funds, criminal justice, reentry and drug court funding and occasional correctional treatment funding.

According to the NSDUH, of the 10 States with the highest reported rates of past year nonmedical pain reliever use within the total population aged 12 or older, 7 out of 10 were in the Western region of the United States (Arizona, Colorado, Idaho, Nevada, New Mexico, Oregon, and Washington). And, of the States with the lowest rates of past year nonmedical pain relievers, 4 were in the Midwest region (Illinois, Iowa, North Dakota, and South Dakota). Within states and regions, illicit use of pain relievers differs substantially by the urban/rural characteristics of the population in the state/region. Interestingly, NSDUH respondents in smaller metropolitan areas reported the highest rate of illicit use of pain relievers (5.4%), while rural areas reported the lowest rate of use (3.5%).

However, research studies that focus specifically on adolescents have suggested that for this at risk population group use rates of illicit pain relievers are higher in rural areas<sup>6</sup>.

These differences in specific population use of illicit prescription opioids and addiction statistics are closely related to the associated geographic and inter-state needs for public and private sector health care and SUD treatments and related medications. This further drives the concomitant need for affected lower income persons for Medicaid and other state and county coverage of these interventions. It is also worth noting that even amongst addicted individuals who are employed or have substantial incomes, as opioid dependence progresses, those incomes may cease and subsequently these once-covered or self-pay addicted patients may have to rely on public funding including Medicaid in order to access addiction treatment and health care if they can.

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<sup>6</sup> April Young, Natalie Glover and Jennifer havens, "Rural Adolescents' Nonmedical Prescription Drug Use: Implications for Intervention" The Prevention Researcher, Volume 19(1), February 2012

### III. FDA-Approved Medications Indicated for the Treatment of Opioid Dependence: Methadone, Buprenorphine and Injectable Naltrexone

#### Methadone

Methadone is a synthetic opioid originally developed as an analgesic in Germany in 1937. In 1949 methadone was repurposed as a potential heroin/opioid treatment by the United States Public Health Service (USPHS) in its Lexington, KY hospital. Later it was developed as a maintenance treatment to correct widely observed opioid addiction relapse after detoxification. In reaction to treatment patients' relapses, Rockefeller University scientist physicians Vincent P. Dole, Marie E. Nyswander and Mary Jeanne Kreek developed methadone as a maintenance treatment in 1964 in New York City to combat a heroin epidemic occurring at that time<sup>7</sup>. Methadone is now widely used as a highly regulated maintenance medication for opioid dependence in opioid treatment programs (OTP's). It is also prescribed by some physicians for severe chronic pain.

As a treatment for opioid addiction in the U.S., methadone has been in the greatest use for the longest period of time of any of the opioid treatment medications ASAM surveyed here. As a Schedule II controlled substance, it is used in the United States in oral form as an evidence-based maintenance treatment for documented opioid addiction. To facilitate the use of methadone as an opioid dependence treatment medication, a unique separate narcotic treatment program (NTP) or opioid treatment program (OTP) regulatory and dispensing system was developed in the U.S., beginning in New York City, Philadelphia and Baltimore in the 1970's and 1980's. Today these clinics operate under detailed federal regulations that stipulate many operational and treatment details, including minimum standards for the provision of counseling to their patients, as well as required national accreditation and reaccreditation. States may impose additional requirements for their operations.

Nationally, in 2011 according to NSSATS data from SAMHSA, there were 1,189 facilities, public and private, accredited and SAMHSA-certified as outpatient methadone maintenance treatment programs (OTP's) in the U.S. Methadone is typically dispensed on site (with take home privileges for certain stabilized patients), rather than prescribed at these specialized clinics, which recently have been allowed to begin to offer buprenorphine under certain circumstances. Some OTP clinics are reportedly also beginning to provide injectable naltrexone, which is a non-narcotic opioid antagonist.

#### Buprenorphine

Buprenorphine, a Schedule III controlled substance, is a more recently introduced synthetic opioid treatment medication for opioid dependence that was initially studied as an analgesic as far back as the 1920's<sup>8</sup>.

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<sup>7</sup> Joseph, et. al, 2000

<sup>8</sup> Campbell, The history of the development of buprenorphine as an addiction therapeutic, Ann NY Acad of Science, 2012 Feb;1248:124-39

It is a partial antagonist/partial agonist that today is combined in the US with naloxone as Suboxone<sup>®</sup> film or generic buprenorphine/naloxone combination tablets to deter abuse and diversion of this synthetic narcotic. It has been brand marketed as Suboxone<sup>®</sup> (buprenorphine/naloxone combination) and Subutex<sup>®</sup>, which is buprenorphine alone, sometimes called the "mono-product". Buprenorphine mono is used for detoxification purposes and the combination of buprenorphine/naloxone is more often used for longer term maintenance treatment. Buprenorphine was first approved in the US by the FDA in 2002 as a medication that did not have to be dispensed at an OTP clinic but instead could be prescribed for opioid dependence and/or detoxification by appropriately qualified, trained office-based MD's with a waiver under DATA 2000.

Although buprenorphine itself had, like methadone, originally been developed as an analgesic, it was only after it was studied as an opioid addiction treatment and later successfully combined with naloxone in order to combat its abuse and diversion potential that it was FDA-approved and accepted by the DEA as an outpatient physician-prescribed treatment for opioid addiction in the U.S., and began to be offered and approved by commercial and public sector payors.

### Medicaid and Buprenorphine

Buprenorphine now has the broadest recognition and coverage amongst state Medicaid programs responding to this 2013 survey of all of the SUD/opioid dependence medication. However, although that availability is broad, buprenorphine is increasingly subject to highly specific and complex Medicaid limitations and requirements that have been adopted in many states.

Buprenorphine was originally FDA-approved in a sublingual buprenorphine/naloxone tablet formulation. Subsequently, the manufacturer introduced a patented film formulation and in March 2013 it ceased production of its tablet formulation due to safety concerns related to possible pediatric ingestion of the tablets.

Several generic tablet formulations of buprenorphine/naloxone were FDA-approved in February 2013 with requirements that the manufacturers provide specific patient risk management strategies comparable to the branded medication. As of June 2013 generic buprenorphine tablets are not widely available but they are expected to enter the market more substantially later in 2013. This ASAM survey found that in most states, there has not been sufficient time as yet for Medicaid plans to update their existing formularies and/or for the prior authorization processes to accommodate these generic buprenorphine/naloxone tablets. However, Massachusetts Medicaid did so as of March 2013 and the generic buprenorphine/naloxone tablets are reported to be currently available at pharmacies in that state.

Manufacturers of the newly approved generic buprenorphine/naloxone tablets may not yet have negotiated rebates with most State Medicaid programs as of the May 2013 date of this survey, so the state Medicaid formulary approval processes for the generic products are likely still developing. The market for generic buprenorphine in state Medicaid programs, as well as utilization management requirements for the tablets to be added to formularies, may look quite different next year. Many states have mandatory generic substitution programs that have not yet

been invoked to cover buprenorphine. In fact, several of the ASAM Medicaid survey respondents contacted by the Avisa Group said that currently the generic buprenorphine/naloxone tablets "cost more than the brand name Suboxone<sup>®</sup> film" and that they were not sure when or if that situation would change.

### **Naltrexone: Tablets and Injectable**

Naltrexone 50 mg daily tablets, now frequently marketed under the trade names of Revia and Depade as a generic medication, have been available since FDA approval in 1984. Naltrexone was first studied as a treatment for opioid dependence, but the marketing effort by DuPont for commercializing the tablet form of the medication fell short of expectations. Actually, the FDA-approved medication's label currently does not recommend or indicate its use as an opioid dependence treatment due to patient compliance issues, although it is still FDA approved. The tablets are now recommended and used primarily for alcohol dependence or for highly motivated opioid dependent patients who are likely to comply with taking the tablet medication, such as impaired health professionals in danger of losing their licenses due to opioid dependence and/or alcohol dependence. In general, the tablets are infrequently prescribed in the U.S, probably due to the patient compliance issues noted on the official label, as well as concerns that the daily dose in the generic tablets leads to more patient side effects.

A long-acting injectable formulation of naltrexone with the brand name Vivitrol<sup>®</sup> was approved by the FDA in 2006 for alcohol dependence and in 2010 for the prevention of relapse of opioid dependence after detoxification. As a physician-prescribed clinician-administered injectable medication, it may be covered under a Medicaid plan's pharmacy benefit or medical benefit, unlike either the generic tablet form of naltrexone or the various formulations of buprenorphine, which are almost always covered as outpatient pharmacy benefits. If listed under medical benefits as an injectable like certain cancer medications, the prescribing physician must first "buy and bill" the medication in order to be reimbursed by Medicaid or other health plans.

This emphasis on the outpatient medical benefit means the prescribing physician must purchase the medication and can only bill for it after it has been administered, unlike a medication that is dispensed to a patient with a prescription by a pharmacy. Visits for medication monitoring by the prescribing physician may or may not be approved. Moreover, under Medicaid it is also quite likely that the prescribing physician must obtain prior authorization for the injectable medication. That process can take from day(s) to weeks, depending upon the state Medicaid agency or vendor. Patient visits for monitoring and for referral to counseling may be subject to separate approvals.

If the injectable naltrexone is covered as a Medicaid pharmaceutical benefit, however, adjudication and approval of the medication is much more rapid and electronic, often taking 24 hours or less if requirements (edits) are met. However, substantial prior authorization requirements may also be embedded in the electronic approval process. Counseling may be dealt with separately under medical benefits. Documentation of "patient is enrolled in approved substance use disorder therapy" may also be required during preauthorization and repeated in reauthorization in order for the treatment plan and the medication involved to be approved.

#### **IV. Initial approvals of SUD Treatment Medications Through Medicaid FFS and Medicaid Managed Care Vendors**

The state Medicaid agency approval or disapproval process for new or reconsidered medications for opioid dependence or other purposes is typically handled by its "Pharmacy and Therapeutics" (P&T) committee processes. Such an approval may also be the subject of related drug utilization review committee deliberations that weigh in the final decision. The process of putting a new or reconsidered medication on the agenda of these committees and then assessing medication for approval can take six months or more if it is controversial or costly or if evidence is not submitted promptly, although priority reviews can be conducted more quickly if the Medicaid agency decides to do so. Typically, each medication is considered separately and is presented by a committee member who may or may not advocate for it with other committee members, depending upon that person's assessment of the product. That committee member may or may not be a specialist in use of that medication. Specialty physicians may or may not be asked to participate in such reviews. P&T approval often involves explicit phased processes, including review of the research literature, proposed protocol provisions and comparison of the proposed new medication to the Medicaid agency or Medicaid managed care vendor's and FDA clinical indications and standards, as well as additional considerations involving cost effectiveness and safety, once efficacy is considered to have been established for the medication.

The amount of discounts/supplemental or initial rebates (see below) a pharmacy manufacturer is willing to offer in exchange for preferred or regular "contract drug list" status for the medication also has an impact on Medicaid and other P&T approval requirements and the time elapsed between initial application and approval or disapproval of coverage. This usually extensive time period, given the type of analyses performed and the fullness or openness of the pharmacy P&T meeting agenda, can either deter or encourage medication manufacturers, as more time spent in supporting application efforts means more dollars spent in the application process, which may or may not result in approval. Results from these assessments are sometimes available on the Internet, although the meetings themselves and the internal committee deliberations involved are often opaque rather than transparent.

This issue of how long it takes to place a medication on the P&T Committee agenda and to consider and approve a medication, as well as the medication's status as contracted and preferred or not preferred, may explain why the Medicaid survey Avisa conducted for ASAM in April and May of 2013 was too early to observe the impact of February 2013's FDA-approved generic buprenorphine/naloxone on Medicaid formularies, preferred drug lists and prior authorization requirements and procedures. The Medicaid status of brand and generic buprenorphine/naloxone will undoubtedly change in many state Medicaid programs and vendors' formularies and contract drug lists as 2014 approaches.

## Terminology Used Loosely and in Confusing Ways

In terms of understanding the depth and breadth of coverage and coverage requirements for medications like opioid dependence medications, terminology in health care and Medicaid programs must be clear to prescribers and patients. However, in Medicaid agencies and in health plans, use of specific terms and jargon is typically not defined and not standardized. For example, the terms "Formulary" and "Preferred Drug List" are often used interchangeably, but there is a difference. Technically, a formulary is a list of all the medications that are normally covered by a health plan or payor; some medications, however, may have a higher or lower co-payment requirement or even specific agency or vendor "code restrictions" regarding their use that are not like those affecting other medications. For example, in one Western state that responded to this survey, there is an ongoing quiet discussion of the potential use of specific "payment code restrictions" that would affect one of the medications for opioid dependence treatment by specifying one specific population to be covered.

In contrast, a Preferred Drug List is usually understood to be list of those drugs with either the lowest co-payment requirements and/or the ability for practitioners to prescribe these medications without a prior authorization or specific restrictions, often due to successful supplemental rebate negotiations with a manufacturer. Thus, a Preferred Drug List may be a subset of a broader formulary. However, some Medicaid agencies surveyed here maintained only a single list that they refer to as a Preferred Drug List. Those agencies distinguish among drugs on that list as to whether or not they are Preferred or Non-Preferred, the latter of which typically require prior authorization or may have other special requirements applied.

"Rebate" is the term used for discounts in Medicaid pharmacy discussions. All drug manufacturers are authorized by Section 1927 of the Social Security Act to provide a standard rebate to Medicaid that varies according to the type of medication. In addition, manufacturers and State Medicaid agencies may negotiate a "Supplemental Rebate" for specific drugs in addition to this more standard discount. A negotiated supplemental rebate from a manufacturer generally entitles an approved medication to placement on a Preferred or Contract Drug List. The Act also prevents pharmaceutical companies from giving others higher discounts than the government obtains.

Typically, manufacturers who seek to have a medication considered for a Medicaid contract or preferred drug list must submit a petition to the state Medicaid agency (usually the pharmacy policy and/or contracting division), stating why they feel their medication should be considered for that list and indicating the current pricing. If the petition is accepted initially (they can be subject to required changes in order to proceed), negotiations can then take place between the state Medicaid agency's pharmacy contracting division and the manufacturer. If the negotiations are successful, the medication may be placed on the Preferred or Contract Drug List. Such a designation makes it easier and quicker for practitioners to obtain approval to prescribe, to possibly by-pass otherwise required preauthorization and reauthorization, and for patients to receive that medication. Opioid addiction can be life threatening and an addicted patient's failure over an extended period of time to obtain a medically necessary medication due to preauthorization and other requirements may lead to treatment drop out, overdose, relapse, and

significant premature morbidity and mortality. That is why these distinctions and timing are especially important in addiction medicine, as they are in the treatment of other chronic, potentially life-threatening diseases such as diabetes.

### **Silos, Silos, Silos: Complicating Integration and MAT**

Just as there are funding silos for addiction and other medical treatments and medications in Federal, state, county and commercial coverage programs, this survey process revealed that there are additional silos within Medicaid agencies themselves. The silos are particularly likely to be found within certain larger state agencies whose organizational charts were available on the Internet. These silos persist despite strong public policy efforts to pay for better "integrated care" and they complicate that integration initiative under the ACA when those efforts involve opioid dependent patients being treated for addiction and other diseases simultaneously, as part of the treatment may be approved while other components handled by other silos do not obtain approval.

The organizational benefit silos are especially salient for accessibility and availability of opioid dependence medications in Medicaid agencies and vendor operations today. Currently, the FDA-approved medications for treatment of opioid dependence can involve as many as four different areas of Medicaid operations that may be handled within that agency or by a host of vendors: Coverage (if any) of Narcotic Outpatient Treatment Programs (methadone), Pharmacy benefits (buprenorphine / buprenorphine/naloxone, naltrexone tablets), and Medical benefits (injectable naltrexone), as well as Pharmacy Contracting and Policy.

These areas may be separate and not well linked to one another's decision systems, staffing or approval processes around the medications and opioid dependence treatment plans. ASAM also found that especially in large states, the professional Medicaid staff responsible for the different silos and the different SUD opioid or alcohol medications may not meet together, have consistent policies or be aware of the details of coverage of the other FDA-approved addiction medications that are available under different benefits.

In some cases, state Medicaid programs reported to ASAM that they cover certain medications, particularly injectable naltrexone, under both their separate pharmacy and medical benefit areas. Typically, the coverage for visits to prescribe the medication and monitor its effects is handled under the medical benefit (unlike methadone in OTP's where the coverage for the medication and the visits is bundled), while the medication coverage itself is pharmaceutical and/or medical and subject to different approval processes. Occasionally, state or county Medicaid agencies may give physicians or programs the option to bill for the medications under either the medical benefit or the pharmacy benefit, while expecting that visits will be approved and billed separately under the medical benefit. Different prior authorization requirements typically pertain to each different area and to each opioid treatment medication. Additional and separate processes may affect opioid dependence or alcohol dependence medications between and within Medicaid agencies' FFS divisions and their managed care or managed care vendor operations. The implication is that patterns of actual use of these medications and the availability of necessary MD-monitoring and counseling visits are a function of the coverage and ease of accessibility as much as of their clinical appropriateness for a specific patient.

Many of the respondents to Avisa's Medicaid 2013 survey were Medicaid pharmacists, although surveys were also sent to Medicaid Directors and to Medicaid medical directors. Pharmacy staff reported little, if any, knowledge of Opioid Treatment Programs (OTP's) or of methadone as a medication for treatment of opioid dependence. Despite explicit written and oral instructions as part of the survey and during arranged telephone interviews requested by some state agencies, sometimes the pharmacists responded to questions about methadone for opioid dependence treatment with respect to methadone prescribed by a physician for treatment of pain, not a subject of this survey. Additionally, the pharmacy respondents reported that they did not know much about medical benefit coverage of visits or of injectables (even though these are medications), so some pharmacists were not familiar with injectable naltrexone (Vivitrol®) and whether or not and under what circumstances it was covered or not covered under medical benefits.

### **Silos within Silos: OTP's and Medicaid**

If covered by Medicaid at all, OTP's typically occupy a special silo within a silo, their own world, with respect to regulatory and Medicaid oversight of their coverage or lack of it, their clinical processes, their reimbursement and their regulations. In the U.S. methadone cannot be prescribed for opioid dependence treatment in outpatient physician practice; it can only be dispensed for that purpose in accredited and licensed methadone clinics. Avisa found in previous surveys and in the work of other policy researchers that medical and other staff involved with the complex and demanding operations, regulation or reimbursement of OTP's typically devote themselves exclusively to OTP's and reported that they know little about other opioid treatment medications and reimbursement or regulatory systems. OTP provider specialists also may not be very familiar with Medicaid agencies or billing, sometimes even when Medicaid covers their costs. Similarly, surveyed Medicaid staff not much involved with OTP's or with methadone for opioid dependence treatment, reported that they know little about methadone programs, even if their Medicaid agency does cover their costs.

### **Medicaid Managed Care**

Medicaid plans are increasingly moving to managed care arrangements. From 2002 through 2011, according to CMS, the number of Medicaid recipients in fee-for-service (FFS) Medicaid declined from 17.0 million to 14.7 million, while the number enrolled in managed care arrangements increased from 23.1 million to 42.4 million. Correspondingly, the percentage of Medicaid enrollees in managed care arrangements reportedly increased from 57.6% to 74.2% (2011). Each managed care plan may be slightly or greatly different from others; as of July 1, 2011 there were a total of 693 managed care entities serving 42.4 million Medicaid enrollees<sup>9</sup>. The migration to managed care arrangements for Medicaid enrollees continues today.

Managed care arrangements for Medicaid enrollees are subject to extensive federal, state and local statutory and regulatory requirements but they still vary substantially in terms of benefits and coverage or preauthorization rules. Although an often-stated reason to move more Medicaid enrollees into managed care plans is the hope that it will increase the quality of care

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<sup>9</sup> Centers for Medicare and Medicaid Services, Medicaid Managed Care Enrollment Report, Summary Statistics as of July 1, 2011



provided to enrollees, cost is of equal or even greater concern. Judging by public secondary sources Avisa found on the Internet and added to or used in lieu of missing ASAM survey results in certain states, deliberations of available state Medicaid committees such as drug utilization review committees made far fewer, if any, references to quality of care issues than to cost issues with regard to the opioid dependence medications. Although this survey did not systematically review DUR committee notes due to time and availability issues, the ones that were found for non-responding states conformed to this general description, especially when the committees were discussing certain of the opioid dependence medications.

Although theoretically it would be possible for managed care plans to provide even better access to approved medication assisted treatment (MAT) for opioid dependence than in Medicaid fee-for-service arrangements, in practice this does not often seem to happen. However, as noted earlier, there were simply too many managed Medicaid vendors for ASAM to survey in this brief time period, even if those numerous plans would have agreed to participate; given the difficulties encountered in interviewing/surveying commercial health plans on the subject of opioid dependence/MAT coverage as discussed in Part II of this set of surveys, it seems as if it would be challenging to motivate the managed care vendors to participate unless they were required to do so by their state Medicaid contracting agencies or by CMS.

Therefore, for reasons of practicality, timing and with the knowledge that FFS benefits and practices provide access to approved medication-assisted treatment for opioid dependence that is at least as good as that offered through managed care arrangements and is sometimes duplicated by managed care plans or required by contracts with the state Medicaid agencies, this survey sent to every state has focused on fee-for-service Medicaid plans and their coverage and utilization review and quality requirements for FDA-approved opioid dependence treatment medications and counseling. This approach provided insights into the likely coverage and actual accessibility of these medications in Medicaid managed care as well.

## **V. Medicaid Agency Survey Methods and Responses**

Surveying state Medicaid agencies proved to be very complicated and time consuming for the researchers. Lists of email addresses and names of Medicaid Directors, Medicaid Pharmacy Directors, and Medicaid Behavioral Health Directors had to be developed for the purposes of communicating and quickly administering this Medicaid sector survey. Except for the names of Medicaid Directors, the names of other key Medicaid officials were often not listed on state Medicaid websites or the CMS website, nor were they published in directories that were found during this brief timeframe. As in "snowball" sampling, the surveyors had to ask officials who were listed and who responded to the survey to identify other relevant staff. This process identified a few additional respondents but also revealed that some key positions were unfilled at the state Medicaid agencies (e.g. no Medical Director, etc.).

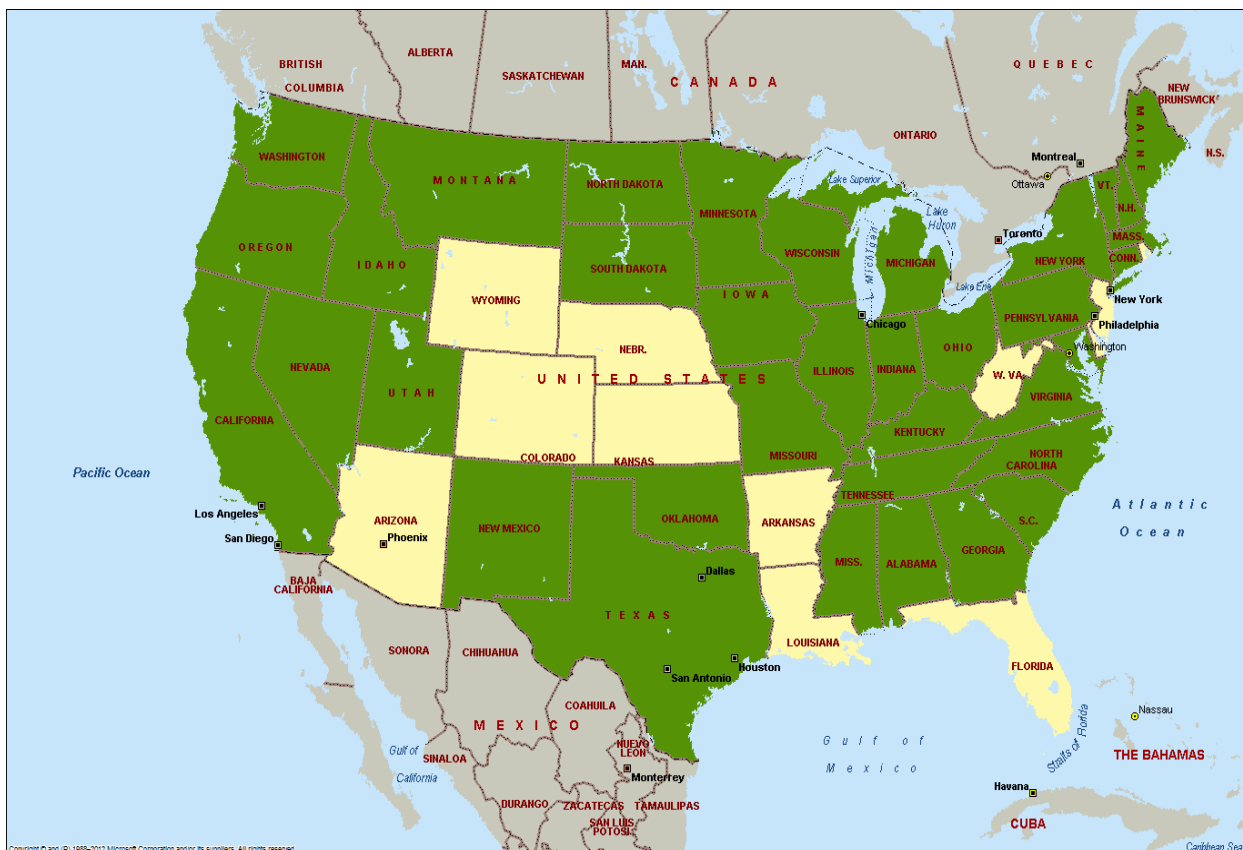
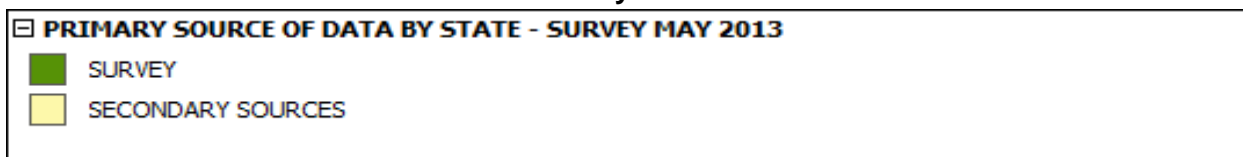
A total of 121 email addresses of Medicaid officials from the fifty states plus the District of Columbia were identified after investigation for the purpose of emailing the survey to potential respondents. The survey was emailed with attachments including an introductory letter from ASAM, supporting letters from the Center for Substance Abuse Treatment, the Office of

National Drug Control Policy, and the Federal Department of Health and Human Services, as well as a transmittal note to each of the identified officials in each State Medicaid agency, in order to increase the probability of a having at least one response from each State. To the extent possible, respondents' answers were cross-checked.

Medicaid officials were given the opportunity to submit their responses by e-mail or to be personally interviewed by senior staff of the Avisa Group. As noted, substantial letters of support accompanied the survey, along with timing expectations. After 10 days to two weeks, a follow up note was sent to each of the non-responders with another copy of the survey and personal notes and e-mail requests or calls to respondents. Additionally, Avisa sought responses through ASAM members and staff and other professional organizations including AATOD and the public policy teams of manufacturers. The timeframe for conducting this survey was extremely short: surveys were initially sent out in mid-April 2013 and were due by mid-May 2013.

With substantial effort, ASAM received completed Medicaid surveys from 37 states; 9 states plus the District of Columbia failed to respond at all and one state promised a response that never arrived despite numerous reminders and appeals. Three states declined requests for a response. Avisa reviewed the web sites and substantial secondary sources for all states that did not submit a completed survey, as well as web sites and other secondary sources of those states that did respond when their information was incomplete, seemed unlikely or unclear. Avisa found it was important to double check some of the responses with secondary and professional sources, as some respondents from Medicaid agencies were very careful while others were not. Therefore, this survey contains information on all 50 states plus the District of Columbia and indicates whether or not the primary source of results came from the survey or from public/state websites or other Internet/professional secondary sources (See Map 1 below).

## MAP 1 - Primary Source of Data



**NOTE: COMPLETE DATA FOR ALL MAPS INCLUDING DATA FOR ALASKA AND HAWAII MAY BE FOUND IN THE APPENDIX**

Where state agencies either refused respond (3) or provided no response despite frequent follow up requests, the Avisa researchers used secondary sources, as stated. The non-responding states are shown in light yellow above.

The remainder of the states (37) did respond to the survey. However, as noted, some agencies required extensive follow up before responding, while others were only able to or chose to answer only the pharmacy benefit sections. This occurred even when the State Medicaid Commissioner was supportive of answering the survey. Some other respondents provided information on the survey form that was contradicted by their state's multiple published secondary sources; in such cases Avisa used the most clearly available information from secondary sources. As noted earlier, an apparently common error by respondents, despite explicit reference in the survey form to methadone provided by narcotic treatment programs as

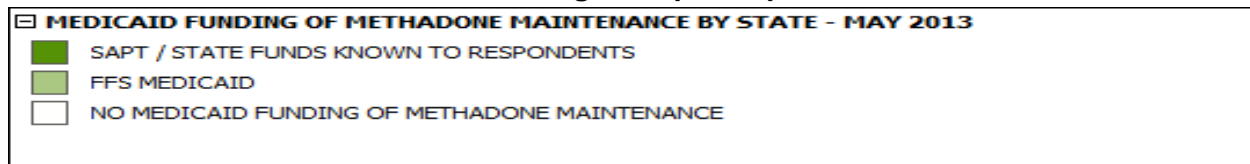
a treatment for opioid dependence, was to respond to the methadone items in terms of the coverage of methadone under the pharmacy benefit as a treatment for pain.

## VI. Survey Results

### Methadone Coverage

A total of 31 state Medicaid FFS programs were found to cover methadone maintenance treatment provided in outpatient narcotic treatment programs. Some of these state Medicaid respondents noted that the states also provide additional public funding through SAPT / state funds for OTP's. Another three (3) states indicated that methadone treatment is funded in their state but only through the SAPT block grant and/or state or county funds. Seventeen (17) states indicated through the survey or secondary sources that there is no Medicaid FFS funding of methadone maintenance treatment in their state programs. Results from responses to the Medicaid survey or from information in published current state secondary sources available via the Internet are displayed below in color-coded maps (See Map 2 below for methadone).

**MAP 2 - Medicaid Funding of Buprenorphine Maintenance**

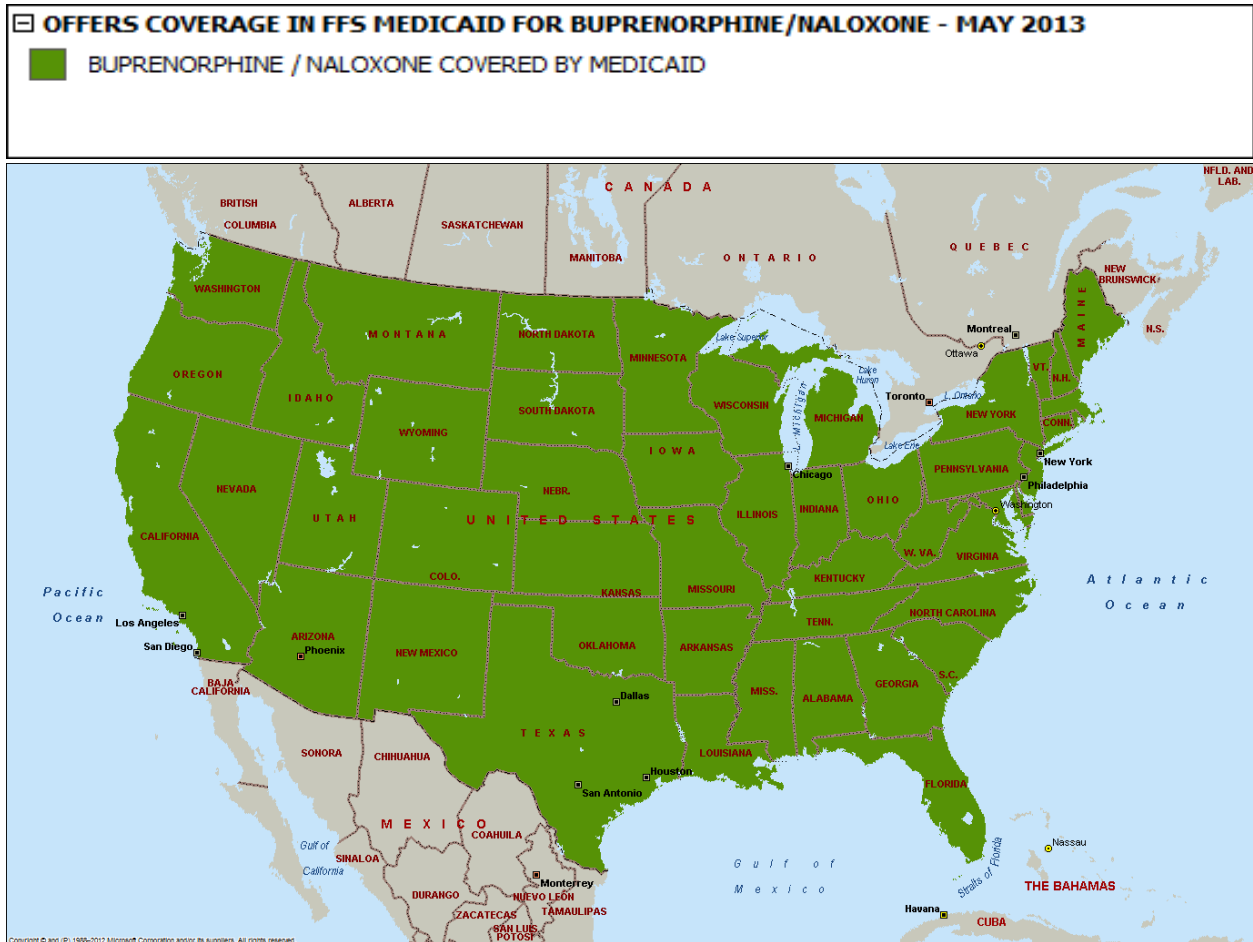


### **Buprenorphine Coverage: Old and New, Brand and Generic Changes Anticipated**

According to survey response and/or secondary source data, every state Medicaid agency covers buprenorphine/naloxone, either in the film form of the branded Suboxone<sup>®</sup> formulation or in the generic sublingual tablet formulation providing buprenorphine and naloxone, or both, always reportedly as an outpatient pharmacy benefit. Despite the fact that the manufacturer of Suboxone<sup>®</sup> announced that the tablet form was discontinued in March of 2013 in favor of the film formulation, many states currently continue to list the tablet form on their Medicaid preferred drug lists or formularies and some pharmacy respondents interviewed said their medication suppliers still had some of the discontinued tablets on hand. And, despite FDA approval for the introduction of generic buprenorphine/naloxone tablets in February 2013, few states explicitly declared that they require providing the generic formulation as of April- May 2013.

As noted in the discussion above, this may be due in part for the time required for Medicaid agencies or vendors to negotiate supplemental rebates with the manufacturers of the generic product and then shepherd the arrangement through the P&T committee process. Medicaid pharmacy respondents who responded to the survey expected that more state Medicaid programs will do so as their processes for implementing generic substitution policies for this generic medication progress and prices and rebates are set (See Map 3 below).

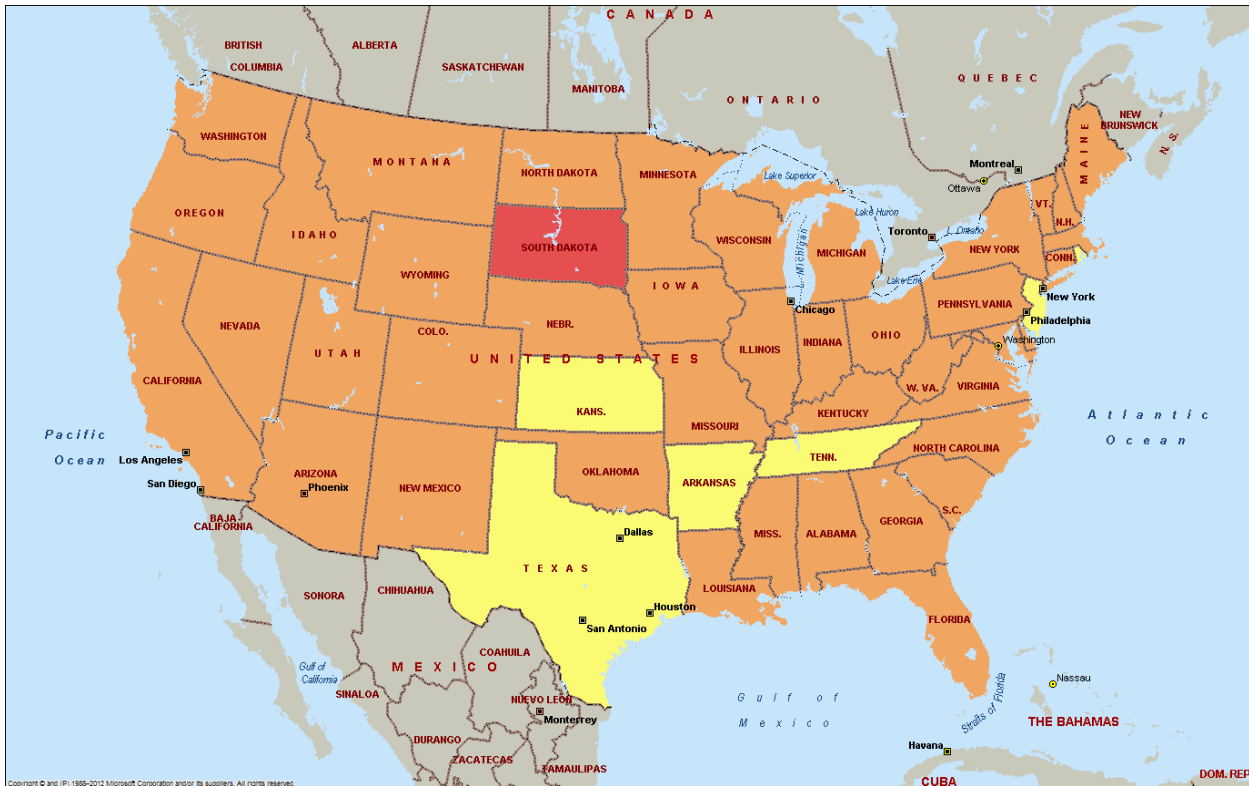
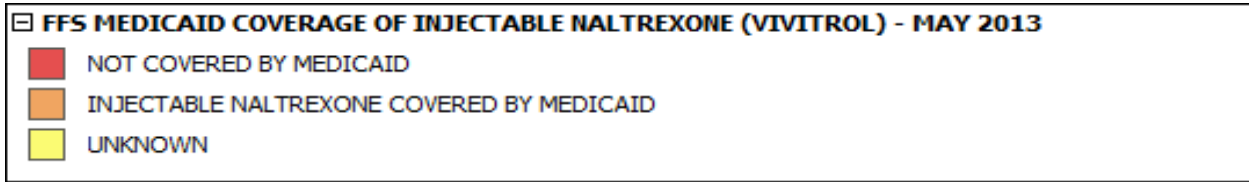
### MAP 3 - Medicaid Coverage Of Buprenorphine/Naloxone



#### Coverage of Injectable Naltrexone (Vivitrol)

A total of 42 states have some evidence via survey or secondary sources that they offer some Medicaid coverage of injectable sustained release naltrexone (Vivitrol<sup>®</sup>), a more recently approved opioid dependence medication than buprenorphine/naloxone or methadone. One state indicated that Vivitrol<sup>®</sup> is not covered. No information was able to be obtained from 8 states. In general, the Medicaid agency information on injectable naltrexone/Vivitrol<sup>®</sup> was far less comprehensive than was the information on buprenorphine/naloxone or on methadone (See Map 4 below).

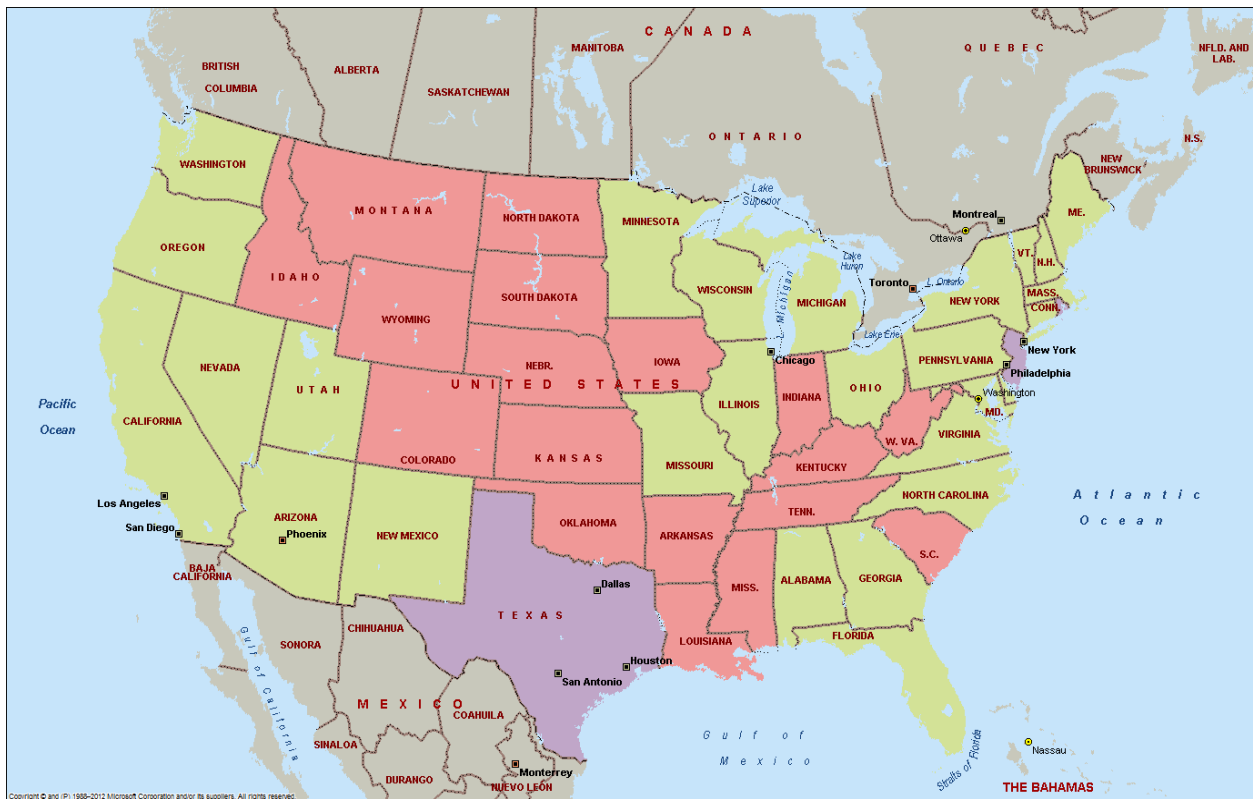
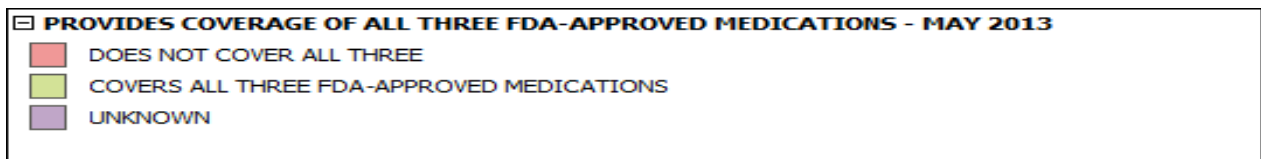
## MAP 4 - Medicaid Coverage of Injectable Naltrexone



### Coverage of All Three FDA-Approved Medications

A total of 28 states have evidence that all three FDA-approved medications for the treatment of opioid dependence are covered under Medicaid. However, it is important to note that the extent of coverage varies greatly among these states, and access requirements attached to any or all of these medications differ from one state to another (See Map 5 below).

**MAP 5 - Provides Coverage of All Three FDA-Approved Medications**

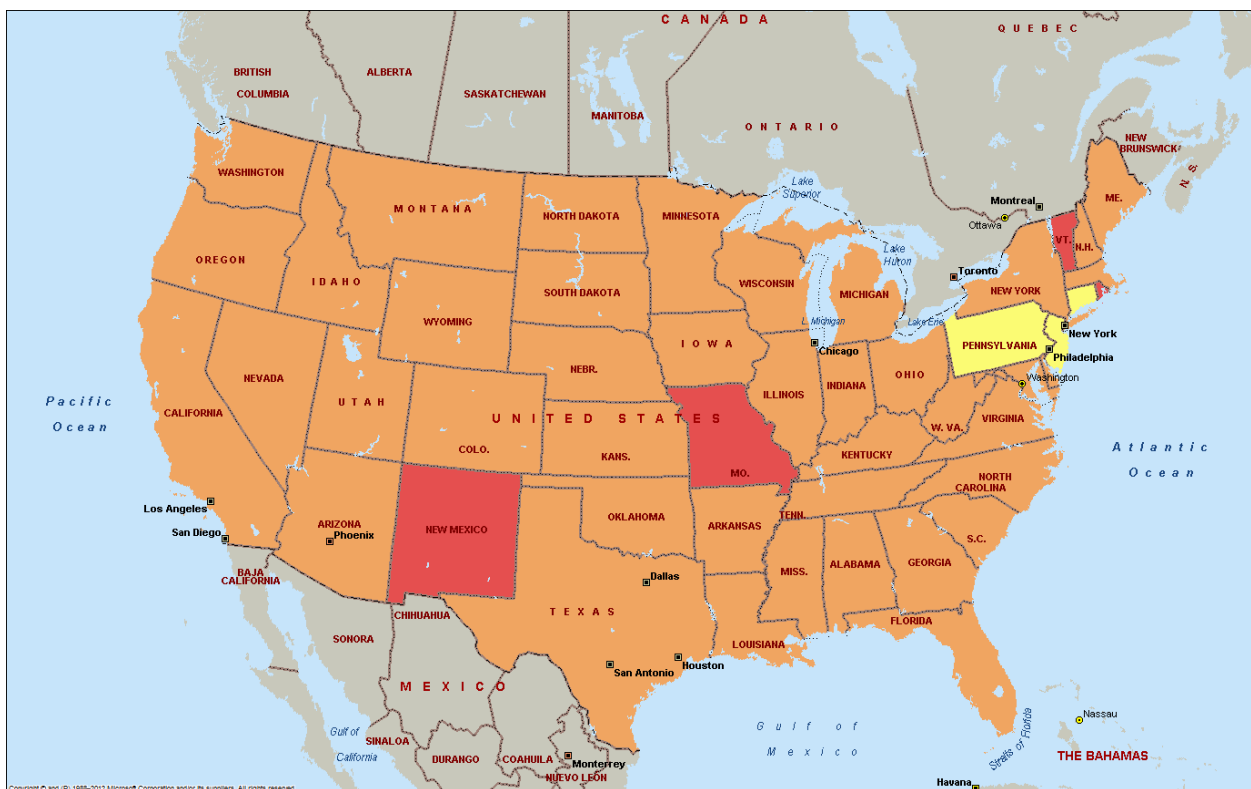
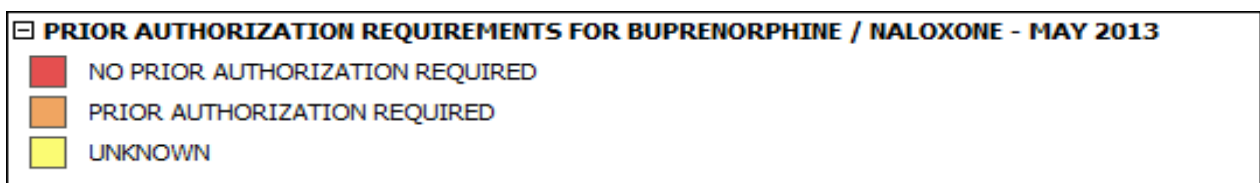




## Prior Authorization Requirements for FDA-Approved Opioid Dependence Medications Buprenorphine / Naloxone

At least 44 states require prior authorization in order to obtain a prescription for buprenorphine / naloxone for opioid dependence treatment. As noted earlier, the criteria for approval vary by state, as do the time periods required to actually process a request for approval. Only 4 states appear to permit qualified physicians to prescribe buprenorphine / naloxone without requiring prior authorization and no information could be obtained for 3 states. In contrast, methadone for opioid dependence treatment, if covered, was not subject to prior authorization (See Map 6 below).

**MAP 6 - Prior Authorization Requirements for Buprenorphine / Naloxone**



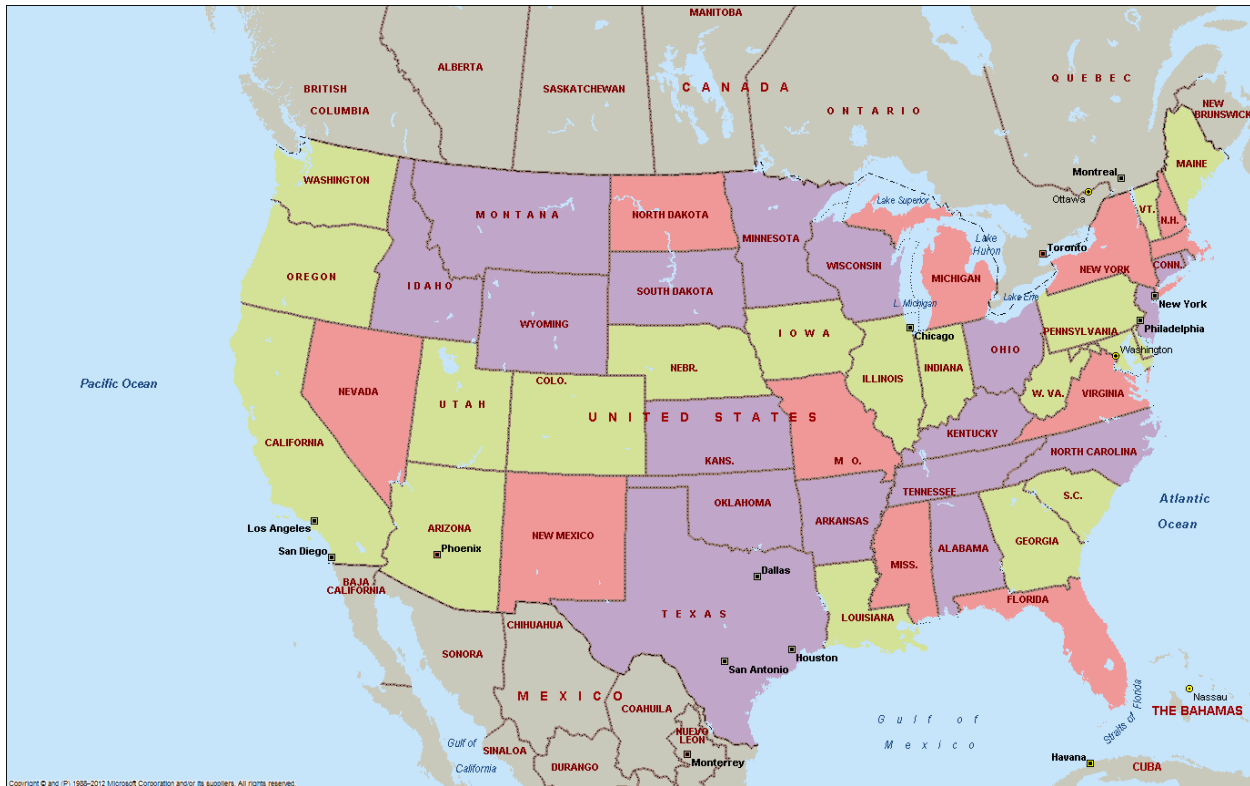
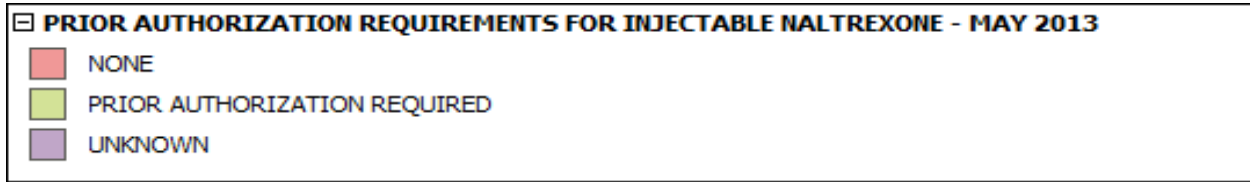
## **Injectable Naltrexone**

As noted previously, less information is available for prior authorization requirements for injectable naltrexone (Vivitrol<sup>®</sup>), the most recently approved medication, FDA-approved in 2010 for treatment of opioid dependence. This is the result of at least three factors:

- The time required for new medications to be added to Medicaid drug lists and formularies;
- The fact that some states treat coverage of injectable naltrexone (Vivitrol<sup>®</sup>) as a medical benefit and not a pharmacy benefit, so the medication is not placed on the drug list at all and therefore is not subject to pharmacy preauthorization but rather to medical division preauthorization that is separate from pharmacy preauthorization; and
- The fact that many respondents to the ASAM survey were pharmacy directors who were unfamiliar with injectable naltrexone (Vivitrol<sup>®</sup>) because it was not covered as a pharmacy benefit.

The data available from the survey and from secondary sources indicate that 20 states require prior authorization for injectable naltrexone, 11 states do not appear to require prior authorization and 20 states had no information available on prior authorization requirements for this alcohol and opioid dependence medication as a component of addiction treatment (See Map 7 on next page).

## MAP 7 - Prior Authorization Requirements for Injectable Naltrexone



### Counseling Requirements Buprenorphine / Naloxone

The Federal application for a waiver that permits a trained and qualified physician to prescribe buprenorphine for the treatment of opioid dependence in the outpatient practice of that physician requires the applicant to certify that "I have the capacity to refer patients for counseling and other appropriate services". There are a substantial number of research studies that suggest that treatment of opioid abuse with an FDA-approved medication combined with effective evidence-based counseling provides outcomes superior to either intervention by itself<sup>10</sup>. Nevertheless, counseling alone still remains an approved treatment for opioid addiction

<sup>10</sup> McLellan et al, The Effects of Psychosocial Services in Substance Abuse Treatment, JAMA, 1993 Apr 21;269(15):1953-9.

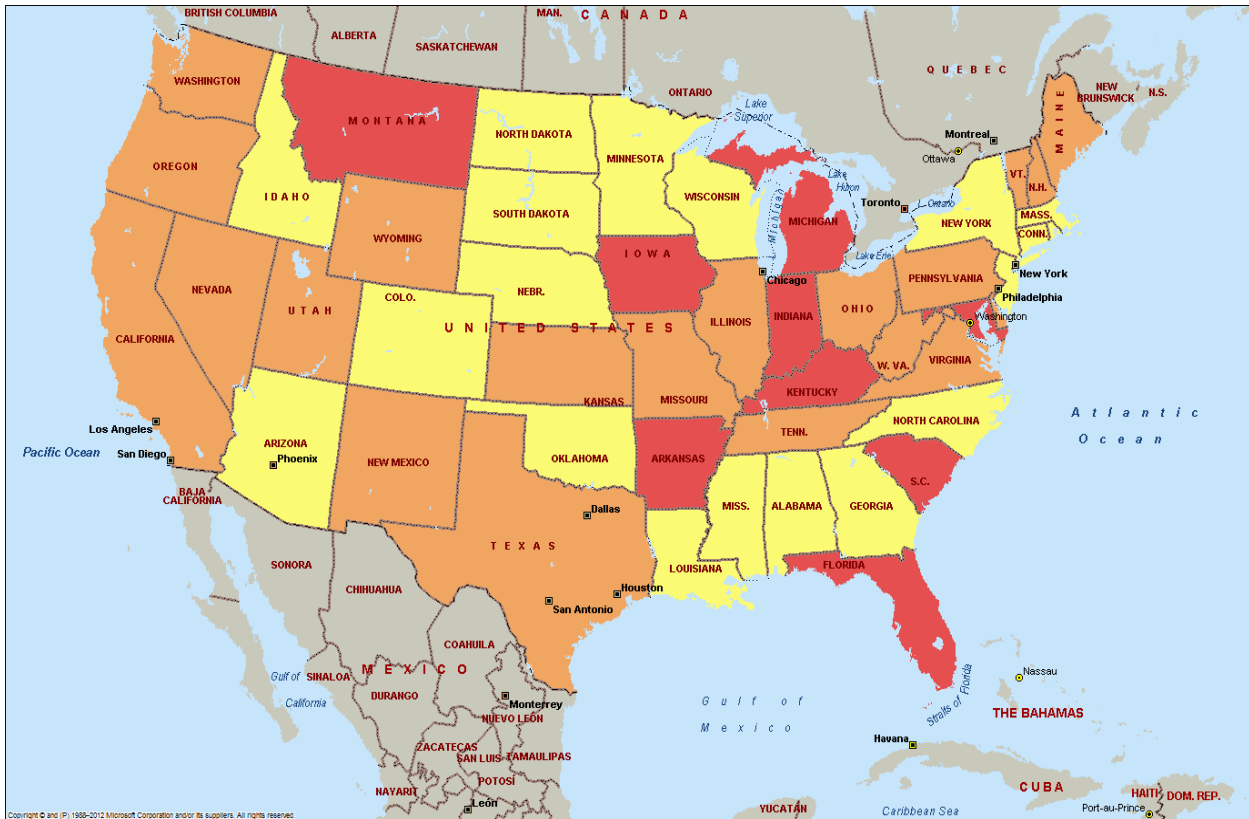
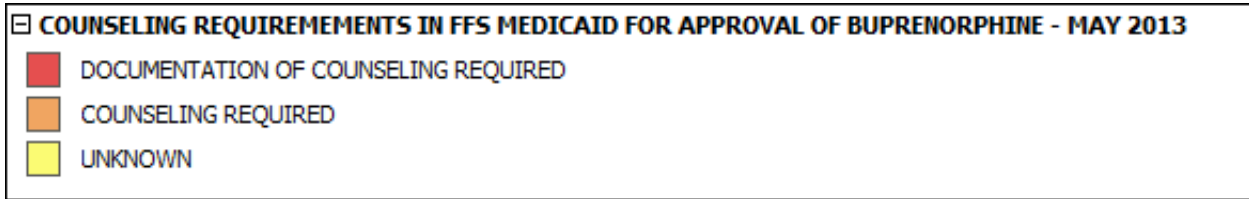
in Medicaid agencies, with no Medicaid requirements that approval of counseling be conditioned on compliance with a associated medication regimen for opioid dependence or alcohol dependence, even though FDA approved medications are available.

However, many state Medicaid agencies do condition approval of the medication on compliance with buprenorphine counseling requirements, with varying levels of physician documentation required in order to approve a prior authorization for the medication, even though Federal physician waivers to prescribe buprenorphine in outpatient practice only require the assertion of the physician's ability to refer the patient to adjunctive counseling.

The results of this survey and information obtained from secondary sources indicate that 21 states require a physician to certify that a patient either is attending or plans to attend counseling in order for a prior authorization for buprenorphine to be approved. At least another 9 states require very specific documentation of that counseling to be submitted, sometimes including requirements about who provides the counseling and whether or not that counseling is to be only by state approved counselors. For example, the initial prior authorization of buprenorphine/naloxone in one Southern state requires "the signed patient-physician contract for treatment of opioid dependency therapy and documentation of counseling or intent of participation of counseling (including what type of meeting and any applicable sign-in sheets)". Additionally, a continuation request in that state Medicaid program requires physician submission of the actual attendance record for counseling sessions and self help activities. "Documentation should include date, time, type of meeting and location. If counseling is done off-site, the phone number and name of the person providing the counseling. If counseling is done on-site, chart notes correlating to the visits should be provided". Additionally, drug screen results must also be included simultaneously in order for a prior authorization to be approved.

Extensive counseling documentation requirements, as opposed to simply requiring a statement that counseling is being provided to enhance the effectiveness of treatment, take much time from prescribing physicians and their patients and represent a substantial barrier for Medicaid patients and physicians to access to the medication. Individuals with commercial insurance coverage typically have approval conversations that focus on the medications and not on the counseling that should accompany them in MAT. And individuals who can pay out of pocket for their opioid dependence treatment medications and related counseling and physician monitoring visits are not subject to any of these access barriers. This disparity is important, inequitable and will not be solved by the ACA or by current Interim Final Rule for the parity law (See Map 8 on next page).

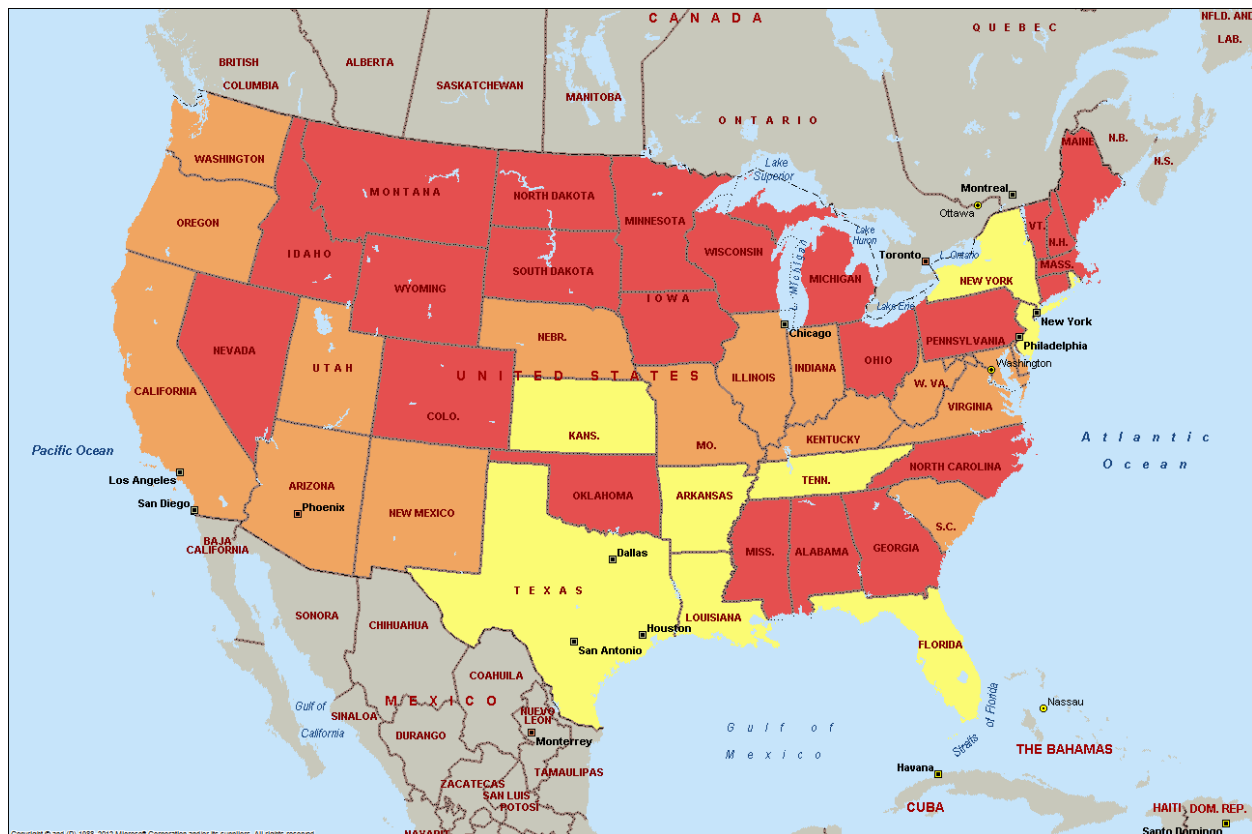
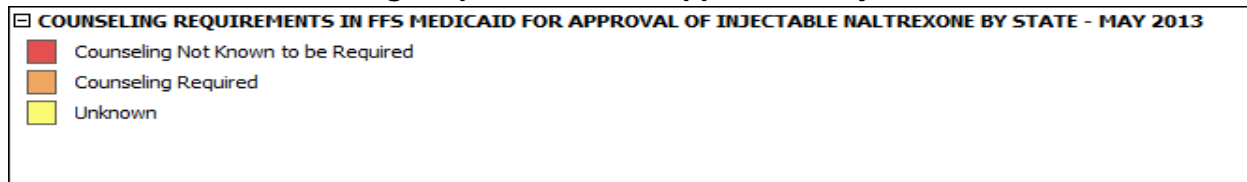
## MAP 8 - Counseling Requirements for Approval of Buprenorphine



## Injectable Naltrexone and Counseling

Once again, less information is available for injectable naltrexone (Vivitrol®). A total of 16 states were found to have imposed a counseling documentation requirement in order to approve administration of injectable naltrexone, while another 24 appear not to have such a requirement. No information was available regarding counseling requirements for injectable naltrexone in 11 states (See Map 9 below).

**MAP 9 - Counseling Requirements for Approval of Injectable Naltrexone**



## Time and Dosage and/or Payment Limits: Methadone

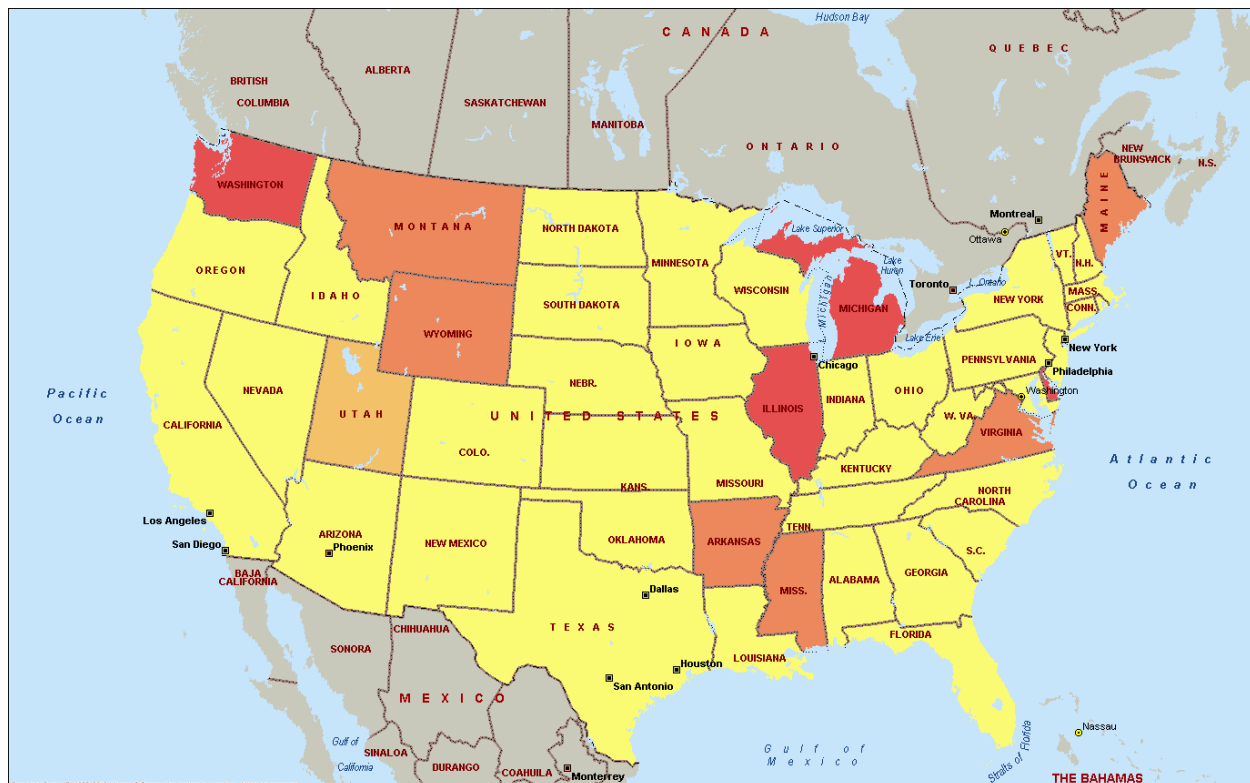
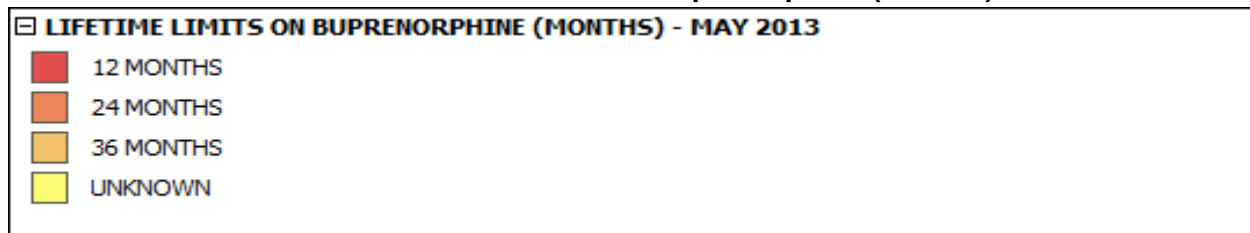
A New England state has established a 24 month lifetime limit for the use of methadone for treatment of opioid dependence. Another state in the same region is considering phase-based reimbursement for methadone treatment payments. Medicaid would pay the current rate for first year of therapy with methadone, a reduced rate for a second year and a further reduced rate for the third year and beyond. Such reimbursement limits do not apply to medications for other chronic disease states such as diabetes, serious mental illnesses or cardiac conditions.

## Time and Dosage Limits: Buprenorphine

A number of state FFS Medicaid plans have implemented lifetime limits on prescriptions for buprenorphine and/or daily dosage limits, some of which appear to conflict with CSAT clinical guidelines and NQF recommendations. As of May 2013, eleven states have implemented lifetime limits on prescriptions for buprenorphine products for treatment of opioid dependence, ranging from 12 months to 36 months; 40 states have no such formal lifetime limit.

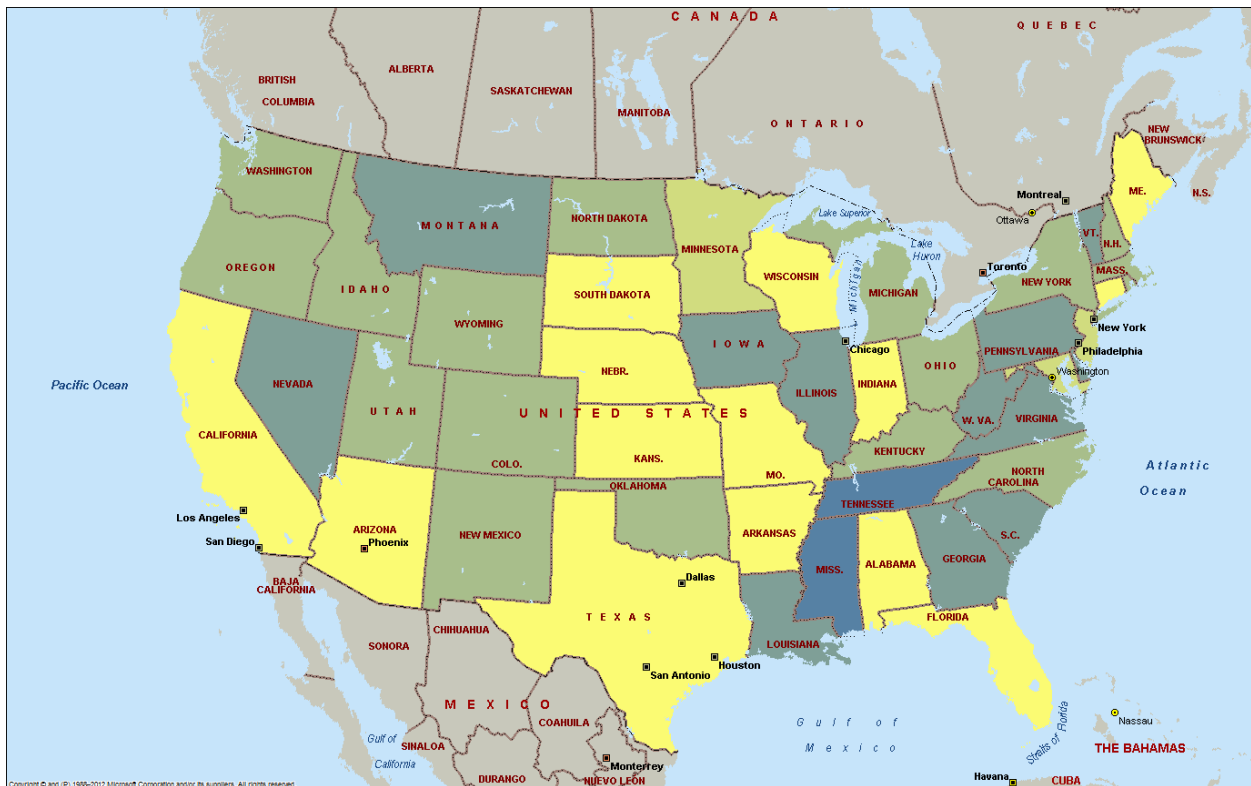
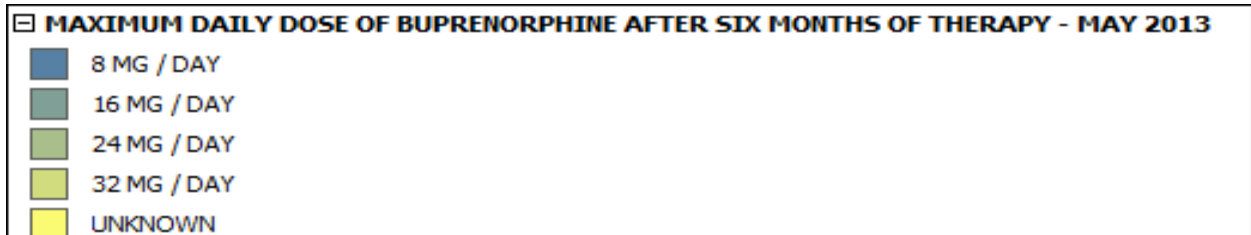
In those states with a Medicaid program lifetime limit there may be exceptions available, although their implementation may not be consistent; for example, in one New England state patients with severe and persistent mental illness are exempt from lifetime limits. Applying for such exceptions, which may need to be appealed if rejected, imposes an additional time and documentation burden on addiction physicians and their staff members (if any) and on the addicted patients themselves. Other states may not have a formal lifetime limit, but may make re-authorizations so difficult that they effectively have such a limit (See Map 10 below).

**MAP 10 - Lifetime Limits on Buprenorphine (Months)**



A total of 14 states have established a maximum daily dose of buprenorphine after six months or more of therapy, ranging from 8 to 16 milligrams (See Map 11 below).

**MAP 11 - Maximum Daily Dose of Buprenorphine**



Note: An ASAM physician in Maine did report that the state Medicaid agency has a 16 mg /day dose limit for buprenorphine



## **VII. Commentary on State Coverage and Utilization/Quality Management Requirements in Medicaid Programs: Injectable Naltrexone and Buprenorphine**

This brief survey and investigation of state Medicaid secondary source data revealed a number of items of interest. Although only a few examples of step therapy requirements for injectable naltrexone were found, some were quite complex and extensive. For example, approval of a prior authorization request for injectable naltrexone in a Southwestern state's Medicaid requires that the physician submit a patient history of two inpatient admissions in the prior twelve months plus documented non-compliance with a regimen of oral naltrexone. This sort of requirement effectively limits use of injectable naltrexone only to the group of patients with the most severe level of addiction, assuming that this can be documented as required. A Mid-Atlantic state requires a documented prior failure with buprenorphine/naloxone and documentation of treatment program adherence in order to approve any prior authorization for injectable naltrexone. Another state in the region requires unsuccessful use of buprenorphine or oral naltrexone as well as compliance with substance use disorder treatment in order to approve injectable naltrexone. And a Western state Medicaid program requires either two documented unsuccessful attempts at short term treatment and failure with oral naltrexone or three or more ER visits / hospital admissions in the past year for substance use disorder related illness in order to approve a prior authorization for injectable naltrexone. These are only a few examples of naltrexone policies that have been implemented by a number of states. Respondents in some states indicated that some of their MAT policies currently in effect are under review.

Some states have implemented a variety of more specific and unusual restrictions on approval of buprenorphine. For example, in one state, buprenorphine is only available through Medicaid if methadone is either unavailable or refused. In others approval of prior authorization renewals requires documentation of attempts to medically taper the patient to a minimum dose of buprenorphine set by the state Medicaid agency, not by clinical guidelines.

## **VIII. Implications of these findings for Medicaid Enrolled Opioid Dependent Patients and their Providers and Families**

Opioid dependent Medicaid patients may be covered for some, all or none of the components of recommended, life-saving medication-assisted treatment, including the FDA-approved medications for opioid dependence. Coverage for MAT clearly depends on which state Medicaid agency, which medication and which official is involved, whether or not counseling and medical monitoring is covered and required. The approval of recommended treatment under Medicaid hinges upon the complicated coverage rules and requirements of the state or county Medicaid plan that covers the patient and the physician or treatment program's ability to comply with those requirements in a timely way, on behalf of the patient at risk.

The patient and the provider must be well informed and aggressive in pursuit of required approvals, sometimes completely repeated every three to six months, and consistently assertive in order for the treatment planned to receive full Medicaid coverage. Clearly, some states make

this process very difficult to understand and time consuming and others do not make it easy but do make it more accessible than others.

Patient, practitioner, legislative and stakeholder and advocacy needs to start and to continue until Medicaid coverage and utilization management requirements and approval processes are made more consistent, equitable and comprehensible to the average patient and provider, regardless of the state of residence. Patient advocacy organizations and professional societies and responsible provider associations and health plans contracted with Medicaid could have a major new role to plan to help erase these disparities in state Medicaid plans in coverage and related requirements for MAT medications, monitoring and counseling. It will take dedication, time, patience and persistence to overcome documented levels of disparity, resistance to use of addiction medications, unrealistic and sometimes arbitrary requirements and bureaucratic opposition to such treatments, as well as to economic discrimination in coverage and accessibility.

Medicaid agencies in the US (and secondary sources on Medicaid coverage) unapologetically reported widely varying coverage and utilization review requirements for each FDA-approved opioid dependence medication, as well as significantly different documentation and counseling requirements related to MAT. Such variance and complexity raises the specter of inequity in these government programs that theoretically offer approved opioid dependence treatments to low income Americans enrolled in state Medicaid programs. This pattern exists when there is the growing incidence of prescription opioid dependence. It is at odds with stated goals of ending the epidemic of prescription opioid dependence and with the significant research investment the Federal government has made to help bring these opioid dependence medications to market.

Given the states' varying Medicaid coverage and utilization management decisions regarding MAT in 2013, it is apparent that there is little agreement amongst and within most state Medicaid agencies regarding this evidence-based group of interventions. In addition, both state and county criminal justice and corrections agencies, ONDCP and the DEA have a special interest in arresting the spread of prescription opioid dependence and in successfully treating those affected even if they are low income Medicaid enrollees. These key state and Federal stakeholders may be able to influence the increasingly important state Medicaid agencies. CMS may also need to step in to limit these disparities in Medicaid coverage and utilization management requirements for MAT that disproportionately affect the low(er) income patients CMS and the states help to support now and in 2014 under the ACA. This may be especially possible when a state has a substantial Medicaid waiver or State Plan Amendment pending approval or renewal, as many now do.

## **IX. State Medicaid Programs That Report Currently Generous, Innovative or Accessible Coverage of MAT for Opioid Dependence**

While serious and inequitable limits are prevalent, some state Medicaid agencies believe that MAT is important and cost effective. Much of this report offers broad survey results that show limited state Medicaid FFS program coverage of MAT for opioid dependence, especially with regard to the three classes of FDA-approved medications (methadone, buprenorphine and injectable naltrexone). However, both the ASAM survey and secondary sources do reveal that some state Medicaid agencies have generous, innovative and/or accessible coverage of these medications and associated counseling. Three examples - one Western state, one Mid Western state and one New England state - stand out from the others because of the extent of their programs, covering all of the FDA-approved opioid dependence medications and counseling.

One Western state Medicaid FFS program offers both Suboxone<sup>®</sup> and Subutex<sup>®</sup> (film and tablets) as on its Preferred Drug List, and also offers Vivitrol<sup>®</sup> on that same drug list, although in a non-preferred status. Associated SUD counseling is a 100% paid covered benefit but it is a recommended benefit, not required for patients on these medications. Methadone clinics must provide counseling to their patients. Except for methadone, the opioid dependence medications are pharmacy benefits under the state's Medicaid FFS program. Buprenorphine/naloxone film and tablets are covered with no duration of treatment or number of prescription limits. Dosages of buprenorphine and injectable naltrexone follow SAMHSA and professional society guidelines (up to 24 mg of buprenorphine, 380 mg shot of naltrexone every 30 days). This state also indicated that in general, generic medications are all approved and preferred unless they currently cost more than the brand medications. Buprenorphine and injectable naltrexone are on the Medicaid formulary; injectable naltrexone is not on the preferred drug list but no prior authorization is required for it or for buprenorphine. Both buprenorphine and injectable naltrexone are covered in physician office settings. The Medicaid Prior Authorization Request Form for Suboxone<sup>®</sup> that does exist is a very simple, one page physician check list. The only major requirement on that form is that all of the relevant sets of boxes must have a check. This state has not yet been well described in other reports.

One Mid Western state Medicaid FFS program covers all FDA-approved medications and counseling for opioid dependence, including methadone, under its pharmacy benefits. Step or fail first therapy is not required for approval of any of these medications, for which the state has standing and recent Clinical Edit Criteria, drawn from the published scientific literature with footnotes. The state allows providers to offer all of the medications in its OTP's, many of its criminal justice facilities and is planning to expand availability that to Community Mental Health Centers next year. The availability of the three opioid dependence medications and associated counseling is statewide. The state program and its behavioral health director have received national recognition for this set of services and benefits.

A New England Medicaid FFS program, described as innovative in other reports as well, also figures prominently here. As a result of a CMS state plan amendment, the state has a unique, Medicaid-supported MAT hub (OTP) and spoke ( 200 office based physicians) regional specialty system that provides methadone and buprenorphine statewide ( as well as creating health

homes for these addicted patients) using a selected network of providers who participate in ongoing quality and cost assessments. In this state each hub is also connected to a hospital that makes referrals to the system. Comprehensive care management and both RN and MD services are provided to patients. Patient satisfaction is assessed annually.

Injectable naltrexone is also covered under Medicaid FFS, subject to step therapy that requires a trial of Suboxone<sup>®</sup> if clinically appropriate, but currently in office based settings. SAMHSA guidelines are followed explicitly in terms of dosing requirements. OTP's are covered under Medicaid FFS and these settings offer both buprenorphine and methadone, but not injectable naltrexone at this time. Injectable naltrexone is covered in physician office-based settings and the state plans to have all FDA-approved addiction medications available eventually in this hub and spoke system.

# APPENDICES

# ASAM MEDICAID SURVEY

COVER PAGE

AMERICAN SOCIETY OF ADDICTION MEDICINE

**SURVEY OF COVERAGE OF MEDICATIONS AND COUNSELING FOR TREATMENT OF  
AND PREVENTION OF RELAPSE TO OPIATE DEPENDENCE**

MEDICAID DEPARTMENT/STATE: (E.G. MEDICAID OREGON)

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**CONFIDENTIAL RESPONDENT CONTACT INFORMATION**

	MEDICAL DIRECTOR - BEHAVIORAL HEALTH	PHARMACY DIRECTOR	MEDICAID DIRECTOR
Name:			
Title:			
Department:			
Street Address with Zip:			
Telephone: (Important)			
Email:(Important)			

The information you will be providing is extremely valuable to improving the field of modern opiate dependence treatment. We will keep the individual responses and names absolutely confidential. Thank you for your help in improving care for SUD disorders in general and for opiate dependence in particular!

→ To begin we would like to discuss the coverage of the following medications with respect to their use for treatment of opiate dependence:

- **Methadone**
- **Buprenorphine/Naloxone Film (Suboxone®)**
- **Buprenorphine/Naloxone tablets (Generic)**
- **Buprenorphine Tablets (Generic)**
- **Injectable Naltrexone (Vivitrol®)**

1. DOES YOUR STATE OFFER COVERAGE UNDER MEDICAID FOR THE FOLLOWING MEDICATIONS WHEN USED FOR THE TREATMENT OF OPIATE DEPENDENCE?

MEDICATION	FEE-FOR-SERVICE		MANAGED CARE	
	YES	NO	YES	NO
METHADONE				
BUPRENORPHINE/NALOXONE FILM (SUBOXONE®)				
BUPRENORPHINE/NALOXONE TABLETS (GENERIC)				
BUPRENORPHINE TABLETS (GENERIC)				
INJECTABLE NALTREXONE (VIVITROL®)				

2. IS SPECIALTY SUBSTANCE USE DISORDER (SUD) COUNSELING A COVERED MEDICAID BENEFIT IN ADDITION TO MEDICATION-ASSISTED TREATMENT (MAT) ITSELF?

	FEE-FOR-SERVICE		MANAGED CARE	
	YES	NO	YES	NO
SUD COUNSELING				

3. DO YOU REQUIRE THAT A PATIENT BE ENROLLED IN OR OTHERWISE HAVE DOCUMENTED SUD COUNSELING IN ORDER TO APPROVE OPIOID-SPECIFIC MAT WITH ANY OF THE FOLLOWING MEDICATIONS?

MEDICATION	FEE-FOR-SERVICE		MANAGED CARE	
	YES	NO	YES	NO
METHADONE				
BUPRENORPHINE/NALOXONE FILM (SUBOXONE®)				
BUPRENORPHINE/NALOXONE TABLETS (GENERIC)				
BUPRENORPHINE TABLETS (GENERIC)				
INJECTABLE NALTREXONE (VIVITROL®)				



4. IS YOUR COVERAGE OF THE MEDICATIONS LISTED BELOW CONSIDERED A MEDICAL BENEFIT, A PHARMACY BENEFIT OR BOTH? (INDICATE ALL THAT APPLY)

MEDICATION	FEE-FOR-SERVICE		MANAGED CARE	
	MEDICAL	PHARMACY	MEDICAL	PHARMACY
METHADONE				
BUPRENORPHINE/NALOXONE FILM (SUBOXONE®)				
BUPRENORPHINE/NALOXONE TABLETS (GENERIC)				
BUPRENORPHINE TABLETS (GENERIC)				
INJECTABLE NALTREXONE (VIVITROL®)				

5. WHAT ARE YOUR QUALITY MANAGEMENT EDITS AND REQUIREMENTS FOR TREATMENT WITH EACH OF THE FOLLOWING MEDICATIONS?

MEDICATION	AGE (LIST)	USE DURING PREGNANCY	DURATION OF TREATMENT (LIST SPECIFIC)	NUMBER OF SCRIPS (LIST PERIOD)	DOSAGE
METHADONE					
BUPRENORPHINE/NALOXONE FILM (SUBOXONE®)					
BUPRENORPHINE/NALOXONE TABLETS (GENERIC)					
BUPRENORPHINE TABLETS (GENERIC)					
INJECTABLE NALTREXONE (VIVITROL®)					

5. QUALITY MANAGEMENT EDITS AND REQUIREMENTS CONTINUED

MEDICATION	DOSING REQUIREMENTS (PER DAY, WEEK, MONTH)	STEP THERAPY (FAIL FIRST; DESCRIBE)	TYPE OF MAT PRESCRIBERS ELIGIBLE (MD, NP, PH.D)
METHADONE			
BUPRENORPHINE/NALOXONE FILM (SUBOXONE®)			
BUPRENORPHINE/NALOXONE TABLETS (GENERIC)			
BUPRENORPHINE TABLETS (GENERIC)			
INJECTABLE NALTREXONE (VIVITROL®)			

6. ARE THESE DRUGS ON YOUR FORMULARY AND/OR PREFERRED DRUG LIST?

MEDICATION	FEE-FOR-SERVICE		MANAGED CARE	
	PREFERRED (YES/NO)	NON-PREFERRED (YES/NO)	PREFERRED (YES/NO)	NON-PREFERRED (YES/NO)
METHADONE				
BUPRENORPHINE/NALOXONE FILM (SUBOXONE®)				
BUPRENORPHINE/NALOXONE TABLETS (GENERIC)				
BUPRENORPHINE TABLETS (GENERIC)				
INJECTABLE NALTREXONE (VIVITROL®)				

7. REGULATIONS GOVERNING USE OF SUD MEDICATIONS IN ACCREDITED OUTPATIENT NARCOTIC TREATMENT PROGRAMS (NTP'S) HAVE CHANGED. DO YOU COVER THE MEDICATIONS LISTED BELOW IN NTP'S TODAY?

COVER IN NTP SETTING?				
MEDICATION	FEE-FOR-SERVICE		MANAGED CARE	
	YES	NO	YES	NO
METHADONE				
BUPRENORPHINE/NALOXONE FILM (SUBOXONE®)				
BUPRENORPHINE/NALOXONE TABLETS (GENERIC)				
BUPRENORPHINE TABLETS (GENERIC)				
INJECTABLE NALTREXONE (VIVITROL®)				

8. DO YOU COVER THESE MEDICATIONS IN A PHYSICIAN OFFICE-BASED SETTING?

COVER IN PHYSICIAN OFFICE-BASED SETTING?				
MEDICATION	FEE-FOR-SERVICE		MANAGED CARE	
	YES	NO	YES	NO
BUPRENORPHINE/NALOXONE FILM (SUBOXONE®)				
BUPRENORPHINE/NALOXONE TABLETS (GENERIC)				
BUPRENORPHINE TABLETS (GENERIC)				
INJECTABLE NALTREXONE (VIVITROL®)				

9. DO YOU COVER THESE MEDICATIONS IN AN ORGANIZED SPECIALTY OUTPATIENT TREATMENT SETTING?

COVER IN AN ORGANIZED SPECIALTY OUTPATIENT TREATMENT SETTING?				
MEDICATION	FEE-FOR-SERVICE		MANAGED CARE	
	YES	NO	YES	NO
BUPRENORPHINE/NALOXONE FILM (SUBOXONE®)				
BUPRENORPHINE/NALOXONE TABLETS (GENERIC)				
BUPRENORPHINE TABLETS (GENERIC)				
INJECTABLE NALTREXONE (VIVITROL®)				

→ **Now, we would like to discuss potential future initiatives and changes in the coverage of medications for the treatment of opiate dependence.**

10. DO YOU HAVE ANY IMPORTANT OPIATE DEPENDENCE MEDICATION **FUNDING, HEALTH REFORM, POLICY AND/OR LEGISLATIVE** CHANGES PLANNED FOR 2013 OR 2014?

AT A LATER POINT, WE MAY WANT TO CONTACT YOU TO ASK ABOUT COVERAGE OF APPROVED ALCOHOL DEPENDENCE MEDICATIONS. WOULD YOU BE WILLING TO BE INTERVIEWED ONCE AGAIN OR WOULD YOU LIKE TO REFER US TO ANOTHER PERSON?

YES \_\_\_\_\_ NO \_\_\_\_\_

PLEASE CONTACT: NAME, TITLE, DEPT, TELEPHONE, E-MAIL, ADDRESS:

THANK YOU FOR YOUR ASSISTANCE AND PARTNERSHIP. PLEASE NOTE BELOW IF YOU WOULD LIKE TO SEE OUR FINDINGS (WITH NAMES REMOVED): CIRCLE ONE:

YES, SEND IT TO: NAME, TITLE, DEPT, TELEPHONE, E-MAIL, ADDRESS:

NO THANKS

# DATA

STATE	PRIMARY SOURCE OF DATA	OFFERS COVERAGE IN FFS MEDICAID METHADONE MAINTENANCE  (1 - MEDICAID; 2 - SAPT; 0 - NO KNOWN PUBLIC FUNDING))	OFFERS COVERAGE IN FFS MEDICAID FOR BUPRENORPHINE /NALOXONE	OFFERS COVERAGE IN FFS MEDICAID INJECTABLE NALTREXONE (VIVITROL)	PROVIDES COVERAGE OF ALL THREE FDA-APPROVED MEDICATIONS	COVERAGE OF SUD COUNSELING FFS	REQUIRES DOCUMENTED COUNSELING IN FFS MEDICAID BUPRENORPHINE/ NALOXONE
Alabama	SURVEY	1	1	1	1	1	0
Alaska	SURVEY	2	1	1	1	1	0
Arizona	STATE MEDICAID WEB SITE	1	1	1	1	1	0
Arkansas	STATE MEDICAID WEB SITE	0	1	99	0	1	2
California	SURVEY	1	1	1	1	1	1
Colorado	STATE MEDICAID WEB SITE	0	1	1	0	0	0
Connecticut	SURVEY	1	1	1	1	1	0
Delaware	STATE MEDICAID WEB SITE	1	1	1	1	1	1
Florida	STATE MEDICAID WEB SITE	1	1	1	1	1	2
Georgia	SURVEY	1	1	1	1	0	0
Hawaii	STATE MEDICAID WEB SITE	1	1	99	99	1	0
Idaho	SURVEY	0	1	1	0	1	0
Illinois	SURVEY	2	1	1	1	1	1
Indiana	SURVEY	0	1	1	0	1	2

STATE	PRIMARY SOURCE OF DATA	OFFERS COVERAGE IN FFS MEDICAID METHADONE MAINTENANCE  (1 - MEDICAID; 2 - SAPT; 0 - NO KNOWN PUBLIC FUNDING))	OFFERS COVERAGE IN FFS MEDICAID FOR BUPRENORPHINE /NALOXONE	OFFERS COVERAGE IN FFS MEDICAID INJECTABLE NALTREXONE (VIVITROL)	PROVIDES COVERAGE OF ALL THREE FDA-APPROVED MEDICATIONS	COVERAGE OF SUD COUNSELING FFS	REQUIRES DOCUMENTED COUNSELING IN FFS MEDICAID BUPRENORPHINE/ NALOXONE
Iowa	SURVEY	0	1	1	0	1	2
Kansas	STATE MEDICAID WEB SITE	0	1	99	0	1	1
Kentucky	SURVEY	0	1	1	0	1	2
Louisiana	STATE MEDICAID WEB SITE	0	1	1	0	0	0
Maine	SURVEY	1	1	1	1	1	1
Maryland	SURVEY	1	1	1	1	1	2
Massachusetts	SURVEY	1	1	1	1	1	0
Michigan	SURVEY	1	1	1	1	1	2
Minnesota	SURVEY	1	1	1	1	1	0
Mississippi	SURVEY	0	1	1	0	0	0
Missouri	SURVEY	1	1	1	1	1	1
Montana	SURVEY	0	1	1	0	1	2
Nebraska	STATE MEDICAID WEB SITE	2	1	1	0	1	0
Nevada	SURVEY	1	1	1	1	1	1
New Hampshire	SURVEY	1	1	1	1	0	1
New Jersey	STATE MEDICAID WEB SITE	1	1	99	99	0	0

STATE	PRIMARY SOURCE OF DATA	OFFERS COVERAGE IN FFS MEDICAID METHADONE MAINTENANCE  (1 - MEDICAID; 2 - SAPT; 0 - NO KNOWN PUBLIC FUNDING))	OFFERS COVERAGE IN FFS MEDICAID FOR BUPRENORPHINE /NALOXONE	OFFERS COVERAGE IN FFS MEDICAID INJECTABLE NALTREXONE (VIVITROL)	PROVIDES COVERAGE OF ALL THREE FDA-APPROVED MEDICATIONS	COVERAGE OF SUD COUNSELING FFS	REQUIRES DOCUMENTED COUNSELING IN FFS MEDICAID BUPRENORPHINE/ NALOXONE
New Mexico	SURVEY	1	1	1	1	1	1
New York	SURVEY	1	1	1	1	0	0
North Carolina	SURVEY	1	1	1	1	1	0
North Dakota	SURVEY	0	1	1	0	1	0
Ohio	SURVEY	1	1	1	1	1	1
Oklahoma	SURVEY	0	1	1	0	1	0
Oregon	SURVEY	1	1	1	1	1	1
Pennsylvania	SURVEY	1	1	1	1	1	1
Rhode Island	STATE MEDICAID WEB SITE	1	1	99	99	0	0
South Carolina	SURVEY	0	1	1	0	1	2
South Dakota	SURVEY	0	1	0	0	0	0
Tennessee	SURVEY	0	1	99	0	1	1
Texas	SURVEY	1	1	99	99	1	1
Utah	SURVEY	1	1	1	1	1	1
Vermont	SURVEY	1	1	1	1	1	1
Virginia	SURVEY	1	1	1	1	1	1
Washington	SURVEY	1	1	1	1	1	1
West Virginia	STATE MEDICAID WEB SITE	0	1	1	0	1	1



STATE	PRIMARY SOURCE OF DATA	OFFERS COVERAGE IN FFS MEDICAID METHADONE MAINTENANCE  (1 - MEDICAID; 2 - SAPT; 0 - NO KNOWN PUBLIC FUNDING))	OFFERS COVERAGE IN FFS MEDICAID FOR BUPRENORPHINE /NALOXONE	OFFERS COVERAGE IN FFS MEDICAID INJECTABLE NALTREXONE (VIVITROL)	PROVIDES COVERAGE OF ALL THREE FDA-APPROVED MEDICATIONS	COVERAGE OF SUD COUNSELING FFS	REQUIRES DOCUMENTED COUNSELING IN FFS MEDICAID BUPRENORPHINE/ NALOXONE
Wisconsin	SURVEY	1	1	1	1	1	0
Wyoming	STATE MEDICAID WEB SITE	0	1	1	0	1	1
District of Columbia	STATE MEDICAID WEB SITE	1	1	99	99	1	1

1 - YES

0 - NO

99 - UNKNOWN

STATE	REQUIRES DOCUMENTED COUNSELING IN FFS MEDICAID INJECTABLE NALTREXONE (VIVITROL)	MEDICAL OR PHARMACY BENEFIT - FFS? BUPRENORPHINE/NALOXONE FILM (SUBOXONE)	MEDICAL OR PHARMACY BENEFIT - FFS? INJECTABLE NALTREXONE (VIVITROL)	PRIOR AUTHORIZATION REQUIRED - BUPRENORPHINE / NALOXONE	PRIOR AUTHORIZATION REQUIRED - INJECTABLE NALTREXONE	LIFETIME LIMITS ON BUPRENORPHINE (MONTHS)	MAXIMUM DAILY DOSE OF BUPRENORPHINE AFTER SIX MONTHS OF THERAPY
Alabama	0	P	P	1	99	99	99
Alaska	0	P	P	1	1	99	24
Arizona	1	P	p	1	1	99	99
Arkansas	99	P	0	1	99	24	99
California	1	P	M	1	1	99	99
Colorado	0	P	M	1	1	99	24
Connecticut	0	P	P	99	99	99	99
Delaware	1	P	M	1	1	12	16
Florida	99	P	M	1	0	99	99
Georgia	0	P	P	1	1	99	16
Hawaii	0	P	0	1	99	99	99
Idaho	0	P	M,P	1	99	99	24
Illinois	1	P	P	1	1	12	16
Indiana	1	P	M,P	1	1	99	99
Iowa	0	P	M,P	1	1	99	16
Kansas	99	P	0	1	99	99	99
Kentucky	1	P	P	1	99	99	24
Louisiana	99	P	P	1	1	99	16
Maine	0	P	0	1	1	24	99
Maryland	1	P	P	1	1	99	32
Massachusetts	0	P	P	1	0	99	24

STATE	REQUIRES DOCUMENTED COUNSELING IN FFS MEDICAID INJECTABLE NALTREXONE (VIVITROL)	MEDICAL OR PHARMACY BENEFIT - FFS? BUPRENORPHINE/NALOXONE FILM (SUBOXONE)	MEDICAL OR PHARMACY BENEFIT - FFS? INJECTABLE NALTREXONE (VIVITROL)	PRIOR AUTHORIZATION REQUIRED - BUPRENORPHINE / NALOXONE	PRIOR AUTHORIZATION REQUIRED - INJECTABLE NALTREXONE	LIFETIME LIMITS ON BUPRENORPHINE (MONTHS)	MAXIMUM DAILY DOSE OF BUPRENORPHINE AFTER SIX MONTHS OF THERAPY
Michigan	0	P	M,P	1	0	12	24
Minnesota	0	M	P	1	99	99	32
Mississippi	0	0	0	1	0	24	8
Missouri	1	P	P	0	0	99	99
Montana	0	P	M	1	99	24	16
Nebraska	1	P	0	1	1	99	99
Nevada	0	P	P	1	0	99	16
New Hampshire	0	P	M,P	1	0	99	24
New Jersey	99	0	0	99	99	99	32
New Mexico	1	M,P	M,P	0	0	99	24
New York	99	P	M	1	0	99	24
North Carolina	0	M,P	M,P	1	99	99	24
North Dakota	0	P	M	1	0	99	24
Ohio	0	P	M,P	1	99	99	24
Oklahoma	0	P	M,P	1	99	99	24
Oregon	1	M,P	M,P	1	1	99	24
Pennsylvania	0	P	P	99	1	99	16
Rhode Island	99	0	0	0	99	99	24
South Carolina	1	P	M	1	1	99	16
South Dakota	0	P	M	1	99	99	99
Tennessee	99	P	0	1	99	99	8

STATE	REQUIRES DOCUMENTED COUNSELING IN FFS MEDICAID INJECTABLE NALTREXONE (VIVITROL)	MEDICAL OR PHARMACY BENEFIT - FFS? BUPRENORPHINE/NALOXONE FILM (SUBOXONE)	MEDICAL OR PHARMACY BENEFIT - FFS? INJECTABLE NALTREXONE (VIVITROL)	PRIOR AUTHORIZATION REQUIRED - BUPRENORPHINE / NALOXONE	PRIOR AUTHORIZATION REQUIRED - INJECTABLE NALTREXONE	LIFETIME LIMITS ON BUPRENORPHINE (MONTHS)	MAXIMUM DAILY DOSE OF BUPRENORPHINE AFTER SIX MONTHS OF THERAPY
Texas	99	P	0	1	99	99	99
Utah	1	P	P	1	1	36	24
Vermont	0	M	P	0	1	99	16
Virginia	1	P	M	1	0	24	16
Washington	1	P	P	1	1	12	24
West Virginia	1	P	P	1	1	99	16
Wisconsin	0	P	P	1	99	99	99
Wyoming	0	P	P	1	99	24	24
District of Columbia	99	P	0	1	99	99	99

1 - YES

0 - NO

99 - UNKNOWN

STATE	NOTES AND COMMENTS	ADDITIONAL NOTES	CHANGES PLANNED IN 2013
<b>Alabama</b>	SURVEY NOTES STEP THERAPY REQUIRED; NO OTHER INFORMATION PROVIDED OR AVAILABLE	SURVEY NOTES STEP THERAPY REQUIRED; NO OTHER INFORMATION PROVIDED OR AVAILABLE	
<b>Alaska</b>	Standard criteria (age, opiate dependence, patient agrees to adhere to trx plan) for PA for Suboxone	Standard criteria (age, opiate dependence, patient agrees to adhere to trx plan) for PA for Suboxone	
<b>Arizona</b>	PA FOR VIVITROL REQUIRES Two inpatient admissions in last 12 months; Documented non-compliance with oral naltrexone	PA FOR VIVITROL REQUIRES Two inpatient admissions in last 12 months; Documented non-compliance with oral naltrexone	
<b>Arkansas</b>	24 MONTHS MAXIMUM FOR SUBOXONE; DOCUMENTATION OF COUNSELING REQUIRED FOR SUBOXONE	24 MONTHS MAXIMUM FOR SUBOXONE; DOCUMENTATION OF COUNSELING REQUIRED FOR SUBOXONE	
<b>California</b>			ALL ARE UNDER REVIEW
<b>Colorado</b>			
<b>Connecticut</b>	BUPRENORPHINE IN ANY FORMULATION AVAILABLE ONLY IF METHADONE IS UNAVAILABLE OR REFUSED	BUPRENORPHINE IN ANY FORMULATION AVAILABLE ONLY IF METHADONE IS UNAVAILABLE OR REFUSED	CONSIDERING PHASE-BASED METHADONE TREATMENT PAYMENTS; WOULD PAY CURRENT RATE FOR FIRST YEAR OF THERAPY, REDUCED RATE FOR SECOND YEAR AND FURTHER REDUCED RATE FOR THIRD YEAR AND BEYOND
<b>Delaware</b>	BUP: TWO MONTH PA'S WITH DOCUMENTATION OF COUNSELING REQUIRED; VIVITROL: ONE YEAR PA'S WITH HISTORY OF NON-COMPLIANCE WITH DISULFRAM OR NALTREXONE AND DOCUMENTATION OF TREATMENT PROGRAM ADHERENCE	BUP: TWO MONTH PA'S WITH DOCUMENTATION OF COUNSELING REQUIRED; VIVITROL: ONE YEAR PA'S WITH HISTORY OF FAILURE OF BUPRENORPHINE/NALOXONE AND DOCUMENTATION OF TREATMENT PROGRAM ADHERENCE	
<b>Florida</b>	BUP: DOCUMENTATION OF COUNSELING AND ADHERENCE TO TREATMENT PLAN REQUIRED	BUP: DOCUMENTATION OF COUNSELING AND ADHERENCE TO TREATMENT PLAN REQUIRED	
<b>Georgia</b>			

STATE	NOTES AND COMMENTS	ADDITIONAL NOTES	CHANGES PLANNED IN 2013
Hawaii			
Idaho			IMPLEMENTING MANAGED CARE
Illinois	BUPRENORPHINE MAY BE AUTHORIZED FOR UP TO 12 MONTHS LIFETIME	BUPRENORPHINE MAY BE AUTHORIZED FOR UP TO 12 MONTHS LIFETIME	
Indiana	COUNSELING REQUIRED	COUNSELING REQUIRED	HEALTH FINANCE COMMISSION HAS UNDERTAKEN A STUDY
Iowa	PA FOR BUP REQUIRES PARTICIPATION AND COMPLIANCE WITH COUNSELING; RENEWALS REQUIRE DOCUMENTATION OF ATTEMPTS TO MEDICALLY TAPER	PA FOR BUP REQUIRES PARTICIPATION AND COMPLIANCE WITH COUNSELING; RENEWALS REQUIRE DOCUMENTATION OF ATTEMPTS TO MEDICALLY TAPER	
Kansas	BUP: SA TREATMENT REQUIRED	BUP: SA TREATMENT REQUIRED	
Kentucky	BUP: SA COUNSELING REQUIRED; REQUIRES TAPERING TO MINIMUM DOSE AFTER EIGHT MONTHS	BUP: SA COUNSELING REQUIRED; REQUIRES TAPERING TO MINIMUM DOSE AFTER EIGHT MONTHS	
Louisiana			
Maine	CERTAIN CONDITIONS SUCH AS SPMI QUALIFY FOR AUTOMATIC RENEWAL	CERTAIN CONDITIONS SUCH AS SPMI QUALIFY FOR AUTOMATIC RENEWAL	
Maryland	BUP: PA REQUIRES DOCUMENTATION OF COUNSELING AND TREATMENT COMPLIANCE, EFFORTS TO TAPER; PA FOR VIVITROL REQUIRES UNSUCCESSFUL USE OF SUBOXONE, SUBUTEX OR ORAL NALTREXONE AND COMPLIANCE WITH SA TREATMENT	BUP: PA REQUIRES DOCUMENTATION OF COUNSELING AND TREATMENT COMPLIANCE, EFFORTS TO TAPER; PA FOR VIVITROL REQUIRES UNSUCCESSFUL USE OF SUBOXONE, SUBUTEX OR ORAL NALTREXONE AND COMPLIANCE WITH SA TREATMENT	
Massachusetts	NO PA FOR GENERIC BUP/NALOXONE TABS LT 16 MG/DAY	NO PA FOR GENERIC BUP/NALOXONE TABS LT 16 MG/DAY	
Michigan	COUNSELING REQUIRED FOR BUP	COUNSELING REQUIRED FOR BUP	CONSIDERING PDMP FOR ALL PRESCRIBERS OF OPIATE DEPENDENCE MEDICATION
Minnesota			CHANGING RULES ON LICENSURE OF OTP'S

STATE	NOTES AND COMMENTS	ADDITIONAL NOTES	CHANGES PLANNED IN 2013
Mississippi	BUP AUTHORIZATION FOR UP TO 2 YEARS LIFETIME; max dose of 8 mg/day months 6 - 24	BUP AUTHORIZATION FOR UP TO 2 YEARS LIFETIME; max dose of 8 mg/day months 6 - 24	
Missouri	MISSOURI HAS CLINICAL EDITS FOR OPIATE DEPENDENCE DIAGNOSIS, WAIVER AND LACK OF PREGNANCY	MISSOURI HAS CLINICAL EDITS FOR OPIATE DEPENDENCE DIAGNOSIS, WAIVER AND LACK OF PREGNANCY	REQUESTING SUPPLEMENTAL APPROPRIATION FOR MEDICATIONS; USE IS INCREASING
Montana	MAX DOSE OF 16 MG/DAY FOR BUP	MAX DOSE OF 16 MG/DAY FOR BUP	
Nebraska			
Nevada			
New Hampshire			
New Jersey			PLANNING TO IMPLEMENT TREATMENT WITH VIVITROL
New Mexico	NO LIFETIME LIMIT	NO LIFETIME LIMIT	
New York			
North Carolina	SUBOXONE INITIAL PA FOR 12 MONTHS; RENEWAL REQUIRES A TREATMENT PLAN	SUBOXONE INITIAL PA FOR 12 MONTHS; RENEWAL REQUIRES A TREATMENT PLAN	
North Dakota			WRITING RULES FOR NTP'S
Ohio	BUP PA FOR 6 MONTHS; RENEWABLE	BUP PA FOR 6 MONTHS; RENEWABLE	OHIO EXPLORING EXPANDING USE OF BUPRENORPHINE IN NTP'S. DEVELOPING NEW LOW-DOSE AND TAPERING PROTOCOL FOR BUPRENORPHINE USE.
Oklahoma	BUP PA FOR 90 DAYS; RENEWABLE	BUP PA FOR 90 DAYS; RENEWABLE	OK DEPT OF MHSA AMENDING RULES FOR OTP'S TO INCLUDE REGULATIONS OF NEW MEDICATIONS
Oregon	SUBOXONE PA FOR UP TO SIX MONTHS; PA FOR VIVITROL REQUIRES PATIENT TO HAVE FAILED ALL THREE OTHER MEDICATIONS: ORAL NALTREXONE, SUBOXONE AND METHADONE	SUBOXONE PA FOR UP TO SIX MONTHS; PA FOR VIVITROL REQUIRES PATIENT TO HAVE FAILED ALL THREE OTHER MEDICATIONS: ORAL NALTREXONE, SUBOXONE AND METHADONE	

STATE	NOTES AND COMMENTS	ADDITIONAL NOTES	CHANGES PLANNED IN 2013
Pennsylvania	INITIAL SCRIP FOR BUP DOES NOT REQUIRE PA; PARTICIPATION IN TREATMENT REQUIRED FOR PA	INITIAL SCRIP FOR BUP DOES NOT REQUIRE PA; PARTICIPATION IN TREATMENT REQUIRED FOR PA	
Rhode Island			
South Carolina	BUPRENORPHINE: 16 MG/DAY MAX;	BUPRENORPHINE: 16 MG/DAY MAX;	
South Dakota			
Tennessee	BUPRENORPHINE: 16 MG/DAY FOR 6 MONTHS; 8 MG/DAY THEREAFTER	BUPRENORPHINE: 16 MG/DAY FOR 6 MONTHS; 8 MG/DAY THEREAFTER	
Texas			
Utah	3 YEARS MAX FOR BUP; COUNSELING REQUIRED	3 YEARS MAX FOR BUP; COUNSELING REQUIRED	
Vermont	PA FOR VIVITROL REQUIRES PATIENT MUST FIRST FAIL SUBOXONE	PA FOR VIVITROL REQUIRES PATIENT MUST FIRST FAIL SUBOXONE	
Virginia	BUP PA FOR 24 MONTH MAXIMUM LIFETIME; COUNSELING REQUIRED; 16 MG MAX DAILY DOSE	BUP PA FOR 24 MONTH MAXIMUM LIFETIME; COUNSELING REQUIRED; 16 MG MAX DAILY DOSE	
Washington	ALL MAT DRUGS REQUIRE PRIOR AUTH; counseling must be performed by DBHR Certified Chemical Dependency Agency; BUP PA FOR 6 MONTHS LIFETIME, WITH ADDITIONAL 6 MONTHS POSSIBLE IF TREATMENT HAS GONE WELL	ALL MAT DRUGS REQUIRE PRIOR AUTH; counseling must be performed by DBHR Certified Chemical Dependency Agency; BUP PA FOR 6 MONTHS LIFETIME, WITH ADDITIONAL 6 MONTHS POSSIBLE IF TREATMENT HAS GONE WELL	REVIEW OF MAT POLICIES TO BE CONDUCTED IN 2013; POLICIES MAY CHANGE
West Virginia	COUNSELING REQUIRED	COUNSELING REQUIRED	
Wisconsin	6 MONTH PA; SUBUTEX, BUPRENORPHINE (MONO) AND SUBOXNE TABLETS ARE ALL NON-PREFERRED AND REQUIRE RATIONALE FOR THEIR USE AS OPPOSED TO SUBOXONE FILM OR METHADONE	6 MONTH PA; SUBUTEX, BUPRENORPHINE (MONO) AND SUBOXNE TABLETS ARE ALL NON-PREFERRED AND REQUIRE RATIONALE FOR THEIR USE AS OPPOSED TO SUBOXONE FILM OR METHADONE	



STATE	NOTES AND COMMENTS	ADDITIONAL NOTES	CHANGES PLANNED IN 2013
<b>Wyoming</b>	BUP HAS 2 YEAR MAXIMUM; CAN RESTART AFTER 3 MONTHS W/O TRX	BUP HAS 2 YEAR MAXIMUM; CAN RESTART AFTER 3 MONTHS W/O TRX	
<b>District of Columbia</b>	COUNSELING REQUIRED FOR BUP	COUNSELING REQUIRED FOR BUP	

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# Report of Commercial Health Plan Medication Coverage and Benefits Survey



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Report developed for the American Society of Addiction Medicine  
by the Treatment Research Institute, 2013

FINAL

# Table of Contents

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Definitions.....	pg. 3
Executive Summary.....	pg. 4
Methodology.....	pg. 10
Results.....	pg. 12
Discussion.....	pg. 18
References.....	pg. 29
Appendices.....	pg. 31
Additional Results Charts.....	pg. 37

## DEFINITIONS

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For the purposes of this report, the following terms shall have the following meanings:

“ACA” = the Affordable Care Act

“AIS” = Atlantic Information Service

“ASAM” = American Society of Addiction Medicine

“AATOD” = American Association for the Treatment of Opioid Dependence

“Community Care” = Community Care Behavioral Health

“DEA” = the Drug Enforcement Administration

“FDA” = U.S. Food and Drug Administration

“MAT” = Medication-Assisted Treatment

“MHPAEA” = the Mental Health Parity and Addiction Equity Act

“NTP” = Narcotic Treatment Program

“OTP” = Opioid Treatment Program

“PATF” = Patient Advocacy Task Force

“Plans” = the commercial insurers identified by TRI for inclusion on the survey

“SAMHSA” = the Substance Abuse and Mental Health Services Administration

“TRI” = Treatment Research Institute

## EXECUTIVE SUMMARY

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Commercial insurance plans, by and large, are including coverage and benefits pharmacotherapy for the treatment of opioid dependence. However, there is not very much known about the extent of coverage and the generosity and/or restrictions on benefits for the FDA-approved medications used as part of comprehensive treatment. TRI researchers, in collaboration with the Avisa Group and the American Society of Addiction Medicine (ASAM), which funded the study, surveyed two commercial plans in each of the 10 largest states (by population) in the United States as well as the largest small group plan in those states, seeking information about coverage and benefits as well as any restrictions on benefits such as prior authorization, quantity limits, step therapy (“fail first”) requirements, duration limitations, and network requirements that may limit patient access to such medications. While commercial insurance plans operate in a competitive environment with no general requirement for transparency, TRI researchers found difficulties in locating clear, concise and useable information. However, researchers were able to combine survey information with secondary sources on an average of 22 of the 30 plans in the survey to be able to arrive at some major findings about coverage and benefits. In summary, the findings of the survey show that:

- Most plans are covering pharmacotherapies for opiate dependence.
- While plans are covering medications, coverage is complex. For some medications such as methadone and buprenorphine there is significant regulation in place. For methadone, regulations require that it be dispensed only in licensed opioid treatment programs only (OTPs); for buprenorphine, physicians must be trained and receive a waiver in order to prescribe the medication in office-based settings. The complexities of these requirements mean that patients and prescribers seeking medications as part of comprehensive treatment will need to

understand the intricacies of both pharmacy and medical benefits. These benefit issues are often unclear, may delay treatment onset, and have significant financial implications for individuals, such as large out-of-pocket costs as well as health implications.

- Inclusion on a plan's formulary does not equate to access due to additional utilization management (UM) requirements. The most common requirements include prior authorization, quantity and dosage limits, and step therapy. Beyond these limitations others include limiting medications to detoxification only, limiting duration of treatment with medications, and restricting access to in-network providers only. Often, the limitations are not supported by evidence-based practices.
- The most widely available medication is Suboxone® (buprenorphine/naloxone) across the plans studied. The expectation is that with new formulations becoming available such as the generic version of Suboxone and the implant, it will become even more available. Whether that will translate into greater use is not clear because the generic may serve only as a substitute..
- Only a small number of plans cover extended-release, injectable naltrexone (Vivitrol®) and it is generally covered as both a medical and a pharmacy benefit with significant cost implications for patients.
- It is important to note that although evidence-based practice strongly suggests that clinical treatment, including counseling, should accompany use of medications, that requirement was rarely found in the survey health plans.

- This study was unable to find any plan that provides coverage for methadone in OTPs; a query of the American Association for the Treatment of Opioid Dependence (AATOD) did not reveal any commercial insurer that is providing coverage and benefits for methadone in OTPs.

### ***Introduction and Background***

Of the 22 million people in the US with addiction to alcohol or an illicit substance (SAMSHA, 2011), 4 million are estimated to have opioid addiction either as the result of addiction to prescription pain medications or heroin (SAMHSA, 2012). Most of this population is under the age of 65 and therefore potentially has health insurance coverage through Medicaid, private insurance or no coverage at all. With the implementation of ACA in 2014, an increasing number of individuals with addiction will have access to insurance coverage either through the Medicaid expansion or expansion of private health insurance coverage. Furthermore, the ACA is required to implement regulations associated with the Mental Health Parity and Addiction Equity Act (MHPAEA). These two landmark pieces of legislation specify that the full spectrum of care for substance use disorders is an “essential benefit” within many healthcare plans; and that the care must be of generally the same type, duration, range of service options and patient financial burden as the care currently available to patients with comparable physical illnesses.

Opioid addiction is a special type of substance addiction also defined by a cluster of cognitive, behavioral, and physiological symptoms associated with regular non-medical use of high doses of opioids in a compulsive manner, with loss of control over use and adverse medical and/or psychiatric consequences. However, unlike cocaine, hallucinogens, solvents, and many other types of addiction, opioids almost always produce significant physiological tolerance and a defined withdrawal syndrome. Approximately 4 million U.S. residents are addicted to opioids (illegal opioids and non-medical use of prescription opioids.(SAMHSA, 2012); rates of current

use, moreover, appear to be increasing (Compton & Volkow, 2006) and are associated with more overdose fatalities (Hall et al., 2008).

Misuse of illegal opioids such as heroin and the non-medical use of certain prescription opioid pain medications such as oxycodone have dramatically increased over the past decade (SAMHSA, 2012). With this dramatic increase in prevalence has come a very significant increase in related health and criminal justice system costs. Heroin abuse is associated with a number of serious health conditions, including fatal overdose and spontaneous abortion. Injection drug use is a well-known route of transmission of blood borne infections, particularly HIV and hepatitis B and C (CDC, 2012; Mathers et al., 2008), and it is associated with increased rates of TB and STDs (Deiss et al., 2009; Nelson et al., 1991). Chronic heroin users may develop collapsed veins, infection of the heart lining and valves, abscesses, constipation and gastrointestinal cramping, and liver or kidney disease. Pulmonary complications, including various types of pneumonia, may result from the poor health of the user as well as from heroin's effects on breathing (NIDA, 2013). Prescription opioid pain medications such as Oxycontin and Vicodin can have effects similar to heroin when taken in doses or in ways other than prescribed. A recent report released from the Centers for Disease Control and Prevention (CDC; 2011) found that deaths involving opioid pain relievers have increased and now exceed deaths involving heroin and cocaine combined.

Growing understanding and acceptance of opioid and other substance use disorders (SUD) as chronic and relapsing but treatable medical disorders has facilitated advances in the use of pharmacotherapies as part of comprehensive treatment of SUDs as chronic illnesses (SAMHSA, 2011; Dennis & Scott, 2007; McLellan et al., 2000). Like other chronic illnesses many cases of opioid addiction cannot be cured - but can be treated and maintained. And as in the case of treatments for other chronic illnesses, medications can be an important part of chronic, comprehensive care for opioid addiction. Medications can interrupt the cycle of



addiction to allow patients to increase their functioning, gain some control over their addiction, and engage in therapeutic recovery.

### ***FDA approved medications for treating opioid addiction***

There are three-approved medications for treatment of opioid addiction: methadone (Dolophine®); buprenorphine (Suboxone® and Subutex®); and extended release naltrexone (Vivitrol®). All of these medications act directly upon the opioid receptors, particularly mu-receptors (32, 33). Methadone is a full mu-receptor agonist; buprenorphine is a partial mu-receptor agonist and naltrexone is a full antagonist. Because of the very different actions of these medications at the receptor level, they can have very different clinical effects during treatment. Methadone and buprenorphine used as detoxification medications can suppress withdrawal symptoms and curb cravings. When used as maintenance medications the suppression of withdrawal and craving helps to reduce non-medical opioid use. Naltrexone can only be administered to fully detoxified patients but as a maintenance medication it can essentially eliminate the rewarding effects of self-administered opioids, thereby dramatically reducing use.

Until 2002, methadone was only the medication available to treat opioid addiction. Unlike any other medication in healthcare, the prescription and dispensing of methadone is restricted to providers registered with the FDA and DEA, and the medication can only be prescribed and dispensed from licensed methadone maintenance programs to treat opioid addiction (aka opioid treatment programs (OTPs)). As a result of these regulations, commercial health plans will not cover methadone as a pharmacy benefit for opioid addiction. Access to this medication to treat opioid addiction in the commercial market is only feasible, if plans cover treatment in licensed methadone maintenance. It should be noted; however, that it is possible for commercial health plans to cover methadone as a pain reliever as a pharmacy benefit.

Beginning in 2002, federal regulations allowed for broader access to buprenorphine, permitting properly trained and DEA-registered physicians to prescribe buprenorphine in most traditional medical settings. There are two formulations of buprenorphine: the monotherapy product which is just buprenorphine and a combination product which includes the short-acting opioid antagonist naloxone. The combination product was developed because it was found that buprenorphine alone could be crushed, mixed with water and injected to produce a significant euphoric effect. The combination product was developed to reduce inappropriate use because when it is crushed and injected, the naloxone will produce withdrawal symptoms. With FDA approval of generic combination tablets, there are now multiple generic and commercial formulations available.

In 2010, the FDA approved an extended-release injectable formulation of naltrexone (Vivitrol) for treatment of opioid disorder. Due to its method of action, naltrexone can only be prescribed to patients who have been completely detoxified from all opioid use, or the medication will produce immediate opioid withdrawal. Unlike methadone or buprenorphine, naltrexone is not a controlled substance; and since it is injected, there are no concerns about misuse or diversion. Furthermore, prescribers do not require any special training or certification, other than learning how to appropriately inject the medication in their offices. Another difference about naltrexone is that it is a specialty pharmaceutical which must be administered by a health care provider. Since it is not a self-administered specialty pharmaceutical, it is typically covered as a medical benefit with implications for the patient in terms of co-payments for office-based injection.

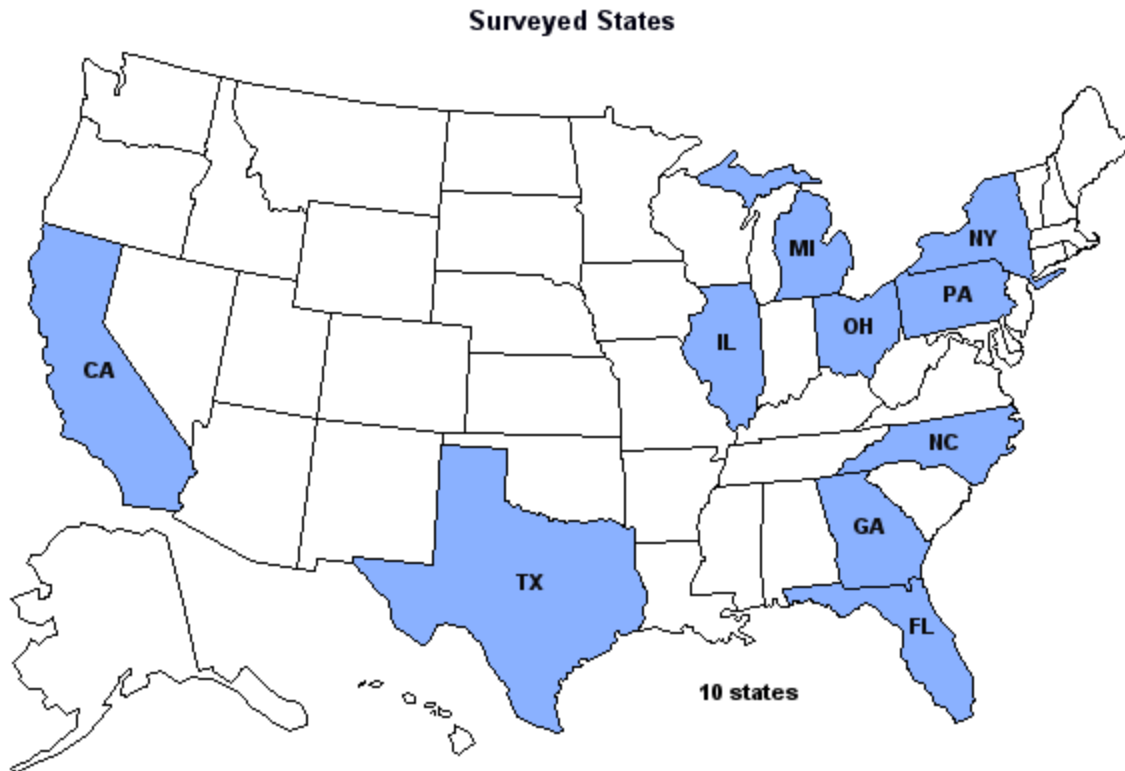
## Methodology

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The American Society of Addiction Medicine (ASAM), the Avisa Group and the Treatment Research Institute (TRI) designed and distributed a survey measuring commercial insurance plans' inclusion and coverage of pharmacotherapy in the treatment of opioid dependence. The study was designed to gather information on coverage, as well as use of pharmacy utilization management techniques including prior authorization, quantity limits, and step therapy, as well as other requirements defining eligibility, prescribers as well as dosage and duration limitations.

Our goal was determine how health plan coverage in the commercial marketplace either facilitates or places barriers on patient access to evidence-based medications for opioid addiction.

The design specified that the survey would be sent to plans that covered the population in the 10 most populous states in the U.S. TRI identified the two largest commercial insurers in each state as well as the largest commercial small group insurer. Plans were identified as "largest" and or "smallest" based on enrollment numbers as reported in the Atlantic Information Service's (AIS) Directory of Health Plans in 2013. The figure below highlights the states that were chosen for survey inclusion. A copy of the survey and details on survey completion are included in the Appendices.



**Medications Targeted for Study:**

TRI, the Avisa Group and the ASAM PATF focused on FDA-approved medications for the treatment of opioid dependence: methadone, buprenorphine, buprenorphine/naloxone and naltrexone. In an effort to collect data regarding both generic and brand-named medications (and any implications this differentiation has on patient access) the specific medications included in the survey were methadone, buprenorphine/naloxone film (Suboxone), buprenorphine/naloxone tablets (generic), buprenorphine (generic) and injectable naltrexone (Vivitrol).

**Use of Secondary Sources:**

Secondary sources were also used to confirm survey responses or serve in place of such responses in the event that health plans did not respond. Secondary sources included, but

were not limited to, health plan published formularies, contract or preferred drug lists, prior authorization requirements and prior authorization request forms.

Given only 90% of those individuals targeted in the initial emails failed to respond to the survey questionnaire, the secondary sources served as the major data source for this report's analysis. In compiling relevant secondary sources, researchers found large numbers of products and formularies listed within individual plans. Plan products and formularies were not obviously connected in any way. Approximately 80% of plans did not clearly identify which formulary was associated with which product. For example, among the formularies listed for one plan are 2-Tier Closed, 2-Tier Open, 3-Tier, 4-Tier and 5-Tier. Such formularies provided no information with respect to a corresponding product (by name) within the plan. Further, once formularies were compiled researchers found that the information there was often insufficient with respect to the necessary level of detail. Step therapy, prior authorization and quantity limitation requirements were generally not addressed on formularies, or were limited to "Yes" and "No" without detail regarding specific procedural steps and/or guidelines required in order to approve treatment plans and medications.

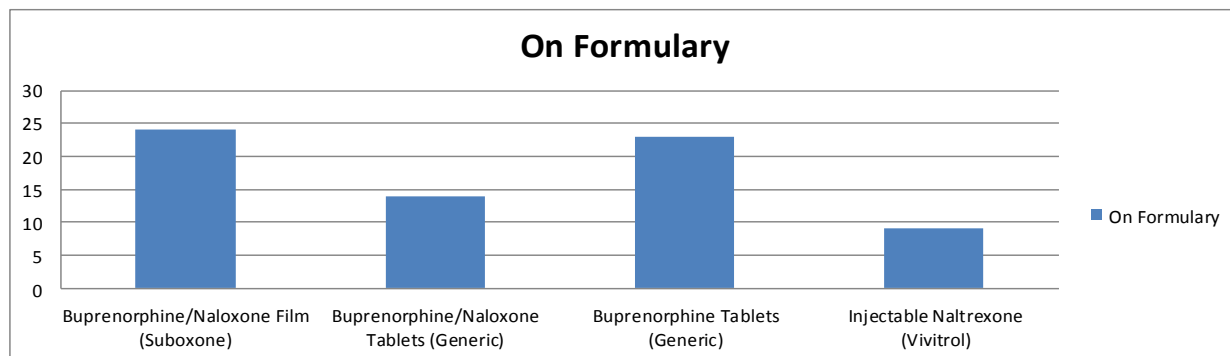
## RESULTS

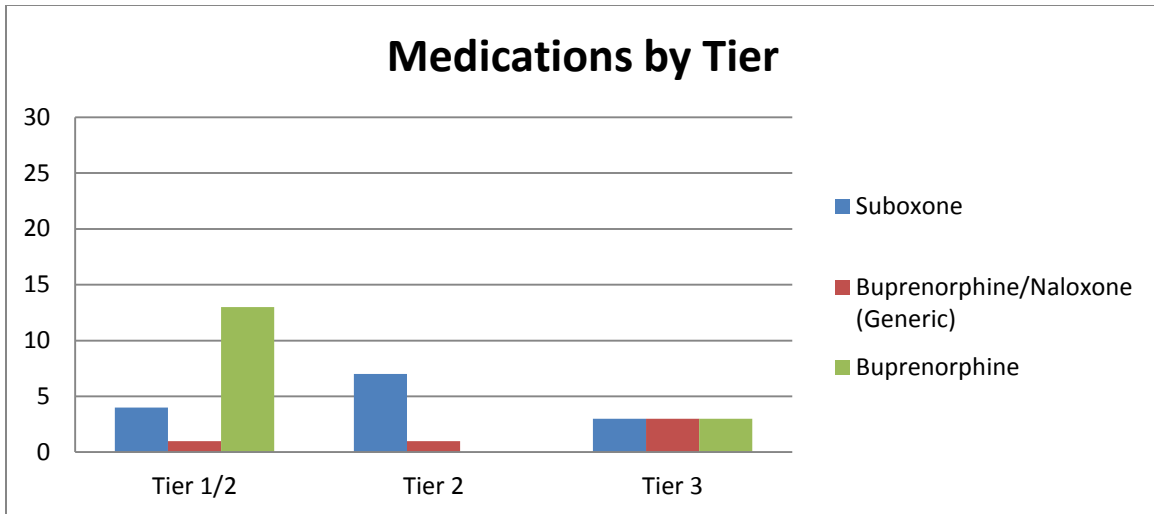
The charts below and in the appendices represent aggregated data procured from survey results as well as secondary sources. As per agreement with the participating Plans all findings have been de-identified.

A mark of “NI” in the charts on pages 38-41 indicates that no information was found with respect to the surveyed question.

### **Formulary Coverage:**

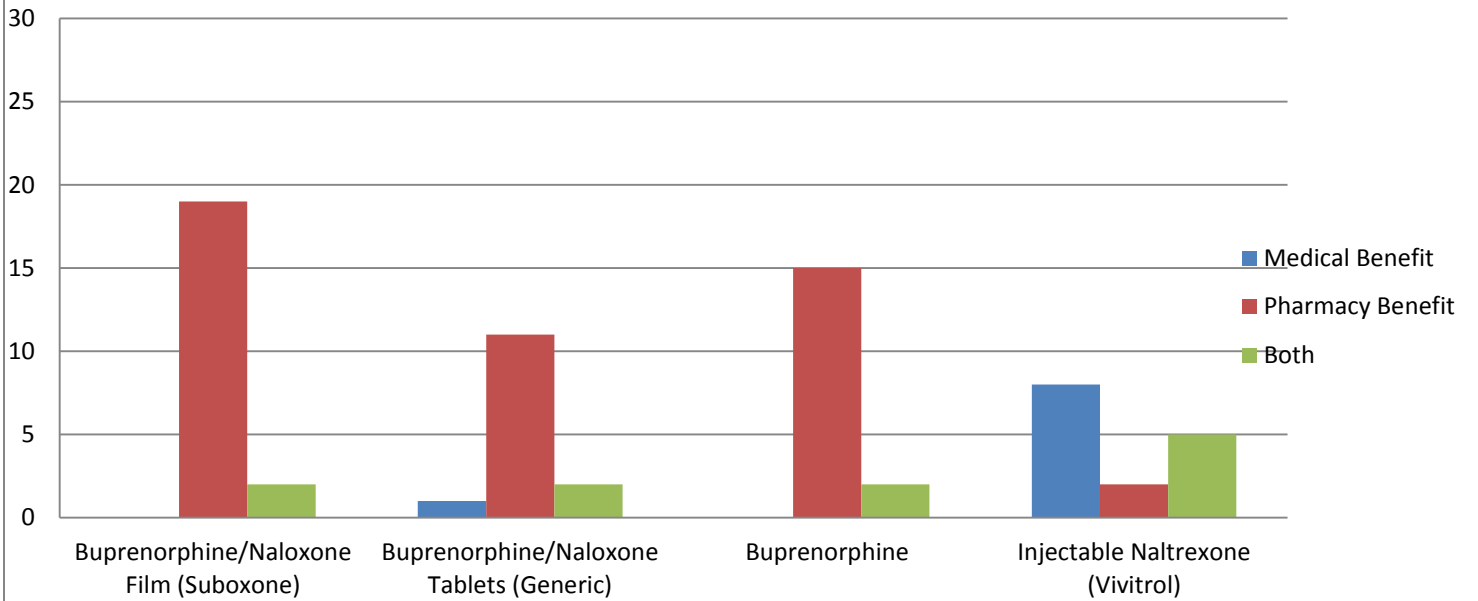
Overall Information Plan Information		
Medication	Information Found	No Information Found
Buprenorphine/Naloxone Film (Suboxone)	28	2
Buprenorphine/Naloxone Tablets (Generic)	22	8
Buprenorphine (Generic)	24	6
Injectable Naltrexone (Vivitrol)	24	6





- Extended release naltrexone (Vivitrol) is covered as a pharmacy and/or medical benefit in 17 out of 30 of the studied plans. It is most covered as a specialty drug dispensed by a specialty pharmacy and therefore in Tier 4. Data on coverage was available only from secondary sources
- Methadone on formularies is not included here; regulations governing dispensing of methadone limit it to OTPs. As noted previously, this study found no commercial health plans that covered methadone in OTPs.
- While the FDA approved generic buprenorphine/naloxone medications in March 2013, nearly half of the plans already list the generic formulation on their formulary. Two plans that do not cover the brand formulation do cover the generic combination product.
- 23 plans cover more than one medication.

## Medical or Pharmacy Benefit Classification





**Dosage Limitations**

Medication	Notable Quantity Limitation Requirements
Buprenorphine/Naloxone Film (Suboxone)	No refills and only for 30 day supply, As clinically indicated. Generally less than 12mg/day.
	60 films/m
	1 year approval duration, Request for quantity greater than 24 mg per day will be reviewed on a case by case basis.
	90 films/m
	Suboxone is only covered for detox
	3/day
	3 films or 3 tablets/day of the 2mg/0.5mg, 8mg/2mg, 4mg/1mg strengths. 2 films/day of the 12mg/3mg
	up to 12 months
Buprenorphine/Naloxone Tablets (Generic)	No refills and only a 30 day supply. As clinically indicated, generally under 12mg/day.
	90 tablets/m
	1 year approval duration
	Request for quantity greater than 24 mg per day will be reviewed on a case by case basis.
	30 tabs/m
	3/day
	3 films or 3 tablets/day of the 2mg/0.5mg, 8mg/2mg, 4mg/1mg strengths. 2 films/day of the 12mg/3mg
Buprenorphine Tablets (Generic)	No refills and only a 30 day supply.
	15 tablets/m
	90 tabs/m
	15 for induction, 3/day for maintenance
	2 mg = 24 tablets/30 day supply
Injectable Naltrexone (Vivitrol)	One injection at a time.
	6m approval duration
	once per month

### Utilization Management Techniques:

The most common drug utilization management (UM) techniques used by payers include the following:

Prior authorization (PA): beneficiary must get approval from the plan before filling a prescription

Step therapy: requirement that the beneficiary must first try one treatment for the condition before another, also known as “fail first”.

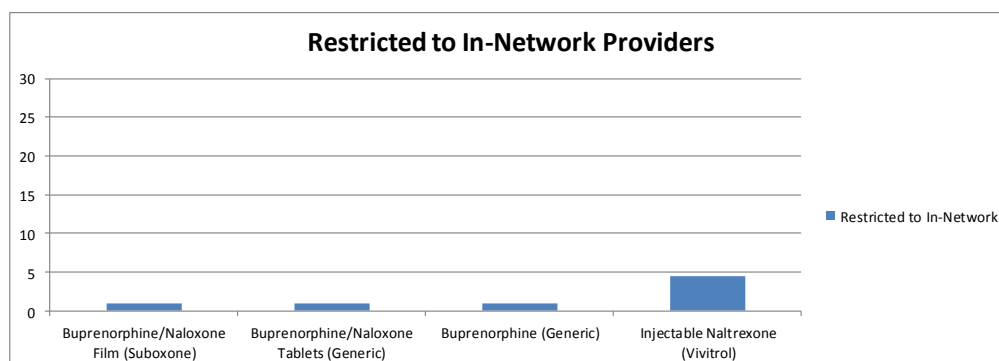
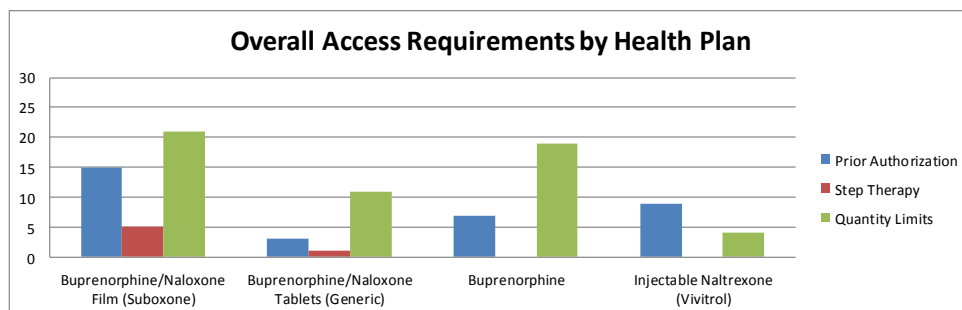
Quantity Limits: requirements that set limitations on medication supply by quantity, duration or number of prescription available.

Access Restricted to In-Network Providers: limits prescription of medications to physicians who are in-network severely limiting the pool of available providers; for buprenorphine physicians must be trained and have waivers to treat a maximum of 100 patients at any one time; these limitations mean that finding a physician who is accepting patients may be very difficult. Use of extended-release naltrexone was often limited to in-network physicians.

Dosage Limits: limitations on the dosage level allowable for a medication; dosages limits may vary for different phases of treatment

Duration Limits: limiting use of medication to detoxification phase or discontinuing use after a specified period (often short-term use rather than maintenance therapy).

The charts below reflect the survey’s findings with respect to UM requirements. See table on Page 35 for Notable Prior Authorization Requirements.



## DISCUSSION

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### PATIENT IMPLICATIONS

From the patient perspective, survey findings and analyses of secondary sources revealed some significant problems with the available information.

#### ***Complex, Confusing Information***

Previously mentioned difficulties in locating clear, concise and useable information related to requirements and guidelines for commercial insurance coverage have numerous adverse implications for patients or providers seeking pharmacotherapy as a component of comprehensive treatment for opioid dependence. Patients, prescribers and programs considering this path will be faced with unnavigable, un-confirmable, unclear and at times contradictory information.

#### ***Complexity of Different Plans Governing the Same Patient***

Patients and prescribers seeking medication as part of a comprehensive treatment plan will be required to understand the intricacies of both pharmacy and medical benefits. These benefit issues are often unclear and may have significant financial implications such as large out-of-pocket costs. For example, patients seeking injectable naltrexone may find that a doctor visit is covered under a medical benefit, the medication itself is covered as a pharmacy benefit while injection of the medication (a medical benefit) may not be covered at all. In the event this patient does not have pharmacy coverage s/he may be required to pay for the injection out-of-pocket; but worse, may become aware of such costs only when subsequently billed.

### ***Phase of Treatment and Dispensing Requirements***

Patients may also face difficulty in understanding requirements regarding where and when certain medications can be dispensed. In addition to adherence to federal regulations governing medication, plans may also implement their own restrictions on when during the course of treatment, and for how long during treatment the medication may be covered and reimbursed.

Methadone offers a good example of the often complex interactions between federal, state, local and insurer regulations. Federal regulations governing methadone stipulate that it can only be administered (for the treatment of opioid dependence) at licensed and accredited Opioid or Narcotic Treatment Programs (OTPs or NTPs) and is not available for use in either in-patient or out-patient general treatment settings. Thus, a patient seeking methadone maintenance therapy is required to first locate a methadone clinic while also checking to ensure that methadone is a covered benefit. This study could not find any commercial plans that provided coverage for methadone in OTPs.

Additionally, insurers may choose to impose limitations on the availability of the medication to specific phases of treatment. In one plan use of Suboxone was not covered for maintenance and was limited to use for acute withdrawal only during detoxification. Thus, patients who have successfully completed acute withdrawal with the assistance of Suboxone may be required to discontinue its use for other phases of their treatment.

### ***Patient Out-of-Pocket Costs***

Tiered formularies are directly related to patient access as well, in that tier classification directly affects patient out-of-pocket costs. Under a tiered formulary, medications are assigned to a specific tier that corresponds to a pricing classification. Typically, lower tiered medications will carry the lowest cost. As illustrated by Huskamp and Keating (2005) “under a 3-tier formulary,

the first tier typically includes generic drugs with the lowest cost sharing (e.g., 10% coinsurance), the second includes preferred brand-name drugs with higher cost sharing (e.g., 25%), and the third includes non-preferred brand-name drugs with the highest cost.” Information about cost-sharing tiers is another challenge for consumers. When the generic form of Suboxone (approved by the FDA in 2013) becomes available, for use, it is possible that plans will move the commercial product to a higher tier and place the generic product on the lower tier. Patients and providers will potentially have to make product choices based on these tier placements.

For patients who are treated with medications such as Vivitrol, the cost sharing issues are different. As a specialty pharmaceutical which is not self-administered, it is reimbursed under the medical benefit of most plans rather than as a pharmacy benefit. As a medical benefit, coinsurance rates may be as high as 20% or more and might be very costly to individual patients.

### ***Limitations Imposed by Prior Authorization Requirements***

With all of the medications analyzed for this study subject to prior authorization requirements, patients seeking coverage for such medications face additional complications. Patients must meet various criteria (as verified by their prescriber) in order for prior authorization requests to be approved. If prior authorization requests are not approved the medication may not be covered. As defined by one plan:

*“Prior Authorization is designed to encourage appropriate use of medications. Select medications on the Preferred Drug List may require prior authorization. Medication utilization must meet FDA-approved indications, as well as our medical necessity guidelines. If a medication requires prior authorization, a prior authorization form needs to be completed by the prescriber for submission to [redacted].”*

An additional example below illustrates that a patient covered under one plan must meet the following criteria when seeking prior authorization for injectable naltrexone:

“Injectable naltrexone (Vivitrol) may be approved for the prevention of relapse to opioid dependence following detoxification when the individual:

1. Is being treated for opioid dependence; AND
2. Has had an initial response and tolerates oral naltrexone (Revia) but is unable to comply with daily dosing; AND
3. Has successfully completed an opioid detoxification program; AND
4. Has been opioid-free (including buprenorphine and methadone) for at least 7 days prior to initiating treatment with naltrexone (Vivitrol) injection; AND
5. Actively participates in a comprehensive rehabilitation program that includes psychosocial support; AND
6. Patient has none of the following:
  - a. Currently on opioid analgesics for pain management; OR
  - b. Currently in acute opioid withdrawal;
  - c. A positive urine screen for opioids; OR
  - d. A failed naloxone challenge test; OR
  - e. Acute hepatitis;
  - f. Liver failure; OR
  - g. Previous hypersensitivity to naltrexone, 75:25 polyactide-co-glycolide (PLG), carboxymethylcellulose or any other component of the diluent.”

Notably, the inclusion of the term “may” implies that approval is not guaranteed even in the event the patient meets all of the required criteria. Additionally, the terms “successfully” and “actively” are included, which may indicate that fulfillment of some criteria are subjective in

nature. Further, in describing preauthorization the plan states “[p]reauthorization requirements are subject to change at any time and without notice” and “[i]f preauthorization for a particular service or treatment is denied, you may be held financially responsible for the expense of the test, equipment, service or procedure.”

Prior authorization requirements, criteria and verification processes were found to be overwhelmingly vague. In one of the surveyed plans the provider was required to submit information with respect to previous episodes of counseling by type/frequency and prior opioid use, however the form indicated nothing about which requested information was required for approval and how such criteria was evaluated with respect to approval decisions.

### ***Timing Restrictions***

Researchers uncovered two types of timing restrictions on medication coverage: First, plans generally gave no indication about the length of time between submission and approval of a prior authorization request; and such information was not readily available on formularies, requiring additional effort to uncover. Second, once approved, prior authorizations often were subject to time limitations on the use of the medication, e.g. six months. Using the above preauthorization requirements for naltrexone as an example, in theory the six month approval limitation may seem reasonable. However, to meet criteria for an additional six month time period, the patient would be required to continuously and “actively” participate in a comprehensive rehabilitation for more than six months, which seems unlikely given the vague and discretionary nature of the plan’s “medical necessity” requirements concerning coverage of rehabilitation.

### ***Quantity Restrictions***

Dosage requirements and quantity limits have significant implications for patients who need pharmacotherapy as part of a comprehensive treatment plan. Existing guidelines suggest

different dosing levels based on treatment phase (e.g., induction, stabilization, tapering) (TIP 40, Community Care Guideline). These guidelines do not specify recommendations for durations of use for maintenance therapy. Where quantity limits were provided, most plans' coverage limits were not connected with a specific phase of treatment, which leads to questions of whether patients are provided with safe adequate dosages during each phase of treatment, whether medication was available for all phases of treatment, and whether provided dosages were safe and effective.

## **POLICY ISSUES RELATED TO COMMERCIAL HEALTH PLANS**

Conducting a survey of commercial health plan coverage and benefits for medications used in comprehensive treatment of opioid dependence, beyond being challenging, revealed a number of policy issues worth considering as health care reform is implemented.

With the implementation of the ACA, it is critical to understand the roles of commercial health plans. In addition to being central to the insurance market, commercial health plans will play a fundamental role in state Medicaid managed care programs as well as health insurance exchanges. Clinical research in the last 10 years has led to significant gains in evidence-based practices in the treatment of opioid addiction both in psychosocial interventions and medications. Further, treatment of substance use disorders as a chronic medical condition (for many) has increased attention to the use of medications and their associated clinical services for patients with opioid dependence. Recent scientific findings, as well as upcoming implementation of the ACA, have resulted in pressure on health plans to perform. Specifically, health plans are being called upon to improve access to information, access to treatment alternatives and access to appropriate, evidence-based treatment services.



In 2014, many previously uninsured adults ages 18-64 will become eligible for coverage through state exchanges created by the ACA. Of those previously uninsured adults, predictions are that about 14.5 percent will have a substance use disorder (SAMHSA, National and state estimates on prevalence of behavioral health conditions. Rockville, MD, 2012). Clearly, this increase has implications for private insurers who are likely to see an increase in demand for behavioral health services. It also points to the pressing need for consistent national guidelines on how medications should be used as part of an overall continuum of care for the treatment of substance use disorders.

This report on commercial health insurance coverage and benefits for medications used to treat opioid dependence is not focused on the units within commercial health plans that administer Medicaid managed care benefits in the states. Nevertheless, a significant proportion of the commercial insurers in the survey are the very same insurers that currently administer such programs and will increasingly administer Medicaid managed care in the states as health care reform is implemented nationally.

### ***Spending by Commercial Insurers***

Growth of spending on behavioral health treatment declined significantly over the past several years, as did overall spending in private health insurance coverage. “Growth in spending for behavioral health and all health treatment slowed substantially [during the recession], declining from 7.2 percent to 2.7 percent for behavioral health and from 5.5 percent to 2.0 percent for all health.” (Levit, K. et al., 2013). The decline was driven primarily by loss of employment-based health insurance by about 8 million people.

On the other hand, from 2001-2009 the share of spending on treatment of substance use disorders by private insurance increased markedly to 16 percent in 2009 -- much less than the 26 percent of mental health and the 34 percent of all health treatment that private insurance

funds -- but nevertheless a significant increase from previous years (ibid.). While spending on medications to treat addictions grew rapidly during the same period of time, it still accounted for only about 4% of substance use treatment spending.

### ***Lack of Transparency***

Commercial insurers believe, with some reason, that they are facing an uncertain future. As 2014 approaches commercial health plans are beginning to consider how to position themselves. The lack of willingness to respond to the survey at this time may be an indication of just how closed commercial health plans want to be regarding discussion of their coverage and benefits. Even with professional and collegial relationships with several of the pharmacy and/or behavioral health directors, researchers found the unwillingness to provide any information relating to the survey quite compelling.

Several of the survey recipients indicated that they did not believe they had the authority to divulge information relating to coverage and benefits for medications and, indeed, were instructed by their CEOs to “discuss nothing” about their medication benefits. Despite assurances that their names would not be revealed, it was made clear to interviewers that health plan executives and pharmacy directors were concerned about becoming vulnerable in one way or another through release of information. If information about medication coverage and benefits continues to be deeply buried, consumers will need a great deal of help as they begin to navigate health insurance plans. Researchers at TRI speculate that a large percent of the lack of response may be due to the timing of survey----just before implementation of health reform about which the plans have indicated to TRI they are quite concerned.

From a policy perspective one might wonder whether plans will be required to “go public” with their coverage and benefits related to essential health benefits and MHPAEA, particularly in the individual healthcare marketplace, i.e. the exchanges. The findings of the survey certainly

suggest that some effort be put into work with consumer and patient advocacy groups to make coverage and benefits information clear so that patients can make more informed choices as they navigate what is now being called the “health marketplace” through web sites in each state used explicitly for this purpose.

It is clear not only from this survey focused on medications, but from Massachusetts’ experience with health care reform and its impact on consumers seeking treatment for substance use disorders, that consumers will need help in relation to affordability (Focus on Health Reform, “Massachusetts Health Care Reform: Six Years Later,” Kaiser Family Foundation, May 2012).

***Employers as Purchasers*** Commercial health plans, in some important respects, are beholden to employers who purchase care. After reviewing the documents related to implementation of health care reform and specifically on behavioral health care that have been produced by the National Business Group on Health (“An Employer’s Guide to Behavioral Health Services,” Center for Preventive and Health Services, National Business Group on Health , 2005) and other employers, it is clear that employers understand how expensive mental illness and substance use disorders can be in lost productivity and absenteeism. Employers also seem to understand that treatment that combines pharmacological management with psychosocial interventions such as psychotherapy is effective.

Addressing the significant additional burden of co-morbid behavioral health conditions for individuals is critical to delivering effective disease management services for chronic medical problems. Therefore, as noted by the National Business Group on Health, limitations on behavioral healthcare benefits may limit the efficacy of disease management programs for individuals with co-morbid medical and behavioral health conditions. Limiting behavioral healthcare services can increase employers’ non-behavioral direct and indirect healthcare costs. According to the National Business Group, the lack of coordination and integration among

managed care vendors of employers has created significant quality and accountability problems.

With this in mind, and with implementation of the ACA, health insurance exchanges and MHPAEA, the need for education of employers about treatment of all substance use disorders, and the role of access to medications and their appropriate use seems to be an important priority.

### ***Contract with Providers and Provider Networks by Commercial Insurers***

Under-utilization of medications in comprehensive treatment is another issue of policy concern. Studies currently underway at TRI and elsewhere have found that access to medications is hampered significantly by the fact that many treatment programs do not have a physician on staff. There are several historical reasons for this. For example, in a number of states licensing requirements for specialty substance abuse treatment programs include restrictions on hiring physicians within treatment programs as well as restrictions on use of specific medications in particular settings. In one state, licensing of specialty treatment programs includes a complete restriction on the use of buprenorphine.

Despite the 2006 law that increased a DATA-waived prescriber's patient limit from 30 to 100, 43% of DATA-waived ASAM members report the 100-patient prescribing limit as a barrier to treatment. A recent proposal by SAMHSA of extending prescribing privileges to Mid-Level Practitioners (i.e., Nurse Practitioners and Physicians Assistants) is an effort to address the addiction treatment workforce gap. (Federal Guidelines for Opioid Treatment, SAMHSA, April 2013).

### ***Advances by Commercial Health Plans***

As health reform nears and commercial health plans become more engaged in thinking about their participation in the health marketplace (exchanges) and in Medicaid managed care, a

number of them are taking steps to engage treatment providers in improving the use of medications in comprehensive treatment. They are taking steps to create internal programs to assist patients and providers with access to medications, remove prior authorization requirements, and work directly with providers to change the culture of many treatment programs that is constraining the use of medications. These health plans are to be commended for understanding that the sea change that is occurring in the treatment of opioid dependence requires them to become more open with patients and providers and to actively assist in making evidence-based practices available and accessible.

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## **APPENDIX 1: Details on Survey Approach and Methodology**

### ***Respondent Identification Within Plans***

Key relevant officials were identified as survey recipients (see below) within each of the commercial health plans to complete the survey. The target individuals were the Medical Directors, Pharmacy Directors, and Behavioral Health Directors for each plan, since the subject matter for the survey was addiction medicine coverage. These individuals were initially contacted by email with a request to complete the survey using a variety of vehicles including Survey Monkey, a form-fillable PDF, a printable word document or a telephone interview with the assistance of a TRI research scientist. After the introductory email multiple follow-up calls and emails were made to assist targeted participants to complete the survey and clarify questions if needed. In addition to the survey, researchers examined a variety of secondary sources to either take the place of or to provide clarification and/or expansion of survey results. Such sources included but were not limited to health plan published formularies, contract or preferred drug lists, prior authorization requirements and prior authorization request forms. Three prospective respondents per survey were contacted, when possible, so that the chance of obtaining at least one formal and accurate response per plan was maximized.

### ***Obstacles to Survey Completion***

Complicating initial identification of individuals were unclear corporate structures and intersecting subsidiary information across health plans in a number of states. Additionally, the issue of “carve-outs” to health plans became relevant; many of the behavioral health components of targeted plans were carved-out to separate commercial organizations, some owned by the plans but separate from them and some completely independent of the plans and not necessarily closely linked. In the event behavioral health components were carved-out



researchers were required to begin anew and identify relevant individuals within the established carve-out.

Initial identification efforts revealed a lack of transparency in plans publicly identifying positions, names of officials and roles within the plans. In addition, even when individuals could be identified, contact information was not publicly available. Medical Directors were routinely listed as members of executive leadership teams; however Behavioral Health Directors and Pharmacy Directors were not. Contact information for those individuals was much more difficult to identify, sometimes resulting in frank questions about “how did you get my name, telephone numbers, and email address?” Researchers were required to consult various non-traditional sources including public stock information and filings, publicly released press statements and various web based search engines including Lead411, White pages, Linked In, Facebook. Using these unreliable sources, researchers were required to piece together information from various sources to compile complete and correct contact information including name, position, phone number and email addresses. Researchers were unable to find complete contact information for approximately 25% of identified targets but the process required much time, effort, persistence and creativity.

Health plans receive many requests to respond to surveys; some indicated in emails to TRI that the health plans policies in place that required upper management, and in some instances, CEO approval before responding. Even when respondents expressed willingness to send surveys “up the chain”, the time necessary to receive approval made response deadlines impossible.

## APPENDIX 2: Survey Instrument

Thank you for taking the time to respond to our questions! The items concern the coverage of the following medications for treatment of opioid dependence:

- **Methadone**
- **Buprenorphine/Naloxone Film (Suboxone<sup>®</sup>)**
- **Buprenorphine/Naloxone tablets (Generic)**
- **Buprenorphine Tablets (Generic)**
- **Injectable Naltrexone (Vivitrol<sup>®</sup>)**

We know that you have many plans, so to make things easier, we will be asking about the private plan with the **largest number of enrollees** for 2013 in the state of \_\_\_\_\_.

What is the name of your largest plan? \_\_\_\_\_

What is your title: \_\_\_\_\_

1. Does this plan offer coverage for the following medications when used for the treatment of opioid dependence?

	<u>YES</u>	<u>NO</u>
Methadone	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine/Naloxone Film (Suboxone <sup>®</sup> )	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine/Naloxone Tablets (Generic)	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine Tablets (Generic)	<input type="checkbox"/>	<input type="checkbox"/>
Injectable Naltrexone (Vivitrol <sup>®</sup> )	<input type="checkbox"/>	<input type="checkbox"/>

2. Is specialty substance use disorder (SUD) counseling a covered benefit in addition to medication-assisted treatment?

<u>YES</u>	<u>NO</u>
<input checked="" type="checkbox"/>	<input type="checkbox"/>

3. Do you require that a patient be enrolled in or otherwise have documented SUD counseling in order to approve opioid-specific medication-assisted treatment with any of the following medications?

	<u>YES</u>	<u>NO</u>
Methadone	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine/Naloxone Film (Suboxone <sup>®</sup> )	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine/Naloxone Tablets (Generic)	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine Tablets (Generic)	<input type="checkbox"/>	<input type="checkbox"/>
Injectable Naltrexone (Vivitrol <sup>®</sup> )	<input type="checkbox"/>	<input type="checkbox"/>

4. Is your coverage of the medications listed below considered a medical benefit, pharmacy benefit, or both? (INDICATE ALL THAT APPLY)

	<u>MEDICAL</u>	<u>PHARMACY</u>	<u>BOTH</u>
Methadone	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine/Naloxone Film (Suboxone®)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine/Naloxone Tablets (Generic)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine Tablets (Generic)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Injectable Naltrexone (Vivitrol®)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. We would like to know about quality management requirements for treatment. Please provide this information for the following medications:

#### **METHADONE**

- Describe any patient age restrictions:
- Describe any limitations on duration of medication treatment:
- Describe any limitations on the number of refills a patient can receive at one time:
- Use during pregnancy:  Yes  No
- Describe dosage amounts:
- Describe quantity limits for the medication (per day, week, or month):
- Describe any requirements for step therapy:
- Describe any prior authorization requirements:

#### **BUPRENORPHINE/NALOXONE FILM (SUBOXONE®)**

- Describe any patient age restrictions:
- Describe any limitations on duration of medication treatment:
- Describe any limitations on the number of refills a patient can receive at one time:
- Use during pregnancy:  Yes  No
- Describe dosage amounts:
- Describe quantity limits for the medication (per day, week, or month):
- Describe any requirements for step therapy:
- Describe any prior authorization requirements:

#### **BUPRENORPHINE/NALOXONE TABLETS (GENERIC)**

- Describe any patient age restrictions:
- Describe any limitations on duration of medication treatment:
- Describe any limitations on the number of refills a patient can receive at one time:
- Use during pregnancy:  Yes  No
- Describe dosage amounts:
- Describe quantity limits for the medication (per day, week, or month): Describe any requirements for step therapy:
- Describe any prior authorization requirements:

#### **BUPRENORPHINE TABLETS (GENERIC)**

- Describe any patient age restrictions:
- Describe any limitations on duration of medication treatment:
- Describe any limitations on the number of refills a patient can receive at one time:
- Use during pregnancy:  Yes  No
- Describe dosage amounts:
- Describe quantity limits for the medication (per day, week, or month):

- Describe any requirements for step therapy:
- Describe any prior authorization requirements:

**INJECTABLE NALTREXONE (VIVITROL®)**

- Describe any patient age restrictions:
- Describe any limitations on duration of medication treatment:
- Describe any limitations on the number of refills a patient can receive at one time:
- Use during pregnancy:  Yes  No
- Describe dosage amounts:
- Describe quantity limits for the medication (per day, week, or month):
- Describe any requirements for step therapy:
- Describe any prior authorization requirements:

6. With respect to MAT prescribers, please tell me whether Nurse Practitioners (NP), Physicians' Assistants (PA) or Medical Doctors(MD) are eligible to prescribe the following medications:

	<u>NP</u>	<u>PA</u>	<u>In Network</u> <u>MD</u>	<u>Out of</u> <u>Network MD</u>	<u>Not</u> <u>applicable</u>
Methadone	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine/Naloxone Film (Suboxone®)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine/Naloxone Tablets (Generic)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine Tablets (Generic)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Injectable Naltrexone (Vivitrol®)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

7. Are these medications on your formulary and/or preferred drug list?

	<u>PREFERRED</u>		<u>NON-PREFERRED</u>	
	<u>YES</u>	<u>NO</u>	<u>YES</u>	<u>NO</u>
Methadone	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine/Naloxone Film (Suboxone®)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine/Naloxone Tablets (Generic)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine Tablets (Generic)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Injectable Naltrexone (Vivitrol®)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

8. Regulations governing use of SUD medications in accredited outpatient Opioid Treatment Programs (OTPs) have changed. Do you cover the medications listed below in OTPs today?

	<u>YES</u>	<u>NO</u>
Methadone	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine/Naloxone Film (Suboxone®)	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine/Naloxone Tablets (Generic)	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine Tablets (Generic)	<input type="checkbox"/>	<input type="checkbox"/>
Injectable Naltrexone (Vivitrol®)	<input type="checkbox"/>	<input type="checkbox"/>

9. Do you cover these medications in physician office-based settings?

	<u>YES</u>	<u>NO</u>
Buprenorphine/Naloxone Film (Suboxone®)	<input type="checkbox"/>	<input type="checkbox"/>
Buprenorphine/Naloxone Tablets (Generic)	<input type="checkbox"/>	<input type="checkbox"/>

Buprenorphine Tablets (Generic)    
 Injectable Naltrexone (Vivitrol®)

10. Do you cover these medications in specialty outpatient or residential treatment settings?

	<u>SPECIALTY OUTPATIENT</u>		<u>RESIDENTIAL TREATMENT</u>	
	<u>YES</u>	<u>NO</u>	<u>YES</u>	<u>NO</u>
BUPRENORPHINE/NALOXONE FILM (SUBOXONE®)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
BUPRENORPHINE/NALOXONE TABLETS (GENERIC)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
BUPRENORPHINE TABLETS (GENERIC)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
INJECTABLE NALTREXONE (VIVITROL®)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Now, we would like to discuss potential future initiatives and changes in the coverage of medications for the treatment of opioid dependence.**

11. Please describe any important opioid dependence medication **funding, health reform, policy,** and/or **legislative** changes planned for 2013 or 2014.

---

**THE END!**

We may want to contact you to ask about coverage of approved alcohol dependence medications. Would you be willing to be interviewed again or would you like to refer us to another person?

YES

NO. Please contact: (Name, title, department, telephone, email address).

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Thank you for your assistance and partnership. Please note below if you would like to see our de-identified findings.

YES, send it to:      Name, title, department, telephone, email address       NO, thanks.

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**ADDITIONAL RESULTS CHARTS**

**Notable Prior Authorization Requirements**

Medication	Prior Authorization Requirements
Methadone	<p>Methadone Maintenance Treatment (MMT): A benefit for opioid addiction treatment is available and covered in accordance with the member/subscriber's contract benefit for inpatient and outpatient substance abuse treatment at a certified facility.</p> <p>I. In [ redacted] State, services must be rendered by the participating chemical dependency treatment facilities licensed by the State Office of Alcoholism and Substance Abuse Services.</p> <p>II. The patient must meet the following criteria:</p> <p>A. If an applicant is 21 years of age or older, verification of dependence on opium, morphine, heroin or any derivative or synthetic drug of that group for a period of one year; or</p> <p>B. If an applicant is under 21 years of age, verification of dependence on opium, morphine, heroin or any derivative or synthetic drug of that group for a period of two years; and</p> <p>C. Must meet the current American Psychiatric Association criteria as stated in the Diagnostic and Statistical Manual of Mental Disorders (DSM4) for opioid dependence.</p> <p>III. The comprehensive MMT program must be licensed and include individual and group therapy as well as medical and psychiatric evaluations.</p>

Suboxone	<p>Suboxone or Subutex/buprenorphine is covered when ALL of the following conditions are met:</p> <ol style="list-style-type: none"> <li>1. The prescriber meets the qualification certification criteria in the Drug Addiction Treatment Act (DATA) of 2000 and has been issued a unique DEA identification number by the DEA, indicating that he or she is a qualified physician under the DATA to prescribe Subutex or Suboxone; AND</li> <li>2. The patient has a diagnosis of opioid dependence; AND</li> <li>3. The patient is 16 years of age or older; AND</li> <li>4. The patient is abstinent from illicit drug use (including problematic alcohol and/or benzodiazepine use) ; AND</li> <li>5. The patient has a psychosocial treatment plan and is compliant with all elements of the treatment plan including: <ol style="list-style-type: none"> <li>a. recovery-oriented activities</li> <li>b. psychotherapy, and/or other psychosocial modalities; AND</li> </ol> </li> <li>6. If Subutex or generic buprenorphine SL tablets are being requested: <ol style="list-style-type: none"> <li>a. The patient must meet the above criteria; AND</li> <li>b. The treatment is being used for induction therapy (if approved, it will be approved for 5 days); OR</li> <li>c. The patient has a medical record documentation of an allergy to naloxone or naltrexone; OR</li> <li>d. The patient is pregnant and has medical record documentation of a treatment plan.</li> </ol> </li> </ol> <p>AND ONE of the following:</p> <ol style="list-style-type: none"> <li>7. The quantity requested is less than or equal to the program quantity limit (see below); OR</li> <li>8. The quantity (dose) requested is within FDA-approved labeling and the prescribed dose cannot be achieved using a lesser quantity of a higher strength; OR</li> <li>9. The quantity (dose) requested is greater than the maximum dose recommended in FDA approved labeling and the prescriber has submitted Documentation in support of therapy with a higher dose or longer duration for the intended diagnosis.</li> </ol>
Suboxone	<p>Concurrent use of buprenorphine tablets or Suboxone (buprenorphine/naloxone) and opioid analgesics will not be authorized. For individuals who have a claim for Suboxone in the past 30 days, opioid analgesics will deny for prior authorization. If needed, the Suboxone prescriber will be contacted to discuss the medical necessity of concurrent use of Suboxone and opioids.</p>
Vivitrol	<p>Injectable naltrexone (Vivitrol) may be approved for the prevention of relapse to opioid dependence following detoxification when the individual:</p> <ol style="list-style-type: none"> <li>I. Is being treated for opioid dependence; AND</li> <li>II. Has had an initial response and tolerates oral naltrexone (Revia) but is unable to comply with daily dosing; AND</li> <li>III. Has successfully completed an opioid detoxification program; AND</li> <li>IV. Has been opioid-free (including buprenorphine and methadone) for at least 7 days prior to initiating treatment with naltrexone (Vivitrol) injection; AND.</li> <li>V. Actively participates in a comprehensive rehabilitation program that includes psychosocial support; AND</li> <li>VI. Patient has none of the following: <ol style="list-style-type: none"> <li>a. Currently on opioid analgesics for pain management; OR</li> <li>b. Currently in acute opioid withdrawal; OR</li> <li>c. A positive urine screen for opioids; OR</li> </ol> </li> </ol>

	<ul style="list-style-type: none"> <li>d. A failed naloxone challenge test; OR</li> <li>e. Acute hepatitis; OR</li> <li>f. Liver failure; OR</li> <li>g. Previous hypersensitivity to naltrexone, 75:25 polyactide-co-glycolide (PLG), carboxymethylcellulose or any other component of the diluent.</li> </ul>
<p>Buprenorphine tablets</p> <p>Buprenorphine/Naloxone film</p>	<ol style="list-style-type: none"> <li>1. Primary Diagnosis: ICD-9:</li> <li>2. Psychosocial Counseling: <ul style="list-style-type: none"> <li>a. Date of last psychosocial counseling session:</li> <li>b. Has patient been compliant with all sessions? <input type="checkbox"/> Yes <input type="checkbox"/> No</li> </ul> </li> <li>3. Please provide plan for method and dates (next 3) of psychosocial counseling going forward: <ul style="list-style-type: none"> <li>a. Method:</li> <li>b. Dates: (1) _____ (2) _____ (3) _____</li> </ul> </li> <li>4. Must submit most current urine drug screen with this form.</li> <li>5. Does patient currently abuse alcohol? <input type="checkbox"/> Yes <input type="checkbox"/> No</li> <li>6. Has patient taken opioids in the past 30 days? <input type="checkbox"/> Yes <input type="checkbox"/> No <ul style="list-style-type: none"> <li>a. If yes, please state reason for opioid use:</li> <li>b. If yes, has patient experienced a relapse in disease? <input type="checkbox"/> Yes <input type="checkbox"/> No</li> </ul> </li> <li>7. If requesting doses above 24 mg per day, state clinical reason current dosing limits are being exceeded: <ul style="list-style-type: none"> <li>a. Has patient tried a dose of 16 mg per day? <input type="checkbox"/> Yes <input type="checkbox"/> No</li> <li>b. If yes, provide dates of therapy:</li> </ul> </li> <li>8. Please indicate a taper schedule if dose exceeds 16 mg/day buprenorphine:</li> </ol>



**METHADONE<sup>1</sup>**

State	On Formulary ?	Tier	Medical Benefit ?	Pharmacy Benefit?	Covered in OTP?	Covered in office based setting?	Covered in residential treatment?	MAT Prescriber Restrictions?	Prior Authorization Requirements ?	Quantity Limits?	Step Therapy?
1.	Y <sup>2</sup>	1	Y <sup>3</sup>	Y	Y	N	N	N	Y <sup>456</sup>	N	Y <sup>7</sup>
2.	Y	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
3.	Y <sup>8</sup>	1	Y <sup>9</sup>	Y	Y	N	N	N	Y <sup>101112</sup>	N	Y <sup>13</sup>
4.	Y	1	N	Y	NI	NI	NI	NI	NI	NI	NI
5.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
6.	Y	1	N	Y	NI	NI	NI	NI	NI	NI	NI
7.	Y	NI	NI	NI	NI	NI	NI	NI	NI	Y <sup>14</sup>	NI
8.	NI	1	N	Y	NI	NI	NI	NI	NI	NI	NI
9.	Y	1	N	Y	NI	NI	NI	NI	NI	NI	NI
10.	Y	1	N	Y	NI	NI	NI	NI	N	N	N
11.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
12.	Y	1	N	Y	NI	NI	NI	NI	N	N	N
13.	Y <sup>15</sup>	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
14.	Y	1	N	Y	NI	NI	NI	NI	NI	NI	NI
15.	Y <sup>16</sup>	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
16.	Y	NI	N	Y	Y	N	N	Y <sup>17</sup>	N	N	N
17.	Y	1	N	Y	Y <sup>18</sup>	N	N	Y <sup>19</sup>	Y <sup>20</sup>	Y <sup>21</sup>	NI
18.	Y	NI	Y	Y	Y	N	N	Y <sup>22</sup>	N	N	N
19.	Y <sup>23</sup>	2/4/1	NI	NI	NI	NI	NI	NI	NI	NI	NI
20.	Y <sup>24</sup>	2/4/1	NI	NI	NI	NI	NI	NI	NI	NI	NI
21.	Y <sup>25</sup>	2/4/1	NI	NI	NI	NI	NI	NI	NI	NI	NI
22.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
23.	Y	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
24.	Y	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
25.	Y	1	N	Y	NI	NI	NI	NI	N	Y <sup>26</sup>	N
26.	Y	1/2/3	N	Y	NI	NI	NI	NI	N	N	N
27.	Y	1	N	Y	NI	NI	NI	NI	N	Y <sup>27</sup>	N
28.	Y	1	N	Y	NI	NI	NI	NI	N	Y <sup>28</sup>	N
29.	Y	1	N	Y	NI	NI	NI	NI	N	N	N
30.	Y	1	N	Y	NI	NI	NI	NI	N	N	N

**BUPRENORPHINE/NALOXONE FILM (SUBOXONE®)**

State	On Formulary ?	Tier	Medical Benefit?	Pharmacy Benefit?	Covered in OTP?	Covered in office based setting?	Covered in residential treatment?	MAT Prescriber Restrictions?	Prior Authorization Requirements ?	Quantity Limits?	Step Therapy?
1.	N	NI	Y	Y	N <sup>29</sup>	Y	Y	N	N <sup>3031</sup>	Y <sup>3233</sup>	Y <sup>34</sup>
2.	Y	2 <sup>35</sup>	NI	NI	NI	NI	NI	NI	Y	Y	N
3.	N	NI	Y	Y	N <sup>36</sup>	Y	Y	N	N <sup>3738</sup>	Y <sup>3940</sup>	Y <sup>41</sup>
4.	Y	2	NI	Y	NI	NI	NI	NI	N	Y <sup>42</sup>	N
5.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
6.	Y	2	NI	Y	NI	NI	NI	NI	N	Y <sup>43</sup>	N
7.	Y	2 <sup>44</sup>	NI	NI	NI	NI	NI	NI	Y	Y	N
8.	NI	3	N	Y	NI	NI	NI	NI	Y <sup>45</sup>	NI	NI
9.	Y	2 <sup>46</sup>	N	Y	NI	NI	NI	Y <sup>47</sup>	Y	Y <sup>4849</sup>	NI
10.	Y	NI	N	Y	NI	NI	NI	NI	N	Y <sup>50</sup>	N
11.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
12.	Y	NI	N	Y	NI	NI	NI	NI	N	Y <sup>51</sup>	N
13.	Y <sup>52</sup>	NI	NI	NI	Y <sup>53</sup>	NI	NI	NI	NI	NI	NI
14.	Y	3	N	Y	NI	NI	NI	NI	NI	NI	NI
15.	Y <sup>54</sup>	NI	NI	NI	Y <sup>55</sup>	NI	NI	NI	NI	NI	NI
16.	Y	NI	N	Y	Y	Y	Y	Y <sup>56</sup>	Y <sup>57</sup>	Y <sup>58</sup>	N
17.	Y	1/2	N	Y	NI	NI	NI	NI	Y <sup>59</sup>	NI	NI
18.	Y	NI	N	Y	Y	Y	Y	Y <sup>60</sup>	Y <sup>61</sup>	Y <sup>62</sup>	N
19.	Y	NI	N	Y	NI	NI	NI	NI	Y <sup>63</sup>	Y <sup>6465</sup>	Y
20.	Y	NI	N	Y	NI	NI	NI	NI	Y <sup>66</sup>	Y <sup>6768</sup>	Y
21.	Y	NI	N	Y	NI	NI	NI	NI	Y <sup>69</sup>	Y <sup>7071</sup>	Y
22.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
23.	Y	2 <sup>72</sup>	NI	NI	NI	NI	NI	NI	Y	Y	N
24.	Y	2 <sup>73</sup>	NI	NI	NI	NI	NI	NI	Y	Y	N
25.	Y	1/2	N	Y	NI	NI	NI	NI	Y	Y <sup>74</sup>	N
26.	Y	2/3	N	Y	NI	NI	NI	NI	N	N	N
27.	Y	1/2	N	Y	NI	NI	NI	NI	Y	Y <sup>75</sup>	N
28.	Y	1/2	N	Y	NI	NI	NI	NI	Y	Y <sup>76</sup>	N
29.	Y	NI	N	Y	NI	NI	NI	NI	N	Y <sup>77</sup>	N
30.	Y	NI	N	Y	NI	NI	NI	NI	N	Y <sup>78</sup>	N

**BUPRENORPHINE/NALOXONE TABLETS (GENERIC)**

State	On Formulary ?	Tier	Medical Benefit?	Pharmacy Benefit?	Covered in OTP?	Covered in office based setting?	Covered in residential treatment?	MAT Prescriber Restrictions?	Prior Authorization Requirements ?	Quantity Limits?	Step Therapy?
1.	Y	NI	Y	Y	N <sup>79</sup>	Y	Y	N	N <sup>80</sup>	Y <sup>81</sup>	N
2.	N	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
3.	Y	NI	Y	Y	N <sup>82</sup>	Y	Y	N	N <sup>83</sup>	Y <sup>84</sup>	N
4.	Y	NI	N	Y	NI	NI	NI	NI	N	Y <sup>85</sup>	N
5.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
6.	Y	NI	N	Y	NI	NI	NI	NI	N	Y <sup>86</sup>	N
7.	N	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
8.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
9.	Y	2	N	Y	NI	NI	NI	Y <sup>87</sup>	Y	Y <sup>8889</sup>	Y <sup>90</sup>
10.	Y	NI	N	Y	NI	NI	NI	NI	N	Y <sup>91</sup>	N
11.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
12.	Y	NI	N	Y	NI	NI	NI	NI	N	Y <sup>92</sup>	N
13.	Y <sup>93</sup>	NI	NI	NI	N	N	N	NI	NI	NI	NI
14.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
15.	Y <sup>94</sup>	NI	NI	NI	N	N	N	NI	NI	NI	NI
16.	Y	NI	N	Y	Y	Y	Y	Y <sup>95</sup>	Y <sup>96</sup>	Y <sup>97</sup>	N
17.	Y	1	N	Y	NI	NI	NI	NI	NI	NI	NI
18.	Y	NI	Y	Y	Y	Y	Y	Y <sup>98</sup>	Y <sup>99</sup>	Y <sup>100</sup>	N
19.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
20.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
21.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
22.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
23.	N	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
24.	N	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
25.	N	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
26.	NI	3	N	Y	NI	NI	NI	NI	N	N	N
27.	N	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
28.	N	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
29.	Y	NI	N	Y	NI	NI	NI	NI	N	Y <sup>101</sup>	N
30.	Y	NI	N	Y	NI	NI	NI	NI	N	Y <sup>102</sup>	N

**BUPRENORPHINE TABLETS (GENERIC)**

State	On Formulary ?	Tier	Medical Benefit?	Pharmacy Benefit?	Covered in OTP?	Covered in office based setting?	Covered in residential treatment?	MAT Prescriber Restrictions?	Prior Authorization Requirements ?	Quantity Limits?	Step Therapy?
1.	Y	NI	Y <sup>103</sup>	Y	N <sup>104</sup>	Y	Y	N	N <sup>105</sup>	Y <sup>106</sup>	N
2.	Y	1 <sup>107</sup>	NI	NI	NI	NI	NI	NI	N	Y	N
3.	Y	NI	Y <sup>108</sup>	Y	N <sup>109</sup>	Y	Y	N	N <sup>110</sup>	Y <sup>111</sup>	N
4.	Y	1	N	Y	NI	NI	NI	NI	N	Y <sup>112</sup>	N
5.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
6.	Y	1	N	Y	NI	NI	NI	NI	N	Y <sup>113</sup>	N
7.	Y	1 <sup>114</sup>	NI	NI	NI	NI	NI	NI	N	Y	N
8.	NI	3	N	Y	NI	NI	NI	NI	Y <sup>115</sup>	NI	NI
9.	Y	1	NI	NI	NI	NI	NI	NI	N	Y <sup>116</sup>	N
10.	Y	NI	N	Y	NI	NI	NI	NI	N	Y <sup>117</sup>	N
11.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
12.	Y	NI	N	Y	NI	NI	NI	NI	N	Y <sup>118</sup>	N
13.	Y <sup>119</sup>	NI	NI	NI	N	N	N	NI	NI	NI	NI
14.	Y	1	N	Y	NI	NI	NI	NI	NI	NI	NI
15.	Y <sup>120</sup>	NI	NI	NI	N	N	N	NI	NI	NI	NI
16.	Y	NI	N	Y	Y	Y	Y	Y <sup>121</sup>	Y <sup>122</sup>	Y <sup>123</sup>	N
17.	Y	1	N	Y	NI	NI	NI	NI	Y <sup>124</sup>	NI	NI
18.	Y	NI	N	Y	Y	Y	Y	Y <sup>125</sup>	Y <sup>126</sup>	Y <sup>127</sup>	N
19.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
20.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
21.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
22.	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
23.	Y	1 <sup>128</sup>	NI	NI	NI	NI	NI	NI	N	Y	N
24.	Y	1 <sup>129</sup>	NI	NI	NI	NI	NI	NI	N	Y	N
25.	Y	1	N	Y	NI	NI	NI	NI	Y	Y <sup>130</sup>	N
26.	Y	1/3	N	Y	NI	NI	NI	NI	N	Y	N
27.	Y	1	N	Y	NI	NI	NI	NI	Y	Y <sup>131</sup>	N
28.	Y	1	N	Y	NI	NI	NI	NI	Y	Y <sup>132</sup>	N
29.	Y	NI	N	Y	NI	NI	NI	NI	N	Y <sup>133</sup>	N
30.	Y	NI	N	Y	NI	NI	NI	NI	N	Y <sup>134</sup>	N

## REFERENCES TO ADDITIONAL CHARTS

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- <sup>1</sup> In accordance with FDA regulations, methadone cannot be prescribed for the treatment of opioid dependence however it may be on found formularies for the treatment of pain.
- <sup>2</sup> Response indicates that medication is on drug formulary. Methadone maintenance/detox is provided by outside contract facilities. Physicians do not prescribe methadone for opioid dependence. Methadone is on formulary only for the treatment of pain.
- <sup>3</sup> All medications in the medical office are covered by the Medical Benefit. Outpatient prescription medications are covered if on the Drug Formulary. If non-formulary, a physician may indicate an exception to prescribe under the drug benefit if they feel it is medically necessary.
- <sup>4</sup> For use during pregnancy only, during gestation and two months postpartum.
- <sup>5</sup> The treating addiction physician personally evaluates the patient and determines medical appropriateness of methadone maintenance. The treating physician authorizes treatment with a signature.
- <sup>6</sup> Residential, Intensive Day Treatment, Intensive Outpatient and graduated levels of care through the entire continuum of recovery are provided when indicated. Patients also receive a counselor or therapist for individual therapy. Community mutual support, urine/breath monitoring, and computerized serial ASI are additional pillars of our programs.
- <sup>7</sup> Per contract facility requirements
- <sup>8</sup> Response indicates that medication is on drug formulary. Methadone maintenance/detox is provided by outside contract facilities. Physicians do not prescribe methadone for opioid dependence. Methadone is on formulary only for the treatment of pain.
- <sup>9</sup> All medications in the medical office are covered by the Medical Benefit. Outpatient prescription medications are covered if on the Drug Formulary. If non-formulary, a physician may indicate an exception to prescribe under the drug benefit if they feel it is medically necessary.
- <sup>10</sup> For use during pregnancy only, during gestation and two months postpartum.
- <sup>11</sup> The treating addiction physician personally evaluates the patient and determines medical appropriateness of methadone maintenance. The treating physician authorizes treatment with a signature.
- <sup>12</sup> Residential, Intensive Day Treatment, Intensive Outpatient and graduated levels of care through the entire continuum of recovery are provided when indicated. Patients also receive a counselor or therapist for individual therapy. Community mutual support, urine/breath monitoring, and computerized serial ASI are additional pillars of our programs.
- <sup>13</sup> Per contract facility requirements
- <sup>14</sup> 248 tablets per 31 days
- <sup>15</sup> On formulary only for Pain. Not indicated for treatment of opioid dependence.
- <sup>16</sup> On formulary only for Pain. Not indicated for treatment of opioid dependence.
- <sup>17</sup> In Network MD, Out of Network MD, NPs and PAs can only rx Methadone for pain mgmt.
- <sup>18</sup> See Prior Authorization Chart
- <sup>19</sup> See Prior Authorization Chart
- <sup>20</sup> The patient must have been stabilized in a MMT program, demonstrated responsible use of take-home dose of methadone through their current MMT program and have been recommended for this program from that current MMT program.
- <sup>21</sup> Recommended Starting Dose for Opioid Exposed Patient's High Doses Leading to High Risks: 2 to 5 mg, 2 to 3 times daily. Recommended Maintenance Dose: 10 to 30 mg per day
- <sup>22</sup> In Network MD, Out of Network MD, NPs and PAs can only rx Methadone for pain mgmt.
- <sup>23</sup> On formulary only for pain
- <sup>24</sup> On formulary only for pain
- <sup>25</sup> On formulary only for pain
- <sup>26</sup> All strengths = 4 tablets/day
- <sup>27</sup> All strengths = 4 tablets/day
- <sup>28</sup> All strengths = 4 tablets/day

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<sup>29</sup> With the exception of methadone, all medications for the treatment of SUDs are provided by our own physicians the Department of Addiction Medicine. Thus, there is no reason to send patients to OTPs for buprenorphine, naltrexone and others.

<sup>30</sup> When a patient visits [redacted], s/he will be evaluated by an Addictionist. That treating Addictionist physician prescribes Suboxone just as any other controlled substance. Suboxone Film would rarely be indicated for patients over the tablet formulation.

<sup>31</sup> Residential, Intensive Day Treatment, Intensive Outpatient and graduated levels of care through the entire continuum of recovery are provided when indicated. Patients also receive a counselor or therapist for individual therapy. Community mutual support, urine/breath monitoring, and computerized serial ASI are additional pillars of our programs.

<sup>32</sup> No refills and only for 30 day supply

<sup>33</sup> As clinically indicated. Generally less than 12mg/day. 30 day supply.

<sup>34</sup> Community Mutual Support (not necessarily 12-Step is a component of recovery program. Participation in the program, with its community support component, are generally required – but individual physicians make clinical judgments about the appropriate level of care and venue for outside report.

<sup>35</sup> On three tier plan

<sup>36</sup> With the exception of methadone, all medications for the treatment of SUDs are provided by our own physicians the Department of Addiction Medicine. Thus, there is no reason to send patients to OTPs for buprenorphine, naltrexone and others.

<sup>37</sup> When a patient visits [redacted], s/he will be evaluated by an Addictionist. That treating Addictionist physician prescribes Suboxone just as any other controlled substance. Suboxone Film would rarely be indicated for patients over the tablet formulation.

<sup>38</sup> Residential, Intensive Day Treatment, Intensive Outpatient and graduated levels of care through the entire continuum of recovery are provided when indicated. Patients also receive a counselor or therapist for individual therapy. Community mutual support, urine/breath monitoring, and computerized serial ASI are additional pillars of our programs.

<sup>39</sup> No refills and only for 30 day supply

<sup>40</sup> As clinically indicated. Generally less than 12mg/day. 30 day supply.

<sup>41</sup> Community Mutual Support (not necessarily 12-Step is a component of recovery program. Participation in the program, with its community support component, are generally required – but individual physicians make clinical judgments about the appropriate level of care and venue for outside report.

<sup>42</sup> 60 films/m

<sup>43</sup> 60 films/m

<sup>44</sup> On three tier plan

<sup>45</sup> See Prior Authorization Chart

<sup>46</sup> A generic equivalent of this drug recently became available or will be available soon. After the generic drug becomes available and notification requirements are met, this brand-name drug will become Tier 3 or may no longer be covered by your prescription drug plan.

<sup>47</sup> In Network MD

<sup>48</sup> 1 year approval duration

<sup>49</sup> Request for quantity greater than 24 mg per day will be reviewed on a case by case basis.

<sup>50</sup> 90 films/m

<sup>51</sup> 90 films/m

<sup>52</sup> Listed on formulary for pain

<sup>53</sup> Suboxone is only covered for detox

<sup>54</sup> Listed on formulary for pain

<sup>55</sup> Suboxone is only covered for detox

<sup>56</sup> In Network MD, Out of Network MD

<sup>57</sup> The physician meets the qualification certification criteria in the Drug Addiction Treatment Act of 2000 and has been issued a unique DEA identification number by the DEA, indicating that he or she is a qualified physician under the DATA to prescribe Suboxone and the member is being treated for opioid dependence

<sup>58</sup> 3/day

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<sup>59</sup> See Prior Authorization Chart  
<sup>60</sup> In Network MD, Out of Network MD  
<sup>61</sup> The physician meets the qualification certification criteria in the Drug Addiction Treatment Act of 2000 and has been issued a unique DEA identification number by the DEA, indicating that he or she is a qualified physician under the DATA to prescribe Suboxone and the member is being treated for opioid dependence  
<sup>62</sup> 3/day  
<sup>63</sup> See Prior Authorization Chart  
<sup>64</sup> Suboxone SL Films/Tags or generic buprenorphine/naloxone: 3 films or 3 tablets/day of the 2mg/0.5mg, 8mg/2mg, 4mg/1mg strengths. 2 films/day of the 12mg/3mg  
<sup>65</sup> up to 12 months  
<sup>66</sup> See Prior Authorization Chart  
<sup>67</sup> Suboxone SL Films/Tags or generic buprenorphine/naloxone: 3 films or 3 tablets/day of the 2mg/0.5mg, 8mg/2mg, 4mg/1mg strengths. 2 films/day of the 12mg/3mg  
<sup>68</sup> up to 12 months  
<sup>69</sup> See Prior Authorization Chart  
<sup>70</sup> Suboxone SL Films/Tags or generic buprenorphine/naloxone: 3 films or 3 tablets/day of the 2mg/0.5mg, 8mg/2mg, 4mg/1mg strengths. 2 films/day of the 12mg/3mg  
<sup>71</sup> up to 12 months  
<sup>72</sup> On three tier plan  
<sup>73</sup> On three tier plan  
<sup>74</sup> 3 films or tablets/day  
<sup>75</sup> 3 films or tablets/day  
<sup>76</sup> 3 films or tablets/day  
<sup>77</sup> 90 films/m  
<sup>78</sup> 90 films/m  
<sup>79</sup> With the exception of methadone, all medications for the treatment of SUDs are provided by our own physicians in our Departments of Addiction Medicine. Thus, there is no reason to send patients to OTPs for buprenorphine, naltrexone and others.  
<sup>80</sup> When a patient visits Department of Addiction Medicine, s/he will be evaluated by an Addictionist physician.  
<sup>81</sup> No refills and only a 30 day supply. As clinically indicated, generally under 12mg/day.  
<sup>82</sup> With the exception of methadone, all medications for the treatment of SUDs are provided by our own physicians in our Departments of Addiction Medicine. Thus, there is no reason to send patients to OTPs for buprenorphine, naltrexone and others.  
<sup>83</sup> When a patient visits Department of Addiction Medicine, s/he will be evaluated by an Addictionist physician.  
<sup>84</sup> No refills and only a 30 day supply. As clinically indicated, generally under 12mg/day.  
<sup>85</sup> 90 tablets/m  
<sup>86</sup> 90 tablets/m  
<sup>87</sup> In Network MD  
<sup>88</sup> 1 year approval duration  
<sup>89</sup> Request for quantity greater than 24 mg per day will be reviewed on a case by case basis.  
<sup>90</sup> Must have failed films before you can get tablets  
<sup>91</sup> 30 tabs/m  
<sup>92</sup> 30 tabs/m  
<sup>93</sup> Listed on formulary only for pain management  
<sup>94</sup> Listed on formulary only for pain management  
<sup>95</sup> In Network MD, Out of Network MD  
<sup>96</sup> The physician meets the qualification certification criteria in the Drug Addiction Treatment Act of 2000 and has been issued a unique DEA identification number by the DEA, indicating that he or she is a qualified physician under the DATA to prescribe Suboxone and the member is being treated for opioid dependence  
<sup>97</sup> 3/day  
<sup>98</sup> In Network MD, Out of Network MD

- 
- <sup>99</sup> The physician meets the qualification certification criteria in the Drug Addiction Treatment Act of 2000 and has been issued a unique DEA identification number by the DEA, indicating that he or she is a qualified physician under the DATA to prescribe Suboxone and the member is being treated for opioid dependence
- <sup>100</sup> 3/day
- <sup>101</sup> 30 tabs/m
- <sup>102</sup> 30 tabs/m
- <sup>103</sup> Covered under a pharmacy benefit as a prescription medication; covered as a medical benefit when administered in the medical office.
- <sup>104</sup> With the exception of methadone, all medications for the treatment of SUD are provided by our own physicians in our Departments of Addiction Medicine. Thus, there is no reason to send patients to OTPs for buprenorphine, naltrexone and others.
- <sup>105</sup> When a patient visits the Department of Addiction Medicine, s/he will be evaluated by an Addictionist physician. That addictionist physician prescribes buprenorphine just as any other controlled substance.
- <sup>106</sup> No refills and only a 30 day supply.
- <sup>107</sup> Listed on 3 tiered drug plan
- <sup>108</sup> Covered under a pharmacy benefit as a prescription medication; covered as a medical benefit when administered in the medical office.
- <sup>109</sup> With the exception of methadone, all medications for the treatment of SUD are provided by our own physicians in our Departments of Addiction Medicine. Thus, there is no reason to send patients to OTPs for buprenorphine, naltrexone and others.
- <sup>110</sup> When a patient visits the Department of Addiction Medicine, s/he will be evaluated by an Addictionist physician. That addictionist physician prescribes buprenorphine just as any other controlled substance.
- <sup>111</sup> No refills and only a 30 day supply.
- <sup>112</sup> 15 tablets/m
- <sup>113</sup> 15 tablets/m
- <sup>114</sup> Listed on 3 tiered drug plan
- <sup>115</sup> See Prior Authorization Chart
- <sup>116</sup> In Network MD
- <sup>117</sup> 90 tabs/m
- <sup>118</sup> 90 tabs/m
- <sup>119</sup> Covered only for pain
- <sup>120</sup> Covered only for pain
- <sup>121</sup> In Network MD, Out of Network MD
- <sup>122</sup> DATA compliance and the member is being treated for opioid dependence and is being treated with induction, may be used for maintenance if intolerant to Suboxone, pregnant or breastfeeding
- <sup>123</sup> 15 for induction, 3/day for maintenance
- <sup>124</sup> Practitioner must meet Federal and State requirements.
- <sup>125</sup> In Network MD, Out of Network MD
- <sup>126</sup> DATA compliance and the member is being treated for opioid dependence and is being treated with induction, may be used for maintenance if intolerant to Suboxone, pregnant or breastfeeding
- <sup>127</sup> 15 for induction, 3/day for maintenance
- <sup>128</sup> Listed on 3 tiered drug plan
- <sup>129</sup> Listed on 3 tiered drug plan
- <sup>130</sup> 2 mg = 24 tablets/30 day supply
- <sup>131</sup> 2 mg = 24 tablets/30 day supply
- <sup>132</sup> 2 mg = 24 tablets/30 day supply
- <sup>133</sup> 90 tabs/m
- <sup>134</sup> 90 tabs/m



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# FDA Approved Medications for the Treatment of Opiate Dependence: Literature Reviews on Effectiveness and Cost-Effectiveness



**FINAL**

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Report developed for the American Society of Addiction Medicine  
by the Treatment Research Institute, 2013

# Table of Contents

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## **Summary of Review Findings and Implications**

*Introduction and Background*.....pg. 3  
*Findings and Implications*.....pg. 8

## **Part 1: Systematic Review of Effectiveness Literature**

*Executive Summary*.....pg. 11  
*Introduction and Background*.....pg. 13  
*Methods*.....pg. 15  
*Results*.....pg. 17  
*Discussion and Future Directions*.....pg. 24  
*Appendices*.....pg. 27  
*References*.....pg. 49

## **Part 2: Systematic Review of Cost-Effectiveness Literature**

*Executive Summary* .....pg. 66  
*Introduction and Background*.....pg. 68  
*Methods* .....pg. 73  
*Results*.....pg. 75  
*Discussion*.....pg. 91  
*Appendices*.....pg. 92  
*References*.....pg. 100

## Introduction and Background

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Addiction is defined as a chronic, relapsing brain disease that is characterized by compulsive drug-seeking behavior and drug use that continues despite harmful consequences. It is a brain disease, because drugs and alcohol change the way the brain is structured and works. Although the initial decision to take drugs is voluntary, physical changes in the brain following successive bouts of use can reduce a person's ability to exert self-control over their drug use. These alterations in the brain's structures and its motivational, cognitive and inhibitory functions result in behavioral changes that persist long after drug use has ceased. This helps to explain why drug abusers are at risk for relapse even after long periods of abstinence and despite the potentially devastating consequences.

Opioid abuse and addiction are associated with a number of serious health conditions, including fatal overdose and spontaneous abortion. Injection drug use is a well-known route of transmission of blood borne infections, particularly HIV and hepatitis B and C (CDC, 2012; Mathers et al., 2008), and it is associated with increased rates of TB and STDs (Deiss et al., 2009; Nelson et al., 1991). Chronic heroin users may develop collapsed veins, infection of the heart lining and valves, abscesses, constipation and gastrointestinal cramping, and liver or kidney disease. Pulmonary complications, including various types of pneumonia, may result from the poor health of the user as well as from heroin's effects on breathing (NIDA, 2013). Prescription opioid pain medications such as Oxycontin® and Vicodin® can have effects similar to heroin when taken in doses or in ways other than prescribed. A recent report released from the Centers for Disease Control and Prevention (CDC; 2011) found that deaths involving opioid pain relievers have increased and now exceed deaths involving heroin and cocaine combined.

Growing understanding and acceptance of opioid and other substance use disorders (SUD) as chronic medical disorders has facilitated advances in the use of pharmacotherapies as part of comprehensive treatment (Substance Abuse and Mental Health Services Administration, 2011; Dennis & Scott, 2007; McLellan et al., 2000). Like other chronic illnesses many cases of opioid addiction cannot be cured - but can be treated and maintained. And as in the case of treatments for other chronic illnesses, medications for opioid dependence can be an important part of chronic, comprehensive care; interrupting the cycle of addiction to allow patients to gain some control over their use and engage in full recovery.

### ***FDA approved medications for treating opioid addiction***

There are now three FDA-approved medications for treatment of opioid addiction: methadone (Dolophine®), naltrexone - oral (ReVia®, Depade®), naltrexone – extended release injection (Vivitrol®) and buprenorphine (Suboxone®, Subutex®). All of these medications act directly upon the opioid receptors, particularly mu-receptors (32, 33). Methadone is a full mu-receptor agonist; buprenorphine is a partial mu-receptor agonist and naltrexone is a full antagonist. Because of the very different actions of these medications at the receptor level, they can have very different clinical effects during treatment.

Methadone and buprenorphine used as detoxification medications can suppress withdrawal symptoms and curb cravings. When used as maintenance medications the suppression of withdrawal and craving helps to reduce non-medical opioid use. Naltrexone can only be administered to fully detoxified patients but as a maintenance medication it can

essentially eliminate the rewarding effects of self-administered opioids, thereby dramatically reducing use.

Since each of these medications has been approved by the Food and Drug Administration (FDA), each has undergone essentially the same procedures and standards applied to all other medications. Specifically, FDA approval requires a demonstration of clinically and statistically significant improvements in target signs, symptoms, or functional impairments in two randomized controlled clinical trials; or one rigorously conducted large-scale population study. The FDA approval process also requires monitoring of all untoward side effects to assure that a medication does not produce unintended health complications. Thus, these medications have shown substantive evidence of effectiveness and safety when used appropriately. Specific measures of effectiveness have included: increased patient retention, decreased frequency and quantity of opioid use, reduced risk of infectious disease transmission, reduced criminal activities, improved social functioning, and reduced the risk of overdose and death.

The use of medications in treating opioid dependence is not new. Methadone, for example, has been used with success for the treatment of opioid addiction for more than half a century (Substance Abuse and Mental Health Services Administration, 2011). Further, all of these medications are covered under Medicaid or other federal health benefit in virtually all states – although there are significant variations in the range and duration of covered benefits (see accompanying report from the Avisa Group, 2013). Finally, there is evidence of substantial medical cost offsets for patients receiving opioid addiction medications (Baser, Chalk, Rawson, Gastfriend, 2011; Bryson, McConnell, Korthius, and McCarty, 2011).

However, in spite of the insurance coverage, the long research history of positive outcomes and the societal and monetary benefit of pharmacotherapies, prescribing is still quite low (See Knudsen et al., 2011) for many reasons. First, there are some unique regulations and insurance limitations that govern the prescribing of medications for opioid addiction. For example, methadone is a truly unique medication. Unlike any other medication in healthcare, the prescription and dispensing of methadone is restricted to providers registered with the FDA and the U.S. Drug Enforcement Agency (DEA), and the medication can only be prescribed for opioid addiction within licensed methadone maintenance programs. Federal regulations have allowed for broader access to buprenorphine through properly trained and DEA-registered physicians. The unique insurance coverage limitations and regulatory restrictions governing prescribing of these medications are covered under a separate report (see accompanying reports from the Avisa Group and TRI, 2013). In the text that follows we describe the clinical uses of each of these three medications to illustrate similarities and differences among them. See **Table 1**.

**Table 1. Medications Used to Treat Opioid Addiction**

Medication	FDA Approval for Opioid Dependence	DEA Schedule	Treatment Setting	Mechanism of Action
Methadone (Dolophine®, Methadose®)	Never formally approved	II	OTP	Full mu-opioid agonist—competes with other opioids by suppressing withdrawal symptoms and cravings
Naltrexone oral (ReVia®, Depade®)	1984	Not scheduled	Physician’s office, OTP, or other health care setting	Mu opioid antagonist—blocks the effect of opioids at the receptor sites
Naltrexone extended release (Vivitrol®)	2010	Not scheduled	Physician’s office, OTP, or other health care setting	Mu opioid antagonist—blocks the effect of opioids at the receptor sites
Buprenorphine (Subutex®)	2002	III	Physician’s office, OTP, or other health care setting	Partial mu-opioid agonist and kappa-opioid antagonist—competes with other opioids by suppressing withdrawal symptoms and cravings
Buprenorphine/naloxone (Suboxone®)	2002	III	Physician’s office, OTP, or other health care setting	Partial mu-opioid agonist and mu antagonist—competes with other opioids by suppressing withdrawal symptoms and cravings

For more information on FDA approval of drugs see: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

**Methadone:** Pharmacologically, methadone is a long-acting (24–30 hours), potent opiate agonist (that is, it imitates the action of an opiate, such as heroin by occupying and activating the body’s opioid receptors). Because the medication is taken orally and because it has a slow and very long period of metabolism, it does not generate the extreme euphoria of short acting, injectable opioids (e.g. heroin or many pharmaceutical opioids) – in properly prescribed doses (which vary from about 30 mg/day to over 100 mg/day depending upon the particular genetics and opioid use histories of patients).

Because of the long-acting nature of methadone; and because it is more potent than most other opioids, it produces physiological tolerance (i.e. the body gets used to a daily dose of

the medication) and cannot simply be discontinued without producing significant withdrawal symptoms. However, the potency of the medication, its slow onset and its consequent ability to produce tolerance without significant euphoria (again, when properly prescribed) are the properties of the medication that reduce opioid craving, and risk of overdose (the patient has an acquired, protective opioid tolerance from less potent “street” opioids). Methadone does not provide protection from use of alcohol or non-opioid drugs of abuse such as cocaine, marijuana or benzodiazepines (tranquilizers).

Because methadone is a potent, long acting opioid it has very special prescribing restrictions. Methadone can only be administered by opioid treatment programs (OTPs) that are licensed by the Drug Enforcement Agency (DEA) and certified by the Substance Abuse and Mental Health Administration (SAMHSA). OTPs are subject to periodic inspections and must comply with a variety of local and national accrediting organizations specifications. Such regulation and oversight has resulted in a treatment system that is separated from other medical care. Patients may be required to visit the OTP daily to obtain their dose of medication under direct clinical observation. Take-home doses are not available until a significant history of stabilization has been established. This system is prohibitive for some opioid dependent individuals who may not have ready access to OTPs, may have a schedule that does not comport with that of the OTP, or may be concerned with the social stigma often associated with this type of treatment.

**Buprenorphine:** A major paradigm shift in opioid pharmacotherapy began with the passage of the Drug Addiction Treatment Act of 2000 (DATA 2000) which allowed for the use of Schedule III, IV, and V medications for the treatment of opioid dependence by physicians who had applied for and received a waiver from the Center for Substance Abuse Treatment of the Substance Abuse and Mental Health Services Administration (to be discussed more thoroughly in a later section). Subsequently, the FDA approval of buprenorphine and buprenorphine/naloxone in 2002, permitted prescribing not only in OTPs but also by specially trained (8 hours of special training) primary care physicians in what is now commonly called office-based opioid treatment (OBOT). These changes resulted in a much larger pool of options from which persons with opioid dependence could receive care.

Because buprenorphine is a partial opioid agonist it is much safer effect than methadone (sedating and respiration reducing properties common to all opioid agonists are significantly reduced in this partial agonist medication) when taken in the prescribed manner (sublingually). Because of its enhanced safety, buprenorphine was FDA-approved for office-based administration. However, it was soon realized that buprenorphine could be crushed, mixed with water and injected to produce a significant euphoric effect. To reduce inappropriate use, the currently approved form of buprenorphine for the treatment of opioid dependence is a combination tablet that adds the short-acting opioid antagonist, naloxone. When taken sublingually as directed the naloxone has no physiological effect; but if the tablet is crushed and injected the naloxone will produce withdrawal symptoms. The buprenorphine-naloxone medication is called Suboxone; its generic form, was approved by the FDA in 2013 and is now the only approved form of buprenorphine indicated for the detoxification or maintenance phases of opioid dependence treatment.

**Naltrexone:** Naltrexone is an orally administered, long-acting opioid antagonist which has been available since 1984 for treating opioid dependence; however, it has not been widely used for this purpose. The medication works by displacing any opioids from a patient's opioid receptors and then tightly binding to those receptors for 24–30 hours (oral) or for up to 30 days (extended release injection). This makes the opioid receptors unavailable for activation by any self-administered opioid such as heroin. Because of its method of action, naltrexone can only be prescribed to patients who have been completely detoxified from all opioid use, or the medication will produce immediate opioid withdrawal. However, once taken at a stable dose, patients will simply not experience any effects from opioid self-administration. There have been many trials of oral naltrexone in the treatment of opioid dependence and virtually all have shown characteristic elimination of opioid use among those who adhere to the medication – but an equally characteristic lack of adherence or outright discontinuation in 50–70% of those prescribed the oral form of the medication. In 2010, the FDA approved an extended-release, injectable formulation of naltrexone (Vivitrol) for treatment of opioid use disorder. Results suggest that this form of naltrexone produces equally significant reductions in opioid use throughout the month-long duration of the injection and that 35 – 50% of patients voluntarily return for additional monthly injections.

## OVERALL CONCLUSIONS FROM THE TWO REVIEWS

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We undertook the current reviews of the effectiveness and cost-effectiveness literature on the three FDA approved medications for the treatment of opioid dependence (methadone, naltrexone and buprenorphine) in order to explore why all of these medications are under-utilized. Specifically, less than 30% of contemporary addiction treatment programs offer medications; and less than half of eligible patients in those programs actually receive medications (Knudsen et al., 2011). Utilization by general practice physicians is even lower. This last finding is particularly concerning at a time when health problems such as opioid-related infectious diseases (HIV, TB, Hepatitis C) and opioid-related overdose and death are all steadily increasing but also clearly preventable.

We first examined the possibility that the medications are simply not effective. This possibility can be ruled out - all are FDA-approved using the same criteria applied to other medications. Beyond the research leading to their initial approvals, this review has revealed substantial, broad and conclusive evidence for the effectiveness of these medications, particularly methadone. The literature on the efficacy of these medications is not new - there are now eight large-scale, rigorously conducted, reviews of the literature on these medications since the early 1980's. While we believe the present review offers a contemporary summary of this research, our findings are very similar to those from all prior reviews.

A second possibility is that these medications are not attractive to patients – perhaps there is no demand for these medications. It is well known that physicians, like any other service provider, are sensitive to the demands of their patients; and perhaps opioid addicted patients are hesitant to demand particular types of medications or medication-related services. The findings from the review indicate that this possibility can also be ruled out, especially with regard to buprenorphine and methadone, adherence is not a problem and there are often waiting lists for these medications. There may be muted demand for oral naltrexone, patient knowledge is limited about the medication, and the majority of patients who are prescribed this medication do not adhere and drop out rapidly. This may be due to side effects associated with administration prior to complete withdrawal from opioids; and/or possibly due to the fact that it is almost completely effective at blocking euphoric effects of self-administered opioids. Extended release, injectable naltrexone appears able to attract patients to receive multiple injections but this possibility requires more research.

A third possibility to explain low levels of medication utilization is that the costs of these medications are prohibitive or simply not worth their added value to patients or payers. Once again, the available data indicate that this possibility can be ruled out. The costs of methadone (~\$40 per monthly dose), oral naltrexone (~\$60 per monthly dose) and buprenorphine/naloxone (~\$130 per monthly dose) are quite low (IMS, 2010). Extended release naltrexone is more expensive (~\$700 per monthly dose) (IMS, 2010). In comparison, typical costs for self-administered (injected) insulin for diabetes are approximately \$180- \$240 (<http://diabeteshealth.com/read/2010/10/09/6898/the-cost-of-diabetes/>). Thus, costs for



maintenance medications to treat opioid addiction are roughly comparable – excluding physician appointments and related fees. It is thus difficult to explain the substantially lower rates of medication utilization (<15% of opioid addicted patients in treatment vs. >80% of diabetic patients in treatment) based upon either the direct costs or the clinical/economic benefits of the medications available.

A fourth possibility for low rates of medication utilization may be unique “environmental factors” affecting these medications. Based on the available effectiveness and cost-effectiveness data on these medications, one must conclude that there are “environmental factors” preventing appropriate access to and utilization of these medications. Three of these factors include: physician training and experience; legal and regulatory controls; and insurance coverage.

Unlike medications for diabetes or any other chronic illness, very few physicians have been trained to diagnose or treat opioid addiction. This is a glaring and correctable problem with medical, nursing and pharmacy education. It is time for much better training and education about addiction for all healthcare professionals.

Governmental restrictions are a second area that appears to restrict availability and utilization of these medications. Methadone can only be prescribed by specialty physicians within methadone programs; buprenorphine also requires specialty certification and DEA registration (as do all opioid medications); and injectable naltrexone is somewhat complex to store and administer. There are also unique legal and regulatory issues surrounding the administration of all these medications but particularly methadone and buprenorphine. There are public health justifications (diversion and related overdose incidents) for some of the unique methadone regulations. The overdose concerns and the prescribing restrictions are less significant for buprenorphine/naloxone. Nonetheless, given the public health problems associated with increasing rates of heroin and pharmaceutical opioid abuse it may be time for a reexamination of prescribing restrictions.

Beyond governmental regulations, there are formal and particularly informal restrictions on utilization of these medications imposed by insurers - both governmental and private insurers. Utilization can be significantly impeded by pre-authorization requirements, limitations on dose and duration of dosing and by patient co-pays that are significantly different than those associated with medications for other chronic illnesses. As the Affordable Care and Parity Acts become implemented in 2014, it is time to investigate and modify insurance issues affecting both patients and physicians. Similarly, reimbursement rates for physicians may be a contributing factor. Importantly, all these environmental factors are related: without appropriate regulations, training in medical and nursing schools and appropriate rates of reimbursement there will be little incentive for physicians to prescribe and low access opportunities for patients to receive these cost-effective medications. For these reasons, it is critical that healthcare payers, policy makers, and treatment providers are aware of these medications; and that they make these options known and available to patients who might benefit from them.

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# PART 1

## **The Effectiveness of Pharmacotherapies for the Treatment of Opioid Disorders: A Systematic Review**

This review was with support from the American Society of Addiction Medicine  
and the National Institute of Drug Abuse

## Executive Summary

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**Aims:** Addiction to heroin and/or pharmaceutical opioids is now a nationally prominent problem producing significant costs to law enforcement and healthcare; but particularly tragic and expanding levels of morbidity and mortality. Effective medications are available to treat opioid addiction, but they are underutilized, in part because of questions related to effectiveness. We thus completed a systematic evaluation of the effectiveness of three, FDA-approved opioid addiction treatment medications: methadone, buprenorphine (Subutex® and Suboxone®) and naltrexone (Revia® and Vivitrol®).

**Methods:** A comprehensive and systematic literature search following Campbell Collaboration guidelines was conducted on all research articles published in English on these three medications, with special emphasis upon the past five years (2008–2013).

**Results:** Our search strategy located 643 unique articles, 75 of which were eligible for coding and analysis.

Methadone: Methadone maintenance treatment, when used as part of a comprehensive treatment approach and in appropriate doses, continues to accrue evidence for its effectiveness in engaging and retaining patients, reducing withdrawal and craving symptoms, reducing opioid but not non-opioid abuse; and reducing many opioid addiction-related health and social problems, particularly risk of infectious diseases.

Buprenorphine: Because it has only been available since 2000 there has been less evaluation of buprenorphine than of methadone. Nonetheless, the effectiveness findings are almost identical to those presented above for methadone. Buprenorphine offers two important advantages over methadone in the US: it is a safer medication due to its partial agonist properties making overdose risks are far lower than for methadone; and buprenorphine is far more accessible as it is available from specially trained primary and generalist physicians.

Naltrexone: Naltrexone is extremely effective in blocking the actions of self-administered opioids for 24–36 hours (oral naltrexone Revia) or for up to 30 days (injectable naltrexone Vivitrol) and thereby reducing opioid use. In part because of its potent pharmacological effects the medication has not been popular with opioid addicted patients and adherence rates with the oral formulation are very poor except in court or employer-stipulated treatments. The injectable form is relatively new but shows significant early promise in producing very significant reductions in opioid use and opioid-related health and social problems.

**Conclusions:** The three pharmacotherapies have all shown clear clinical evidence of effectiveness in reducing opioid use and opioid use-related symptoms of withdrawal and craving as well as risk of infectious diseases and crime – when used as part of a comprehensive treatment approach and in appropriate doses. The effectiveness of these medications is true only when used in continuing care, maintenance regimens; there remains almost no evidence of enduring benefits from any of these medications when used only in detoxification regimens.

These medications have very different pharmacological properties and clinical roles. It is not presently known which of these medications is best for which type of patient or under which circumstance – this should be the focus of additional research; particularly explorations of pharmacogenetic subtypes.

Particularly in the face of increasingly serious national epidemics of opioid abuse and dependence, all three of these medications are under-utilized. Knudsen and colleagues found that only about 30% of licensed addiction treatment programs offer any of these medications; and only about 50% of potentially eligible patients within these programs receive any of these medications (See Knudsen et al., 2011). Availability is even poorer among primary care and generalist physician providers – not because of undue risks or side effects but primarily because of lack of knowledge about their use and effectiveness, the possible burden of determining insurance coverage and approval from the insurer, and in some cases the lingering vestiges of an outdated and clinically unsound philosophical understanding of addiction.

## Introduction and Background

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### **Measures of Effectiveness**

For many decades it was thought that withdrawal was the major and perhaps only driving force maintaining abuse and addiction; and in turn, that once that withdrawal had been effectively managed, there should be no driving force to maintain continued drug seeking. In fact, the many processes by which irregular, voluntary, euphoria-driven opioid “use” becomes regular, compulsive, withdrawal-avoiding “addiction” are varied and still only partially understood. Suffice it to say for this report that mechanisms of gene expression, prolonged changes in brain function in the areas of cognition, motivation and inhibition; and a myriad of changes in social and family relationships are just some of the many direct and indirect sequelae of opioid dependence that both result from prior opioid use and also promote future use. In this regard, none of the medications discussed here can be considered an effective treatment for opioid dependence by itself – all medications reviewed here are designed for use as part of more comprehensive treatment strategies that usually include counseling, social supports (as needed) and behavioral change strategies. With this as background, we now suggest four key outcomes that are expectable from an “effective” medication to treat opioid dependence – at least during the active course of that treatment.

Withdrawal Symptom Suppression - Persistent use of opioids is reliably associated with many physical problems. It is reasonable to expect that effective opioid treatment medications should be able to reduce or eliminate these direct physiological symptoms and thereby lead to physiological stabilization and relatively normal behavioral function. Withdrawal and craving have been reliably measured by several standard self-report questionnaires and by recording of physiological signs.

Patient Retention – Because each of the medications is considered part of a more comprehensive treatment strategy one of the expectations of “effective” pharmacotherapy for opioid dependence is that patients should find symptom relief from the prescribed medication and thus should engage remain actively participating in the available constellation of therapeutic components of comprehensive care. Patient retention is typically measured as the proportion of intended patient visits actually attended in a fixed time period (e.g. past 30 days).

Reduction of Opioid Use – The cardinal measure of effectiveness for any opioid addiction treatment medication has been reduction of opioid use, typically measured by urine drug screening and self-report. The mechanisms by which this expected outcome should occur differ for the medications discussed (reduction of withdrawal and craving symptoms, prevention of euphoric effect, etc.) but all are expected to produce significant reductions in frequency and amount of opioid use.

Reduction of Opioid-Related Health and Social Problems – Some of the health and social problems associated with opioid addiction are directly associated with the use itself, such as infectious diseases (HIV, Hepatitis, TB) associated with unsafe injection and needle sharing. Some other related problems are indirectly related to opioid use such as employment, reduction or elimination of criminal acts, improved mood and physical health, and improved family and social relationships. These important and highly desirable outcomes typically require a combination of reduced opioid use as well as the acquisition or re-acquisition of new

behaviors. Most of these outcomes are measured by self-report but most can be validated (pay stubs, crime records).

### ***Scope of literature review***

Numerous individual studies and systematic literature reviews have already examined the efficacy and effectiveness of these medications, particularly methadone. So many, in fact, that the Drug and Alcohol group from the Cochrane Collaboration has published 14 systematic reviews on various aspects of medication-assisted treatment for opioid dependence in several different populations. Taken together, these systematic reviews provide strong evidence for the effectiveness of methadone (Faggiano et al., 2003; Mattick et al., 2009) and buprenorphine (Mattick et al., 2008), in particular, and for oral substitution therapy (either methadone or buprenorphine) for opioid dependence in general (Amato et al., 2011; Gowing et al., 2011). However, because of its rather recent approval for opioid addiction treatment, there are still relatively few studies examining the effectiveness of injectable, extended-release naltrexone (Lobmaier et al., 2008; Minozzi et al., 2011).

Despite the FDA approval-related research on all these medications and the robust body of research done over the past decades, few physicians outside the addiction specialty field are familiar with these medications, there are many unique insurance and regulatory restrictions on their use; and yet with the passage of the Affordable Care and Parity Acts, it is likely that there will be far greater patient demand for opioid addiction treatment among generalist and primary care physicians. For these reasons, a systematic literature review was undertaken of the published research literature, emphasizing studies done over the past five years (2008–2013) to provide guidance to general practice physicians and policy-makers; and to provide recommendations for future research to further improve outcomes.

### ***Objectives***

The objective for this systematic review was to gather, evaluate, and summarize empirical research on the effectiveness of pharmacotherapies (e.g., methadone, buprenorphine, buprenorphine plus naloxone, naltrexone, extended release naltrexone) in the treatment of opioid disorders.

## Methods

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Our review was conducted by searching electronic bibliographic databases (e.g., PsychINFO and PubMed) using pre-defined search terms and established selection criteria as well as by reviewing citations in published studies. In addition to searching electronic databases for published reports, we followed Campbell Collaboration guidelines and searched for unpublished reports and international publications using web-based search engines (e.g., Google and Google Scholar). Abstracts and reports from web-based searches were reviewed for preliminary inclusion, and a random sample of the abstracts were re-viewed by another reviewer to ensure that all potentially relevant studies were coded and analyzed. Details regarding our search and inclusion criteria as well as our coding and analytic procedures are provided below. The review protocol can be found in the appendices (see Appendix 4).

### ***Search criteria***

In the PsychINFO and PubMed data bases from 2008 to the present, we used the terms effectiveness, substance use or abuse, addiction in conjunction with the terms methadone, buprenorphine, buprenorphine + naloxone, naltrexone, extended release naltrexone with some search modifications by medication (see Appendix 4 for additional detail). Searches included all fields (e.g., titles, abstracts, texts, etc.) and results focused on journal articles. The search approach was broad in order to reduce the likelihood of missing a relevant article. Ten unique searches were conducted in PsychInfo and PubMed each. Lastly, references from prominent articles and literature reviews were examined to located studies not previously identified in previously described searches.

### ***Inclusion/Exclusion criteria***

We included all articles and reports in which the stated objectives of the research pertained to any evaluation of the effectiveness of our target medications. However, we excluded studies focused only on pregnant women and adolescents due to the highly specialized issues concerning pharmacotherapies for these populations.

A target medication was considered effective if its outcome measures displayed an improvement on any of the previously described outcomes, compared to a clinically comparable group. The most common outcome measures used in medication effectiveness studies were reductions in use or abstinence, but other outcome measures were included if there was a distinct difference between an experimental group and a matched comparison group.

We *excluded* non-empirical articles such as commentaries (however, we searched these articles for additional empirical studies not previously identified). A member of the study team performed pre-screening of titles and abstracts identified from the searches and excluded any articles not making inclusion criteria. Due to the large number of search results, the scope of publication dates was contracted to cover 2008 to present, approximately five years. We also excluded studies of off-label use of the target medications and use of the target medications for conditions other than opioid addiction. To ensure appropriate application of the exclusion criteria, a study team member reviewed the titles and abstracts of a random sample (5%) of articles.

### ***Coding and data analysis***

We constructed a database to: (1) track the methods used to locate the studies; (2) identify the scope and objectives of the studies; (3) categorize the nature and quality of the studies; and (4) classify the findings from the studies. Regarding the scope and objectives, we coded characteristics of the sample being studied, the type of medication being investigated, and the outcomes used to evaluate effectiveness.

Regarding the nature and quality of studies, we created a numeric field to capture key features of the effectiveness component of the study. Our coding scheme was based on the Scientific Methods Scale of Sherman et al. (1997; 2002). This hierarchical scale was scored from 1-5. At the lower end of the scale, a value of 1 indicated a correlational study and, at the highest end of the scale, a value of 5 indicated a fully randomized experimental design in which appropriate measures were taken to test for the effects of the intervention. The source of data used in the study was coded as were details on the types of outcomes studied, how they were measured, and what was found about them. We also coded author-noted study limitations and “key” findings. Frequencies examined the distribution of categorical variables and content analysis was performed to identify patterns and differences among coded studies.

### ***Results***

A total of four searches were conducted for each medication, two via PubMed and two via PsychInfo for a total of twenty searches. The initial searches were conducted and covered the years 2001 to present. The results are as follows:

- Methadone: 1,068 total results
- Buprenorphine: 445 total results
- Buprenorphine plus naloxone: 120 total results
- Naltrexone (oral): 193 total results
- Naltrexone extended-release: 33 total results

Duplicates were eliminated as were articles published in non-English publications. Also, it was decided that the scope of years be truncated to include articles published between 2008 to the present. This resulted in the following count of unique articles: methadone (329), buprenorphine (125), buprenorphine plus naloxone (63), naltrexone (115), naltrexone extended-release (11). In total, our search strategy located 643 unique articles/reports pertaining to effectiveness of medications for opioid dependence (see Appendix D).

Of the 643 articles located, only 75 (11.7%) were eligible for coding and analysis. Those identified as ineligible; 8.6% (n = 55) were literature reviews; 9.8% (n = 63) were non-English language; and the remaining 80% (n = 513) were for other reasons, including non-empirical studies focusing on alcohol, smoking or pain, using non-human subjects, or being a case study. To help prevent the exclusion of potentially useful articles, a study team member reviewed a random sample of 5% of these abstracts/documents (n=32). Of the 32 abstracts reviewed twice, the reviewers agreed on whether to include/exclude all but eight (84% agreement).



## Methadone Review Results

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*Note: see Appendix 1 for background and clinical information pertaining to methadone.*

Methadone for the treatment of opioid dependence remains among the most thoroughly researched medications. It has been shown to reduce opiate use more than no treatment (Dole et al., 1969; Yancovitz et al., 2003; Dolan et al., 2003; Schwartz et al., 2006; Kinlock et al., 2007), outpatient treatment with no medication (Gunne & Gronbladh, 1981); outpatient treatment with placebo medication (Newman & Whitehill, 1979), or detoxification only (Vanichseni, Wongsuwan, Choopanya, & Wongpanich, 1991; Gruber, Delucchi, Kielstein, & Batki, 2008; Sees et al., 2000) in clinical controlled trials. These trials - using different research groups in culturally diverse settings – have shown convergent results, suggesting broad potency of the medication. In fact, several researchers have advocated methadone as the front line treatment for opiate addiction (Amato, Davoli, Perucci, et al., 2005; van den Brink & Haasen, 2006; White and Lopatko, 2007).

Prior to 2008, there were several systematic literature reviews of methadone maintenance therapy. For example, Amato et al, 2005 evaluated 52 studies comparing different types of maintenance treatment and concluded that methadone maintenance treatment was effective at curbing opiate use, retaining patients in treatment, and reducing criminal activity. A meta-analysis conducted by Johansson, Berglund, and Lindgren (2007) demonstrated similar results as measured by treatment retention, opioid use, and criminality compared with untreated controls. Similar findings resulted from the 2004 meta-analysis of Booth, Corsi, and Mikulich-Gilbertson (2004) but also reported that MMT was effective at reducing drug-related deaths, unemployment and HIV risk behavior. Mattick, Breen, Kimber, and Davoli (2009) evaluated 11 clinically controlled trials of MMT against other non-opioid replacement therapies and found evidence of superiority of methadone over control in treatment retention, reductions in both self-reported heroin use and positive hair/urine analyses.

Since the outbreak of AIDS, researchers have investigated methadone as HIV risk reduction and generally conclude that the reductions in the frequency of intravenous drug use (IDU) and sharing of needles associated with methadone treatment translates into reduction in new HIV cases (see reviews by Gowing et al., 2011; Gowing et al., 2013, and Marsch, 1998; review and meta-analysis by MacArthur et al. 2012; Qian et al., 2008; Metzger, Woody, & O'Brien, 2010) and HCV infections (see review by Bao & Liu, 2009; see Hagan, Pouget, Des Jarlais, 2011).

Fourteen new studies since 2008 were selected for inclusion in this review spanning six countries and focusing on a range of outcomes. Anglin et al., 2009 reported a longitudinal study of opioid addiction careers, within which this investigator found significant reductions in illegal activity among methadone maintenance treatment patients relative to opioid addicted individuals not in treatment. He also found improvements within the methadone maintenance group across various time periods on HIV risk behaviors, employment and criminal justice involvement (Anglin et al., 2009). Similarly, Löbmann and Verthein (2009) working in Germany found improvements on all self-reported and police-recorded criminal justice outcome measures for a methadone maintained group from baseline to one year follow-up.

In the United Kingdom, Oliver and associates (2010) conducted a study in which a cohort of methadone maintenance patients was followed for five years after initiating care. Those who remained in treatment or who discontinued treatment for positive reasons (e.g., drug free, discharged to the care of their own physician, or transferred to another agency) had diminished criminal justice involvement when compared to persons who dropped out of treatment or were ejected from the program.

Karow and her study team (2010) evaluated health related quality of life (QOL), testing four conditions (heroin maintenance treatment, methadone maintenance, and two forms of psychosocial treatment). At baseline and one year after treatment initiation, the methadone maintenance group experienced significant improvements relative to the other groups, on all measures of (QOL; i.e., physical health, spare time, vitality, psychosocial QOL, material satisfaction, affective QOL, and the overall core QOL index. In Malaysia, a similar study (Musa, Bakar, Zafri, & Khan, 2012) of methadone maintained heroin dependent persons also showed significant QOL improvement from the time of initiating treatment to follow-up two years later. Further, approximately 63% of the original participants remained in treatment over the two year period. This group experienced significant improvements in terms of all four of the QOL domains evaluated (physical, psychological, social relationships, and environmental).

Finally, Reimer and colleagues (2011) evaluated a group of opioid-dependent patients randomized to receive either heroin or methadone maintenance treatment. There were significant improvements on the Global Assessment of Functioning scale between baseline and one year follow-up for those in methadone maintenance.

Three other studies evaluated the efficacy of prison-initiated methadone treatment at one month (Kinlock, Gordon, Schwartz, O'Grady, Fitzgerald, & Wilson, 2007), three months (Kinlock, Gordon, Schwartz & O'Grady, 2008) and six months post-release (Gordon, Kinlock, Schwartz, & O'Grady). The primary outcomes were the number of days in community-based drug abuse treatment and urine tests for heroin and cocaine. Randomization was to three conditions: 1) Counseling only: participants were advised upon release to seek drug abuse treatment in the community; 2) Counseling + Transfer: participants were given a directive to report to treatment within ten days of release and were given instruction for methadone induction; 3) Counseling + Methadone: participants were initiated onto methadone while in prison and were given instructions similar to group two. The primary outcomes were community treatment retention and subsequent urine drug tests for heroin and cocaine. Results showed that the prison-initiated group significantly outperformed the other two groups. Compared with Counseling Only, the Counseling + Methadone group spent seven times more days in treatment; and were less than half as likely to test positive for heroin (Kinlock et al., 2007).

Methadone has particular success in maintaining participants in treatment, perhaps more than of the other two medications (Bell, Burrell, Indig & Gilmour, 2006; Darke, 2005; Pinto, Maskrey, Swift, Rumball, Wagle, & Holland, 2010). Opiate dependent participants in one of three community treatments were offered a choice between either buprenorphine or methadone. Over the course of the two-year study period, patients selecting buprenorphine were fifty percent more likely to leave treatment than those selecting methadone. The researchers also found a positive association between higher methadone dosage and treatment retention—in other words, those receiving higher doses of methadone tended to remain in treatment longer

than those on lower doses of methadone. This finding corroborates much previous research (see review and meta-analysis by Faggiano, Vigna-Taglianti, Versino, & Lemma, 2003).

In fact, a recent study conducted in Italy revealed a positive association between higher doses of methadone and higher rates of retention (Salamina et al., 2010). The longitudinal study, VEdeTTE—an Italian acronym meaning “the evaluation of the effectiveness of treatment for heroin dependence”) focuses on mortality and treatment retention. Of the 5,457 participants receiving under 60 mg daily of methadone were 40% more likely to discontinue treatment. Also, comparison of three different treatment modalities—MMT, therapeutic community (TC), and abstinence-only oriented outpatient treatment (AOT)—among new participants revealed comparable rates of retention between MMT and TC. For participants who were returning to treatment after having discontinued, retention rates in MMT exceeded those of TC for the 18-month study period.

Two studies (Soyka, Zingg, Koller, Kuefner, 2008; McKeganey, Russell, & Cockayne, 2013) evaluated the effects of methadone and buprenorphine on drug use. The Soyka team conducted a small, naturalistic study to evaluate drug use and rates of relapse in a sample of 109 opiate dependent adults at two points in time—after six months of replacement medication and after 14 months of replacement medication. Participants had to have participated in opioid replacement therapy for the six months prior to the study onset. Results demonstrated that when controlling for patient-level characteristics (e.g., age, age at first use, number of days of heroin use during the 90-day pre-intake period) both medications significantly reduced use of heroin between pre-intake and eight-month follow-up. Additionally, rates of 90-day abstinence at intake and at the eight month reassessment were statistically equivalent for both medications.

McKeganey and associates (2013) focused their efforts on a group of opiate dependent patients in Bavaria who had no prior replacement therapy in the four weeks prior to the study. In this small randomized prospective study, patients received either buprenorphine or methadone-replacement therapy and standardized psychosocial intervention over a period of six months. Results indicated that buprenorphine and methadone were equally effective in increasing rates of retention and decreasing opioid use during therapy.

A unique treatment modality designed to address the problem associated with the long waiting lists for admission to methadone maintenance programs, has undergone extensive evaluation. While wait lists have existed for the past four decades (Friedmann, Lemon, Stein, & D’Aunno, 2003; Wenger & Rosenbaum, 1994), no solution to the problem has taken hold. Early experiments with minimal service methadone—methadone administered to wait-listed patients with no counseling—were undertaken and demonstrated positive results, but the practice failed to proliferate (Yancovitz et al., 1991; Calsyn et al., 1994). Renewed effort is currently being spearheaded by Dr. Robert Schwartz at the Friends Institute of Baltimore, Maryland. The concept, rebranded “interim methadone (IM) treatment,” has been the focus of several studies, five of which fall within the scope of this review (Schwartz et al., 2008; Schwartz et al., 2009; Schwartz, Jaffe, O’Grady, Das, Highfield, & Wilson, 2009; Schwartz, Kelly, O’Grady, Gandhi, & Jaffe, 2011; Schwartz, Kelly, O’Grady, Gandhi, Jaffe, 2011). Through their series of studies these researchers have demonstrated that patients maintained on IM for four to 12 months dramatically reduce their use of illicit opiates, obtain less money through illegal activities, and significantly reduced opiate-positive urine tests. Patients randomly assigned to IM had a high likelihood of entering comprehensive methadone treatment and submitted fewer opioid-positive

urine tests from baseline to time of transfer. Similar reductions in opiate-positive urine tests were found under similar conditions involving a large-scale, multi-site feasibility study that included 1,000 patients. These studies also demonstrated the benefit of IM over no treatment. And, when patients were randomly assigned to IM, standard MMT, or standard MMT with a counselor that had a reduced caseload they found no significant differences among the groups on treatment retention or drug use at either four or 12 months on IM.

To summarize, more than 50 years of clinical and research evaluation has been conducted, and despite the ideological controversy that has surrounded the practice of prescribing long-acting opioids to opioid addicted individuals, methadone maintenance remains one of the most effective treatments for opioid addiction. Because of its potency, methadone can produce profound respiratory depression among those not tolerant and this has led to very high rates of overdose incidents and deaths primarily among those seeking to use the medication to get high. Thus, there is public health reason for the unique restrictions and regulations that govern the administration of this medication.

## Buprenorphine and Buprenorphine/Naloxone Review Results

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*Note: see Appendix 2 on for background and clinical information pertaining to buprenorphine.*

Buprenorphine (either alone or in combination with naloxone) has been effectively used for both acute opiate detoxification and longer-term maintenance therapy. Initial studies in the late 1990s found buprenorphine to be a safe and effective treatment for opioid dependence (Ling et al, 2008; Fudala et al, 2003). More recently, a meta-analysis found that buprenorphine as well as methadone were superior to placebo in retaining patients in treatment and in suppressing heroin or other opioid use (Mattick et al, 2008).

Several other studies have shown that relative to outpatient, abstinence-oriented drug abuse treatment, office-based outpatient treatment (OBOT) with buprenorphine improves six-month treatment engagement (50-60% retention at six months vs. 25 to 40%); significantly reduces cravings, illicit opioid use and mortality (Fiellin et al, 2006; Fiellin et al, 2008; Fudula et al, 2003; Mattick et al, 2008; Gundersen & Fiellin, 2008; Gibson et al, 2008; Amass et el, 2012; Parran et al, 2010; Fareed et al, 2011) ; and improves psychosocial outcomes (Parran et al, 2010; Ponizovsky et al, 2010). Other recent studies have found positive correlations between patient engagement with buprenorphine maintenance therapy and reductions in criminality (Soyka et al, 2012; Bukten et al, 2012).

In addition, there is substantive research evidence that long-term, positive outcomes (both at the patient and system-level) can be achieved in primary care and other outpatient settings with buprenorphine maintenance treatment,-even for traditionally vulnerable patient populations (i.e.. those who have HIV, are homeless or marginally housed, or are extremely low SES (Alford et al, 2007; Parran et al, 2010; Sullivan et al, 2008; Fiellin et al, 2008; Korthuis et al, 2011; Stancliff et al; 2012).

Although the majority of research reviewed evaluated the effectiveness of buprenorphine maintenance, there are indications that detoxification with buprenorphine may be more effective than non-opioid based detoxification approaches (Gibson et al, 2008; Wittchen et al, 2008), the greatest evidence of clinical effectiveness is for buprenorphine maintenance. A recent National Institutes of Health sponsored multi-site trial found significant reductions in opioid use and psychosocial function among patients tapered off of buprenorphine after 4 weeks (Amass et al, 2012).

In summary, the results from substantial clinical and research experience with buprenorphine since its FDA approval in 2000, suggest effectiveness that is comparable to methadone maintenance in retaining patients, reducing opioid withdrawal and opioid use; and in improving psychosocial outcomes. Advantages to buprenorphine accrue from its safer profile and lower rate of side effects (due to its partial agonist properties) and relatedly, because it is much more widely available from trained primary care practitioners.

## Naltrexone Oral and Extended Release Injection Review Results

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*Note: see Appendix 3 for background and clinical information pertaining to naltrexone.*

Despite the fact that naltrexone has been available as an oral medication for the treatment of opioid addiction for over 35 years, there is far less research on this medication. This is largely due to the very poor adherence results seen among most clinical populations. These high drop-out rates are illustrated by the meta-analysis done by Minozzi et al (2011) as part of a Cochrane Systematic Review involving 13 studies and 1158 participants. Less than a third of participants were retained in treatment over the expected duration of the included studies (range one to 10 months). That review concluded that oral naltrexone, with or without psychotherapy, was no better than either placebo or no pharmacological treatments in retaining patients in treatment; and thus no better than placebo in reducing opioid use.

Adherence is important because oral naltrexone's blocking action typically lasts no more than 24 to 36 hours. A missed dose may lead to a relapse, requiring a new detoxification and naltrexone induction. Some of the poor adherence and early drop out may be due to medication induction. Induction onto oral naltrexone can be difficult for many patients due to the 7 to 10-day period of abstinence required prior to beginning naltrexone therapy and because the length of this duration may promote withdrawal, relapse, and early dropout (Tetrault & Fiellin, 2012).

We also questioned whether low retention was due to adverse side effects. In this regard, a study comparing low-dose (192 mg) and high-dose (384 mg) extended release naltrexone to placebo showed that high doses were associated with *higher* retention rates than the placebo or low-dose naltrexone; less than 10% of patients reported significant side effects; and these were usually short term effects such as headache, nausea and some fatigue (Comer et al., 2006). Dropout rates with naltrexone lessen when there are powerful external motivations, such as contingent loss of an important job or criminal justice sanctions; or when positive rewards are contingent upon adherence. Finally, adherence improves with involvement of family members in monitoring adherence, in some cases doubling retention rates between 12 and 24 weeks (Kleber, 2007).

The prevailing clinical wisdom is that the consistently large drop-out rates found with oral naltrexone trials are largely due to the fact that the medication works too well. Naltrexone completely blocks euphoric effects from heroin or other injected opioids and most opioid addicted individuals forego the medication and return to active opioid use. Until the availability of the extended release injectable form in 2010, naltrexone was used almost exclusively with patients who were taking it by the criminal justice system. Results suggest that treatment with the extended-release, injection formulation of naltrexone may increase treatment compliance (Baser et al., 2011; Fishman et al., 2010). For example, a study by Krupitsky et al. (2012) randomized trial; 306 opioid-addicted but recently detoxified patients in Russia to either 1) naltrexone implant, oral placebo, 2) placebo implant oral naltrexone, 3) placebo implant oral placebo. Naltrexone implants are not FDA approved so this Russian study is outside the parameters of this review. Nonetheless, the findings showed that oral naltrexone was not statistically different from placebo, while the implanted (sustained release) form of the medication produced essentially complete abstinence for the six month duration of the study.

Similarly, a quasi-experiment comparing extended-release to oral naltrexone involved 69 oral patients treated with behavioral therapy and 42 extended-release patients receiving the same therapy in two concurrently running randomized clinical trials. Results showed that the extended release treatment produced significantly better retention in treatment (M = 42.3 days, SD = 18.2) compared to oral patients (M = 31.9 days, SD = 22.42) (Brooks et al., 2010). Krupitsky et al. (2011) conducted a double-blind, placebo-controlled, randomized, 24-week trial of patients with opioid dependence disorder in Russia with the 250 patients being randomized to extended-release naltrexone or placebo. Primary findings showed a longer proportion of weeks of confirmed abstinence of 90% in the extended-release group vs. 35% in the placebo group. In that study the median retention was greater than 168 days in the extended-release group compared with 96 days (95% CI 63, 165) in the placebo group ( $p=0.0042$ ). Also, the extended-release group, combined with psychosocial counseling, outperformed the placebo group in terms of lower opioid use, craving, and treatment retention. However, two other studies of extended release naltrexone showed only moderate compliance without incentives (DeFulio et al., 2012; Everly et al., 2011).

In summary, there are comparatively fewer trials of oral naltrexone in the treatment of opioid addiction, but despite the small number it is safe to conclude that it is not a viable treatment for most populations of patients simply because it can be discontinued at any time and active addiction resumed. Because the injectable, extended release medication has only recently been available for use with opioid addicted patients there is inadequate data for a true systematic review. Nonetheless, several studies with extended release forms of the medication suggest that it is safe, generally well tolerated and results in immediate and complete blockade of opioid receptors and thus discontinuation of self-administered opioids. It remains to be seen whether early experience with this form of the medication will result in greater patient willingness to continue the monthly injections and the protection from opioid relapse afforded by those injections.

## Discussion and Future Directions

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Opioid abuse and addiction occur in approximately 1-2% of the adult population; and result in dramatic costs to society – particularly healthcare. (Substance Abuse and Mental Health Services Administration, 2010). Especially troublesome is the fact that less than 12% of these seriously affected individuals seek treatment. Relatedly, opioid overdose and death have reached epidemic status in the US (Substance Abuse and Mental Health Services Administration, 2012; Compton & Volkow, 2006 Hall et al., 2008). This review was commissioned to address the question of whether the observed reluctance to enter treatment might be due to the absence of effective medications to treat opioid addiction.

The results from this review are both satisfying and frustrating. It is satisfying to be able to report conclusively that there is overwhelming evidence for the effectiveness of three very different FDA-approved medications: methadone (Dolophine & Methadose), buprenorphine (Subutex & Suboxone) and naltrexone (oral Revia & extended release injectable Vivitrol). Methadone and buprenorphine have particular efficacy in reducing the physiological and emotional symptoms of opioid withdrawal. Naltrexone has the ability to essentially eliminate self-administration of opioids. All of the medications – when properly prescribed and as part of more comprehensive care – have shown clear, longstanding and broad evidence of effectiveness in reducing the frequency and intensity of opioid abuse and with it, the public health and safety threats of opioid-related infections (HIV, Hepatitis C, TB, etc.), crime and social decay.

Three important caveats to the effectiveness findings bear emphasis. First, these medications have their primary effects on opioid self-administration; it is not reasonable to expect comparable changes in reduction of *non-opioid* substance use even following stabilized maintenance on any of these medications. There have been indications that buprenorphine might reduce cocaine self-administration but these effects may be due to reductions in so-called “speed-ball” combinations of cocaine and opioids. It is also true that naltrexone has been FDA approved for the treatment of alcohol dependence. Naltrexone has shown the ability to reduce alcohol use among opioid addicted individuals and while some of this may be due to the direct blockage of alcohol-mediated euphoria it is impossible to eliminate the general effects of a naltrexone-assisted recovery lifestyle.

The second caveat follows from the first. Each of these medications has been approved as part of a broader, more comprehensive recovery-oriented set of medical and social support services. These medications are not incompatible with a recovery-oriented treatment approach (McLellan, 2010). Indeed, the research reviewed here suggests that can be an essential – but not adequate - part of a recovery oriented approach to rehabilitation from opioid addiction. Any of these potent, safe medications can provide important assistance in reducing opioid use among addicted patients. However, it is equally clear that most opioid addicted patients concurrently suffer from related physical and mental problems, deteriorated personal and social relationships and often inability to self-support a productive lifestyle. The role of counseling, social services, monitoring with consequences and peer supports can provide much of what these potent medications cannot provide. But these medications can also offer pharmacological assistance in stabilizing signs and symptoms that so often lead to patient termination from so-called abstinence-oriented treatments. It is simply efficient and prudent to combine the best of



recovery-oriented social services with these medications to offer patients the best chance of a full recovery.

Finally, it must be said that while each of these medications has shown clear evidence of effectiveness when used in a long-term maintenance strategy, there is very little indication that short term courses of any of these medications are effective – particularly as used in detoxification. This has been a source of frustration for many of those in policy making, insurance and regulatory positions – but also among many physicians. There has been the pervasive and long-standing wish among patients and providers for a medication that could be prescribed for a relatively short period that would produce enduring abstinence. This wish likely stems from what we now know is a relatively antiquated understanding of opioid addiction that assumed withdrawal and craving were essentially the cardinal, identifying features of addiction and were likely responsible for the observed compulsive use despite serious negative consequences. Withdrawal and craving *are* important features of the addiction syndrome but so are “track marks” from intravenous injections. None of the medications reviewed here can reverse the (typically) decade or more of opioid-induced genetic expression, brain changes in reward, motivation and memory circuits, or the cue-induced craving and withdrawal that are so characteristic of chronic opioid addiction.

Those attempting to treat serious, chronic opioid addiction are wise to adopt essentially the same medication maintenance strategy used to treat patients with serious, chronic diabetes. Like seriously and chronically affected diabetic patients maintained on insulin (See Look AHEAD Research Group, 2010) it is possible for some severely affected opioid addicted patients to taper off from their medications – but only with rather dramatic and well-practiced lifestyle changes and significant social supports. This too is an area that is important for continued study. Interestingly, recent studies with seriously, chronically affected diabetic patients have begun to show very positive effects from “radical lifestyle interventions” that combine regular exercise regimens (walking 3 hours per week), with significant reductions in caloric intake and diet (target of 8% weight loss) (Look AHEAD Research Group, 2010).

Each of the medications reviewed here also has side effects that merit attention but not apprehension. Methadone and buprenorphine produce the euphoric properties common to all opioids and thus physicians must be active in promoting safe use and storage of these medications by their patients to reduce diversion. Methadone in particular is a powerful opioid agonist with the ability to produce significant respiratory depression – especially among those not tolerant to opioids – and has become a prominent cause of overdose. Naltrexone has significant opioid antagonist properties and will induce withdrawal symptoms (headaches, nausea, etc.) if prescribed to patients prior to complete opioid withdrawal. These cautionary issues are important but can be successfully avoided with appropriate clinical management techniques such as those now recommended for physicians prescribing analgesic pain medications (National Pain Management Guidelines).

This review has not been able to identify specific patient characteristics (demographics, disease history, etc.) that predict which of these very different medications are most likely to be effective for an individual patient. There are some promising indications from the still nascent study of pharmacogenetics and this is of course an important topic for more research. But this important gap in our knowledge is not by any means unique to the pharmacotherapy of opioid addiction: classic studies of three different forms of antihypertensive therapies (ALLHAT, 2002)

and more recently antidepressant therapies (Rush et al., 1999) and more recently antidepressant therapies (Texas Medication Algorithm Study) showed the same findings in those diseases. This simply means that prescribers should become familiar with all of these medications, negotiate an initial prescription strategy with their patients based on realistic, measurable expectations; and then employ careful, regular monitoring to adjust or change the medication based on side effects and effectiveness. Of course this is typical of medication trials with any other illness where multiple and different pharmacotherapy options exist.

## APPENDIX 1

### Detailed Medical Discussion of Methadone Prescribing Practices and Contraindications

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Methadone hydrochloride (methadone) is a synthetic opioid developed in Germany in 1937 for the treatment of pain. It was first used for the treatment of opioid addiction in 1965 (Dole & Nyswander) and since has steadily been building a body of research evidence supporting its effectiveness. Although methadone has never been formally approved by the FDA for the treatment of opioid dependence, maintenance treatment with methadone has been used for many decades in the United States. And, according to the World Health Organization (WHO; 2011), methadone treatment for opioid dependence is available in 65 countries. It is the only long-acting, full opioid agonist currently used for opioid pharmacotherapy. Taken in optimal doses, it acts to normalize neurological and endocrinological processes in individuals whose endogenous ligand-receptor function has been altered by the use of powerful narcotic drugs (Dole, 1988). Methadone does not provide protection from use of alcohol or non-opioid drugs of abuse such as cocaine, marijuana or benzodiazepines (tranquilizers). Guidelines for use specify that the medication be used in conjunction with appropriate social and medical services.

Pharmacologically, methadone is a long-acting (24–30 hours), potent opiate agonist, imitating the action of an opiate by binding with mu opiate receptors on the surface of brain cells, thereby mediating the analgesic and euphoric effects of opioids. Because methadone is taken orally and has a slow and lengthy period of metabolism, when taken in properly prescribed doses it does not generate the extreme euphoria of short-acting, injectable opioids such as heroin and many pharmaceutical opioids. Its potency, slow onset and ability to produce tolerance without significant euphoria (again, when properly prescribed and utilized) are the properties that reduce opioid craving and risk of overdose. Doses vary from about 30 to over 100 mg/day depending upon the genetic profile and opioid use histories of patients. While suppressing opioid craving and withdrawal symptoms, methadone does not have adverse toxicological effects that impede users' functional capacities. However, because of its potency and long-acting nature, it produces physiological tolerance (i.e. the body gets used to a daily dose of the medication) and it cannot be discontinued abruptly without producing its own significant withdrawal symptoms.

As a Schedule II controlled substance in the U.S., methadone used for the purpose of opioid dependence can, with few exceptions, only be legally dispensed in authorized detoxification and maintenance programs known as opioid treatment programs (OTPs) that must be certified by the Substance Abuse and Mental Health Administration (SAMHSA) and approved by the appropriate state agency. After two or more years on a methadone-maintenance program, an increasing take-home supply may be permitted up to a maximum one-month supply (Kleber, 2007). These programs are licensed by the Drug Enforcement Administration and must pass regular inspections to ensure compliance with national accrediting organizations and local requirements. Regulations specify who is eligible for treatment and the required administration procedures, including rules governing take-home doses and medication storage security. Violations of regulations have resulted in sanctions and even criminal prosecution in a few cases (Woody & Fudala, 2008). In addition, it has very special prescribing restrictions. Only licensed physicians who have a Drug Enforcement Administration (DEA)

registration can prescribe the medication and it can only be prescribed for the treatment of opioid dependence by physicians working within licensed methadone maintenance programs (it can be prescribed by other DEA-registered physicians for the treatment of pain). Thus, methadone is the most restricted and regulated medication in history.

There are various forms of methadone—diskettes, tablets, oral solution, liquid concentrate and powder. The diskettes, tablets, and powder are mixed with water for dosing. In the United States, methadone is almost always used in liquid form for opioid dependence because it allows for complete dosing flexibility (particularly with a computer-assisted dispensing pump system) and it precludes diversion.

Long-term methadone therapy is associated with few major long-lasting side effects. In fact, methadone prescribed in high doses for a long period of time has no toxic effects and only minimal side effects for adult patients maintained in treatment for up to 14 years and for adolescent patients treated for up to five years (Kreek, 1978). The most common adverse effects reported by methadone patients are sweating and constipation caused by slowed gastric motility. Respiratory depression is the principal serious risk associated with methadone use. Respiratory depression is a particular concern with elderly or debilitated patients, and patients suffering from conditions that accompany hypoxia (lacking adequate oxygen) or hypercapnia (excess of carbon dioxide in the blood) even with moderate doses.

It has only recently been established that methadone, especially in high doses, can cause cardiac problems in the form of an arrhythmia named *torsade de pointes* (Krantz, Rowan, Schmittner, Bucher, & Bartelson, 2003; Martin et al., 2011). This occurs evidently because the methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of *torsade de pointes* have been reported in patients taking high doses of methadone (average daily dose of approximately 400mg; Krantz et al. 2007). In addition, Martell and colleagues (2003) reported statistically significant increases in QT intervals regardless of the size of the methadone dose during the first two months of methadone treatment. In clinical practice, it is necessary to be cognizant of the possible synergistic effects of psychotropic medications and methadone on QT prolongation and the risks involved. Patients with a history of heart disease should not be automatically excluded from treatment with methadone, particularly in light of the substantial morbidity and mortality associated with untreated opioid addiction. It is essential, however, that physicians perform an individualized comprehensive evaluation of the risks and benefits of methadone treatment. Careful medical history taking, risk stratification and obtaining a baseline and a follow-up electrocardiogram after a month of initiating therapy are practices that can help clinicians address potential risks.

Though methadone is metabolized by the liver, according to Kreek et al. (1972), it is not hepatotoxic. While liver disease is not a reason to exclude a patient from methadone therapy, it is a reason to monitor liver functions regularly and to be cautious when making dosage adjustments. Because the liver is a major storage site for methadone, patients with liver disease will have slower medication metabolism that may shorten the medication's duration of action. Other side effects include sleep abnormalities (including insomnia, nightmares and early awakening) and diminished libido or sexual performance (Hardman et al. 2001). In one study, methadone-maintained patients reported significantly greater sexual excitation disturbances and lower sexual life satisfaction than buprenorphine-maintained patients (Giacomuzzi, Khreis,

Riemer, Garber, & Ertl, 2009). Other potential side effects of opioid agonists and partial agonists are shown in Table 1.

**Table 1. Possible Side Effects of Opioid Agonist and Partial Agonist Therapy**

<p><b>Whole Body Effects</b></p> <ul style="list-style-type: none"> <li>Weakness, loss of energy (asthenia)</li> <li>Back pain, chills</li> <li>Fluid accumulation (edema)</li> <li>Hot flashes</li> <li>Flu syndrome and malaise</li> <li>Weight gain</li> </ul> <p><b>Gastrointestinal Effects</b></p> <ul style="list-style-type: none"> <li>Constipation</li> <li>Dry mouth</li> <li>Nausea and vomiting</li> <li>Abdominal pain</li> </ul> <p><b>Musculoskeletal Effects</b></p> <ul style="list-style-type: none"> <li>Joint pain (arthralgia)</li> <li>Muscle pain (myalgia)</li> </ul> <p><b>Nervous System Effects</b></p> <ul style="list-style-type: none"> <li>Abnormal dreams</li> <li>Anxiety</li> <li>Decreased sex drive</li> <li>Depression</li> <li>Euphoria</li> <li>Headache</li> <li>Decreased sensitivity to tactile stimulation (hypesthesia)</li> <li>Insomnia</li> <li>Nervousness</li> <li>Somnolence</li> </ul>	<p><b>Respiratory Effects</b></p> <ul style="list-style-type: none"> <li>Cough</li> <li>Rhinitis</li> <li>Yawning</li> </ul> <p><b>Cardiac Effects</b></p> <ul style="list-style-type: none"> <li>Electrocardiogram changes (possible QT prolongation with LAAM or high doses of methadone)</li> <li>Postural hypotension</li> <li>Slowed heart rate (bradycardia)</li> </ul> <p><b>Hepatic Effects</b></p> <ul style="list-style-type: none"> <li>Abnormal liver function tests</li> </ul> <p><b>Endocrine Effects</b></p> <ul style="list-style-type: none"> <li>Hyperprolactinemia</li> <li>Absence of menstrual periods (amenorrhea)</li> </ul> <p><b>Skin and Appendage Effects</b></p> <ul style="list-style-type: none"> <li>Sweating</li> <li>Rash</li> </ul> <p><b>Special Sensory Effects</b></p> <ul style="list-style-type: none"> <li>Blurred vision</li> </ul> <p><b>Urogenital Effects</b></p> <ul style="list-style-type: none"> <li>Difficult ejaculation</li> <li>Impotence</li> </ul>
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Methadone is contraindicated in patients with a known hypersensitivity to the medication as well as for patients for which opioids in any form is contraindicated. These include individuals with respiratory depression and patients with acute bronchial asthma or hypercarbia, and those who have or are suspected of having a paralytic ileus

(<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=e6af84de-cbfc-4a3b-bd73-6bcf77337168#nmlm34070-3>)

Methadone is primarily metabolized by the CYP3A4 enzyme system (part of the CYP450 system), so drugs that affect the CYP450 system can change the pharmacokinetic properties of methadone, causing clinically significant increases or decreases in the serum and tissue levels of opioid medications. Drugs that induce the CYP450 enzyme system can precipitate withdrawal in patients receiving methadone due to the resulting increases in metabolism and potential decreases in methadone effects. Conversely, drugs that inhibit the CYP450 enzyme system may reduce metabolism and potentiate methadone's effects (Center for Substance Abuse Treatment, 2005). Antiretroviral drugs such as abacavir, amprenavir, efavirenz (Clarke, et al., 2001a), nelfinavir, nevirapine (Clarke, et al., 2001b), ritonavir, lopinavir + ritonavir combination co-administered with methadone result in either increased clearance or decreased plasma levels of methadone (<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=e6af84de-cbfc-4a3b-bd73-6bcf77337168#nmlm34070-3>).

A number of reports indicate that methadone interacts pharmacokinetically with SSRIs and other psychiatric medications, affecting blood plasma or tissue levels of methadone (for SSRI interactions see, e.g., Greenblatt, D. J., von Moltke, L. L., Harmatz, J. S., Shader, R. I., 1999 and Iribarne, Picart, Dreano, & Berthou, 1998). For a full review see Saber-Tehrani, Bruce, & Altice, 2011. In short, drugs administered concomitantly with methadone should be evaluated for interaction potential and clinicians are advised to closely evaluate individual response to drug therapy.

There are a couple of populations for which opioid substitution therapy must be considered with special weight: adolescents and pregnant women. Opioid use has risen dramatically among adolescents in recent years (National Institute on Drug Abuse, 2012). In treating adolescents for opioid use, including methadone-assisted therapy, they should not be seen as simply "little adults" but rather as a unique population with characteristic needs (Center for Substance Abuse Treatment, 1999). There is evidence of a high rate of psychiatric disorders among adolescents addicted to opiates, with those who seek treatment for opiate use disorder having greater impairment in substance use, depressive symptoms, and injection drug use-related HIV-risk behaviors than adolescents who seek treatment for cannabis or alcohol use, suggesting a need for specialized interventions (Subramaniam, Stitzer, Woody, Fishman, & Kolodner, 2009). There appear to be no special requirements for methadone dosages recommended for this population as a whole. The patient's age, individual substance use history, medical status, and particular situational factors must be taken into account in determining proper drug dosages. SAMHSA does emphasize that if an adolescent is also taking psychoactive medications for a coexisting psychiatric disorder, this fact requires careful psychopharmacological management (Center for Substance Abuse Treatment, 1999). For adolescents who may have a shorter duration of opioid use, some sources recommend that withdrawal or opioid replacement detoxification and intensive counseling may be more appropriate (Kleber, 2007; The College of Physicians and Surgeons of Ontario, 2011).

Another special population consists of opiate-addicted women who are pregnant. These patients may experience any of a number of conditions not conducive to a successful pregnancy, including inadequate nutrition and rest, inadequate antenatal care, self- and fetal-exposure to fluctuating blood levels of drugs, and exposure to HIV, HCV, and other blood-borne pathogens associated with injection drug use. For such women, providing methadone maintenance treatment results in an increased likelihood of carrying pregnancy to term, fewer birth complications, and larger infants for the same gestational age (Ward, Mattick, & Hall, 1998). For women using methadone, it is crucial that a comprehensive medical examination be conducted if they are thought to be pregnant. If the woman is determined to be pregnant, comprehensive pregnancy and birth services need to be provided. Since methadone blood levels decrease with the same dosage as pregnancy progresses, methadone-maintained women may experience symptoms of withdrawal in later stages of pregnancy. Blood levels therefore need to be monitored and dosages may need to be adjusted over time to maintain proper blood levels of methadone and avoid withdrawal symptoms. A risk factor of a pregnant woman's use of methadone is the probability that this may result in neonatal abstinence syndrome (NAS) in the infant (National Institutes of Health, 2012) and about half of these infants will need to be withdrawn (Kleber, 2007). If neonatal care is adequate no birth defects are associated with methadone exposure. While lower dosages of methadone to reduce the chance of NAS were previously recommended by treatment providers, currently the consensus of the Center for Substance Abuse Treatment is that the main consideration for proper methadone dosages is to determine the therapeutic levels that are most appropriate for the individual woman (Center for Substance Abuse Treatment, 2005).

Decades of research has revealed that methadone treatment predicts a lower risk of HIV infection (Metzger, Woody, O'Brien, 2010). Patients engaged in methadone treatment use significantly less while they are in treatment as they did prior to treatment (Qian, Hao, Ruan, et al., 2008; Coplehorn, Ross, 1995; Metzger, Woody, McLellan, et al., 1993). They also use less often than those not in treatment (Lawrinson, Ali, Buavirat, et al., 2008; Haverkos, 1998; Gowing, Farrell, Bornemann, et al., 2006; Hartel & Schoenbaum, 1998). Further, those who attend their methadone program regularly use significantly less than those in methadone treatment with poor attendance and regardless of treatment intensity (McLellan, Arndt, Metzger, et al., 1993; Avants, Margolin, Sindelar, et al., 1999; Avants, Margolin, Usubiaga, et al., 2004; Wong, Lee, Lim, et al., 2003).

For patients being treated for HIV infection, certain medications they may be taking have been shown to retard or accelerate the body's transformation of methadone (as previously described). It is critical to obtain a full listing of any medications the patient may be using to treat HIV. Patients on these medications may need to increase or decrease their methadone dosage. Any change in dosages should be based on observation of the patient during the first month of treatment (Gourevitch & Friedland, 2000).

There is no set recommended duration of use for methadone for opiate addiction. The appropriate duration depends on the progress of the particular individual, any contraindications that may develop during methadone's use, and the patient's preferences. Treatment with methadone for less than three months generally results in little improvement in the patient, and the most successful are those who stay in treatment for more than a year. Long-term methadone maintenance that is accompanied by appropriate psychosocial interventions results

in better outcomes, with the most successful outcomes occurring with long-term maintenance accompanied by appropriate psychosocial interventions. Considering the high relapse rate following withdrawal of methadone even after long periods of maintenance, lifetime maintenance may be indicated. If withdrawal is desired, it traditionally consists of quickly decreasing the dosage to 30 mg and then slowly reducing the dosage (e.g., by 5 mg/week) or switching to clonidine. A newer method is to transfer the patient to buprenorphine or naloxone before making reductions in dosage (Kleber, 2007).

Currently, no standards exist that guide clinicians to match patients with methadone treatment. Kleber (2007) suggests that methadone may be more suitable for patients with the following characteristics:

- unstable lifestyle (e.g., homeless or marginally housed)
- would benefit from the structure of regular attendance in a dispensing situation
- would benefit from the wider range of services available at a comprehensive methadone maintenance program
- few financial resources or uninsured or underinsured

Additionally, patients who lack social support might also benefit from the more systematized environment that is characteristic of the methadone treatment paradigm. Pinto and associates (2010), however, emphasizes that the decision as to which medication is prescribed is based on understanding the known pharmacology of the drugs, patient characteristics and preferences, and ultimately on the clinicians' opinions.



## APPENDIX 2

### Detailed Medical Discussion of Buprenorphine Prescribing Practices and Contraindications

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Buprenorphine, a synthetic opioid, is a partial mu-opioid agonist and kappa-opioid antagonist (Martin et al. 1976, Sadée et al. 1982). When used properly, Buprenorphine suppresses withdrawal symptoms by displacing morphine, methadone, and other opioid full agonists from the receptor. Because it is a partial agonist, it possesses many clinical benefits such as lower abuse potential, lower level of physical dependence, a ceiling effect at higher doses, and greater safety in overdose compared to full agonists (including Methadone). Because the sedating and respiration-reducing properties common to all opioid agonists are significantly reduced in this partial agonist medication, the risk of fatal respiratory depression is also significantly reduced (Villiger & Taylor 1981; Rothman et al., 1995).

Buprenorphine has been available internationally as an analgesic for approximately 30 years, but was first approved by the FDA for use in the United States in 2002 for the treatment of opioid dependence. Because of Buprenorphine's safer effect profile, it received FDA-approval for office-based administration by DEA-registered physicians who pass a brief training course. Almost immediately after the medication was approved for administration in office-based settings, it was discovered that patients could easily abuse it by crushing the tablet, mixing with water and injecting it to produce a significant euphoric effect. To reduce the risk of inappropriate use, the medication was quickly reformulated to include the short-acting opioid antagonist, naloxone. The buprenorphine/naloxone combination product contains each component in a 4:1 ratio; 2 mg/0.5 mg and 8 mg/2 mg sublingual tablets are available. Naloxone is only poorly absorbed when administered sublingually. Thus when taken as directed the naloxone has no physiological effect; but if the tablet is crushed and injected the naloxone will produce withdrawal symptoms. Individuals may be inducted onto therapy with either buprenorphine or buprenorphine/ naloxone, but the latter should be used for unsupervised (e.g., take-home) administration unless the combination product cannot be tolerated due to the above properties that are hoped to reduce its potential for abuse as compared to buprenorphine alone (the "mono product"). The buprenorphine-naloxone medication is called Suboxone®, (its first generic formula was approved by the FDA early in 2013) and is indicated for the detoxification or maintenance phases of opioid dependence treatment. Currently, over 40 countries have approved buprenorphine and/or buprenorphine/ naloxone for the treatment of opioid dependence.

Because of its safer effect profile, buprenorphine was FDA approved for administration in office based or outpatient treatment programs by physicians who have met specific criteria, including:

- Holding a subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties; or a subspecialty board certification in addiction medicine from the American Osteopathic Association; or an addiction certification from the American Society of Addiction Medicine.
- Having completed a minimum of 8 hours of training about the treatment and management of opioid-addicted patients (through classroom situations, seminars at professional society meetings, electronic communications, or otherwise), provided by the

American Society of Addiction Medicine, the American Academy of Addiction Psychiatry, the American Medical Association, the American Osteopathic Association, the American Psychiatric Association, or any another organization as approved by the Secretary of Health and Human Services.

Once these criteria are met, a physician must apply for a waiver from the Department of Health and Human Services (HHS) to administer buprenorphine, and also register with the Drug Enforcement Agency (DEA). Physicians are limited to a caseload of 30 patients simultaneously treated with buprenorphine in the first year of receiving their waiver, and can apply to increase their caseload to 100 patients in subsequent years.

Although the medication is very safe when taken as directed, it may exacerbate withdrawal symptoms if given too soon after use of an opioid agonist (Kleber, 2007?). As such, patients should not be given buprenorphine to relieve withdrawal symptoms until at least 12 hours after use of any short-acting opioids and 36 hours after use of methadone (Berg, Idrees, Ding, et al., 2007). For the management of heroin detoxification, buprenorphine can be administered at an initial dose of 2 to 4 mg sublingually, and increased in increments of 2 or 4 mg, depending on patient's distress. Most patients are well-managed with a dose of 8 to 12 mg of buprenorphine on the first day of detoxification. For most patients, a slow taper over a week or so is a safe and well tolerated strategy. Any buprenorphine dose that worsens withdrawal symptoms suggests the buprenorphine dose is too high compared with the level of withdrawal (Kleber, 2007). The recommended target dosage for buprenorphine is between 12-24 mg daily. A review of the literature found that higher buprenorphine doses (over 12 mg/day) are associated with better retention in treatment than lower doses of buprenorphine (Fareed et al, 2012). Other research has demonstrated that buprenorphine at dosages higher than 24 mg have not been demonstrated to provide any clinical advantage, either for detoxification or maintenance (Kleber, 2007). However, even at this dosage, Buprenorphine may not suppress all symptoms of withdrawal if the patient had a very severe habit (Lintzeris, Bell, Bammer, et al., 2002). Following the detoxification stage, many patients are gradually tapered to an effective maintenance dosage or complete cessation. It is not recommended that patients are abruptly withdrawn from buprenorphine, as studies have shown that patients may experience significant withdrawal symptoms after abrupt stopping (Lopatko, White, Huber, et al., 2003). Numerous studies have documented the effectiveness of buprenorphine for both detoxification and maintenance therapy. A recent systematic review compared buprenorphine to other detoxification strategies (Gowing, Ali, & White, 2006). Compared with clonidine, buprenorphine was found to be more effective in ameliorating withdrawal symptoms. In addition, patients treated with buprenorphine stayed in treatment longer, especially in outpatient settings. When compared with methadone-aided withdrawal, patients treated with buprenorphine experienced more rapid resolution of withdrawal symptoms, but there was no significant difference in treatment completion, or severity of withdrawal.

When used as recommended, buprenorphine is generally well-tolerated and patients experience very few serious side effects. However, like other opioids, buprenorphine can produce several uncomfortable side effects such as constipation, headache, nausea and vomiting, and dizziness (Fudala et al. 2003; Ling et al. 2009). Because buprenorphine is metabolized by the liver, patients with liver disease will respond differently. For these patients, dosage adjustments should be made cautiously and liver function should be regularly monitored

(Kraus et al., 2011). Patients who are HIV positive and are taking antiretroviral medications, especially atazanavir (with and without ritonavir), should also be closely monitored when treated with buprenorphine since the medication interaction may prevent the buprenorphine from properly metabolizing, resulting in increased levels of opiates and sedation effects (<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=17b63f10-c9df-44be-80fa-6f1c305583b8#section-4>) There have been numerous reports of coma and death associated with concomitant use of buprenorphine and benzodiazepines. However, in the majority of these cases, buprenorphine was misused by self-injection. Studies have shown that the combination of buprenorphine and benzodiazepine increases the likelihood of respiratory depression. As such, buprenorphine should be prescribed with great caution to patients also being treated with benzodiazepines, and patients should be warned of the extreme danger of taking either medication in a non-prescribed format.

There are some populations for whom buprenorphine should be completely avoided, including pediatric patients and pregnant women. In the case of pediatric patients, the safety and efficacy of buprenorphine has not been established. And for pregnant women, naloxone is contraindicated, so it is particularly important to ensure that a woman who becomes pregnant while taking combination buprenorphine and naloxone is immediately switched to monotherapy buprenorphine or methadone.

### APPENDIX 3

## Detailed Medical Discussion of Naltrexone Prescribing Practices and Contraindications

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Naltrexone (in the oral and extended release formulations) is a long-acting pure opioid antagonist, the only one currently approved for the treatment of opioid-use disorders. As an opioid receptor antagonist, naltrexone binds to opioid receptors in the brain, blocking the receptors from activation by opioids or alcohol. Naltrexone also blocks the action of methadone and, in sufficiently high doses, overrides buprenorphine. Due to its method of acting, naltrexone will produce immediate opioid withdrawal in patients who have not abstained from short- and long-acting opioids for at least 7 to 10 days, respectively (O'Connor & Fiellin 2000). This can be very difficult for patients and the wait may promote withdrawal, relapse, and early dropout (Tetrault & Fiellin, 2012). Once detoxification has been accomplished and naltrexone is being taken at a stable dose, patients will simply not experience any euphoric effects from use of heroin and other opioids, removing the reward of taking such drugs (SAMHSA, 2012). Because naltrexone itself has no narcotic effect, there are no withdrawal symptoms and it does not have abuse potential. Research shows that tolerance for naltrexone's antagonist properties does not develop, even after many months of regular use (Kleber et al., 1985).

The clinical utility of naltrexone for maintenance treatment of opioid disorders has been not been established (Tai et al. 2001). Initiation onto the medication can be difficult for many patients due to the 7- to 10-day period of abstinence required prior to beginning naltrexone therapy and because the length of this duration may promote withdrawal, relapse, and early dropout (Tetrault & Fiellin, 2012). Dropout rates with naltrexone lessen when there exists powerful external motivation, such as with those who are facing the loss of an important job or with physicians for whom opioid use is impairing performance. For naltrexone taken orally, very close adherence is required because the medication's blocking action typically lasts no more than 24 to 48 hours. A missed dose may lead to a relapse, requiring a new detoxification and naltrexone induction. Behavioral treatments such as vouchers awarded for dose adherence and the involvement of family members in monitoring adherence have been shown to improve naltrexone adherence and treatment retention, in some cases doubling retention rates between 12 and 24 weeks. It is recommended that all doses be monitored by a family member or a health professional and that three times per week dosing in the amounts of 100 mg, 100 mg, and 150 mg be considered if daily monitoring is difficult to establish (Kleber, 2007). For patients who are deemed to be at risk of adhering to scheduled doses of naltrexone in the oral form, results of some research suggest that treatment with the extended-release formulation may increase treatment compliance (Baser et al., 2011; Fishman et al., 2010). However, results regarding treatment compliance with the extended-release formulation remain mixed, with other studies showing only poor to moderate compliance without incentives (DeFulio et al., 2012; Everly et al., 2011).

Oral naltrexone was developed in 1963 from the opioid agonist drug oxymorphone. It was approved by the FDA for use in treating opioid addiction in 1984 and for treating patients dependent on alcohol in 1995. When problems of compliance became evident in the early 1980s, the National Institute on Drug Abuse (NIDA) issued contracts to six separate research programs aimed at developing a long-acting version of naltrexone; as a result, extended-release

naltrexone was developed. The extended-release formulation was approved for treating alcohol dependence in 2006 and opioid dependence in 2010.

Naltrexone oral is sold under the trade names Trexan®, Revia® and Depade®. It is taken in pill form every one to three days in 50 to 150 mg tablets that block opioid effects for 24 up to 72 hours, respectively (O'Brien et al. 1975). The extended-release form of naltrexone is sold under the trade name of Vivitrol® and is administered monthly by gluteal intramuscular injection. Both oral and extended-release naltrexone can be prescribed by any healthcare provider licensed to prescribe medications and can be administered in physicians' offices, opioid treatment programs and other approved substance abuse programs.

Naltrexone in either formulation may benefit some patients when they are still in the beginning stages of opioid addiction, but the medication appears to be especially useful for highly motivated patients who have undergone detoxification from opioid use and need additional support to avoid relapse or desire a faster detoxification schedule. Studies have shown that very low doses (0.125 – 0.250 mg/dose) of oral naltrexone may diminish withdrawal symptoms in patients who are being tapered from long-term opioid therapy (Mannelli et al., 2006, 2009). Research suggests that despite the significantly higher cost of extended-release naltrexone, total healthcare costs are not significantly greater than for treatment with the oral form or with buprenorphine, and are significantly lower than for treatment with methadone (Baser, Chalk, Fiellin, & Gastfriend, D. R., 2011). Naltrexone is effective in preventing relapse when used as directed; however, because the medication does not ease cravings for illicit opioids and does not produce withdrawal symptoms when discontinued, poor compliance with long-term naltrexone therapy has been found for the oral formulation, with 70 to 80 percent dropout rates from naltrexone therapy reported (Stine et al., 2003). Retention rates are especially poor for patients receiving methadone treatment before oral naltrexone treatment (Adi et al., 2007; Sullivan et al., 2007; see review by Minozzi, Vecchi, Davoli, Kirchmayer, & Verster, 2011). Despite its promising potential, the relatively poor results relating to compliance and relapse have limited the clinical utility of naltrexone oral formulation for treatment of opioid addiction in the United States (Aklin et al., 2012; O'Connor & Fiellin, 2000).

The extended-release form of naltrexone has only been FDA-approved since 2010 and research on results is limited. There is some evidence that the extended-release form may partially ameliorate the problem of prescription persistence that affects the oral version and improve compliance with naltrexone therapy, as the medication remains active for 30 days with a single injection (Baser et al., 2011). However, recent studies of opiate-addicted adults have found poor to modest compliance to treatment with extended-release naltrexone (Everly et al., 2011; DeFulio et al., 2012), as well as to treatment with the oral formulation (Dunn et al., 2013), though for both the extended-treatment and oral formulation studies, treatment compliance was substantially higher when employment-based reinforcement incentives were made contingent on treatment. Compliance with treatment with extended-release naltrexone was much higher among opioid-dependent patients in a 24-week study conducted in Russia, where methadone and buprenorphine are not approved and where family members were recruited to help ensure compliance to therapy (Krupitsky et al., 2011).

Both the oral and extended-release formulations of naltrexone have been associated with patient deaths due to accidental overdoses of opioids while taking one or other of the medications (Diguisto, Shakeshaft, Ritter, O'Brien, & Mattick, 2004). In many cases, overdosing

may be due to the blocking effect of naltrexone, with relapsing patients taking large amounts of opioids to try to overcome the blockage (Substance Abuse and Mental Health Services Administration, 2009; Kleber, 2007). In addition, patients treated with extended-release naltrexone may have reduced tolerance to opioids and be unaware of their potential sensitivity to the same, or lower, doses that they used to take of opioids. For such patients who relapse after a period of abstinence, the dosages of opioids previously used may have life-threatening consequences, including respiratory arrest and circulatory collapse (Alkermes, Inc., 2010; Substance Abuse and Mental Health Services Administration, 2013). Patients undergoing naltrexone therapy should be clearly cautioned about these dangers.

Injection site reactions have been reported for extended-release naltrexone, including induration, cellulitis, abscess, hematoma, and necrosis, with some reactions requiring surgical intervention (Comer et al, 2006; Garbutt et al., 2005; Johnson, et al., 2004; Kranzler, Wesson, & Billot, 2004; Mitka, 2008). Treatment guidelines emphasize that extended-release naltrexone must be injected only intramuscularly and never intravenously, subcutaneously, or into fatty tissues, using the kit included with the medication (Substance Abuse and Mental Health Services Administration, 2013).

The side effects of naltrexone itself are similar and generally mild in both the oral and extended-release formulations. Patients taking oral naltrexone may experience mild stomach upset, though approximately 10 percent have gastrointestinal side effects that may require stopping the medication (Stine et al., 2003). The medication can also result in anxiety, nervousness, sleep problems, tiredness, joint or muscle pain, and headaches in some patients. Similar side effects of extended-release naltrexone have been reported, including nausea, vomiting, headache, fatigue, and muscle cramps (Onchen, Van Kirk, & Kranzler, 2001; see review by Lobmaier, Kornor, Kunoe, & Bjorndal, 2008), with these generally being mild to moderate (Hulse, Morris, Arnold-Reed, & Tait, 2009; Kunoe et al., 2009; Comer et al., 2006). See Table 3 for common side effects of naltrexone.

Contraindications of naltrexone include physiological dependence on opioids. Those currently physiologically dependent on opioids should be offered detoxification treatment or be referred to specialist services. Patients must have been fully withdrawn from all opioids before considering therapy with naltrexone. Other contraindications include acute hepatitis or liver failure, as naltrexone can be hepatotoxic in high doses. In view of its hepatotoxic effects, its use in patients with active liver disease must be carefully considered, with doses causing hepatic injury being at most fivefold of those that appear to be safe (TIP 49). Use of naltrexone for treatment of chronic pain requires specialist assessment (Bell et al., 2003) and is contraindicated in patients with a history of sensitivity to the medication, to structurally similar compounds such as naloxone or nalmefene, or to any inactive ingredients in the tablet. Naltrexone should be used with careful monitoring of patients with moderate to severe renal impairment as the medication and its active metabolite are excreted through the urine (SAMHSA, TIP 49).

**Table 3. Possible Side Effects of Naltrexone—Oral and Extended Release Injection**

<b>More Common</b>	<b>Less Common</b>
Nausea	Diarrhea, constipation, stomach pains, cramps
Vomiting	Chest pain, joint/muscle pain
Headache	Rash
Dizziness	Difficulty sleeping
Fatigue	Excessive thirst, loss of appetite
Nervousness	Sweating
Anxiety	Increased tears
Somnolence	Mild depression
	Delayed ejaculation

Reprinted from: SAMHSA, Center for Substance Abuse Treatment, 2009, *Incorporating alcohol pharmacotherapies Into medical practice (TIP 49)*, Chapter 4, oral naltrexone.

Naltrexone in both the oral and extended-release formulations has been shown to have various interactions with other medications. Lethargy and somnolence have been reported when naltrexone is used with chlorpromazine (Thorazine®) or thioridazine (Mellaril®), and caution should be taken when naltrexone is used with antipsychotic drugs. Patients who are taking yohimbine at the same time may experience anxiety, increased pulse, and elevated blood pressure (SAMHSA, Center for Substance Abuse Treatment, 2009). Patients taking naltrexone experience significant blockade of opioid effects from medications taken for analgesia. This blockade is present only when naltrexone is taken regularly and will cease 24 to 72 hours after the medication is discontinued (O'Connor & Fiellin, 2000). Cough/cold and antidiarrheal medications containing opioids may decrease the benefit of naltrexone, and patients may require a greater amount of opioid analgesics than usual, possibly resulting in deeper and more prolonged respiratory depression (Bell et al., 2003).

There is limited data on the use of naltrexone for the treatment of opioid dependency among adolescents. The results of one small study of the medication in the oral formulation indicated that naltrexone was well tolerated by adolescents seeking treatment for alcohol dependence (Deas, May, Randall, Johnson, & Anton, 2005). Another small study on treatment of opioid dependence among adolescents and young adults showed that extended-release naltrexone was well tolerated over a period of four months and was associated with good

outcomes (Fishman, Winstanley, Curran, Garrett, & Subramaniam, 2010). However, there is limited data on naltrexone's safety and effectiveness when used by adolescents, and additional research is needed before the medication can be recommended for wide use in the treatment of opioid use among this population. In particular, the safety and efficacy of extended-release injectable naltrexone have not been established for patients who are younger than age 18, and use for this population is not approved by the FDA (Substance Abuse and Mental Health Services Administration, 2013).

Research on the use of naltrexone with pregnant women also is limited, and caution is advised in prescribing the medication in either formulation to pregnant or breast-feeding women as naltrexone is classified as a B3 risk in pregnancy and its effects on the fetus are unknown. It is recommended that sexually active women of childbearing age being treated with naltrexone be counseled to use effective birth control methods. If a patient using the medication becomes pregnant, it is recommended that the patient and clinician decide whether to continue naltrexone therapy after discussing the risks and benefits of doing so (Substance Abuse and Mental Health Services Administration, 2009). Caution is also recommended in using naltrexone for patients currently on multiple drugs or with depression or other major psychiatric illness.

While there are no clear recommended guidelines for the duration of naltrexone therapy, 6 to 12 months is probably a minimum in most cases. Naltrexone can be stopped abruptly without withdrawal symptoms, but before discontinuing this medication, a careful clinical evaluation of the risk for relapse should be conducted (Kleber, 2007).



## APPENDIX 4

### Review Protocol – Pharmacotherapies Effectiveness Literature Review

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#### ***Background***

Recent survey data show that over 4 million US residents either initiated use or were dependent on opioids (including illegal opioids and non-medical use of prescription opioids) in 2011 (Substance Abuse and Mental Health Services Administration, 2012); rates of current use, moreover, appear to be increasing (Compton & Volkow, 2006) and are associated with more overdose fatalities (Hall et al., 2008) and visits to emergency departments (Substance Abuse and Mental Health Services Administration, 2006). Patients and practitioners seek better treatments but counselor and patient reluctance to use medication-assisted treatments and weak linkages with medical care lead to an underutilization of pharmacotherapy.

Growing understanding and acceptance of substance use disorders (SUD) as chronic and relapsing but treatable medical disorders has facilitated advances in the use of pharmacotherapies as part of comprehensive treatment of SUDs. In the last 5 years in the published literature, SUDs have been compared to other medical conditions such as diabetes, hypertension, and asthma which have both physiological and behavioral components (Dennis & Scott, 2007; McLellan et al., 2000). Like these chronic conditions, while many SUDs cannot be cured, SUDs can be treated and maintained with medication which interrupts the cycle of addiction and, if used as a component of comprehensive treatment that includes other clinical services, enables patients to increase their functioning, gain some control over their addiction, and engage in therapeutic recovery.

The use of medications in treating opioid dependence is not completely new. Methadone, for example, has been used with success for the treatment of opioid addiction for more than half a century (Substance Abuse and Mental Health Services Administration, 2011). An array of new medications is currently available for alcohol/opioid treatment which help curb cravings, suppress withdrawal symptoms, and some which prevent the rewarding effects of substances (i.e., buprenorphine, buprenorphine plus naloxone, methadone, naltrexone, and naltrexone XR). In addition, there is evidence in the literature of large medical cost offsets for patients receiving medications particularly with regard to reduced use of inpatient hospitalization for detox and treatment (Baser, Chalk, Rawson, & Gastfriend, 2011) as well as reduced visits to ERs (Bryson, McConnell, Korthius, & McCarty, 2011). However, in spite of the evidence of the positive outcomes associated with the use of medications as a component of treatment, the acceptance of addiction medications as an evidence-based practice, and the societal and monetary benefit of pharmacotherapies, there remains a severe lack of medications usage.

## ***Objectives***

The objective for this systematic review is to gather, evaluate, and summarize empirical research on the effectiveness of pharmacotherapies (e.g., methadone, buprenorphine, buprenorphine plus naloxone, naltrexone, extended release naltrexone) in the treatment of opioid disorders.

## ***Methods***

A systematic literature review will be conducted by searching electronic bibliographic databases (e.g., PsychINFO and PubMed). A predefined set of search terms will be created and tested to ensure the most inclusive and most relevant search results. Citations within published articles will also be reviewed and evaluated for inclusion.

## ***Search Criteria***

In the PsychINFO data base, we will use the terms effectiveness, substance use or abuse, addiction in conjunction with the terms methadone, buprenorphine, buprenorphine + naloxone, naltrexone, extended release naltrexone with some search modifications by medication (see Table 1 for additional detail). Searches will include all fields (e.g., titles, abstracts, texts, etc.) and results will focus on journal articles. A similar set of searches will be conducted in PubMed. Finally, references in all articles and reports found through these search criteria (regardless of type article) will be reviewed to find any additional studies not previously identified in the searches.

Table 1. Matrix of anticipated searches concerning the effectiveness of pharmacotherapies in the treatment of opioid dependence

	Search								
	1	2	3	4	5	6	7	8	9
<b>Search Terms</b>	METHADONE	detoxification	opiates	(opiate\$ or opioid\$ or heroin\$ or narcot\$ or prescript\$)	(substance abuse or substance use or addiction)	(effect, effective &/or effectiveness)	(1 & 2) and (3 & 4)	(5 & 7)	(6 & 8)
<b>Search Terms</b>	METHADONE	maintenance	opiates	(opiate\$ or opioid\$ or heroin\$ or narcot\$ or prescript\$)	(substance abuse or substance use or addiction)	(effect, effective &/or effectiveness)	(1 & 2) and (3 & 4)	(5 & 7)	(6 & 8)
<b>Search Terms</b>	BUPRENORPHINE	detoxification	opiates	(opiate\$ or opioid\$ or heroin\$ or narcot\$ or prescript\$)	(substance abuse or substance use or addiction)	(effect, effective &/or effectiveness)	(1 & 2) and (3 & 4)	(5 & 7)	(6 & 8)
<b>Search Terms</b>	BUPRENORPHINE	maintenance	opiates	(opiate\$ or opioid\$ or heroin\$ or narcot\$ or prescript\$)	(substance abuse or substance use or addiction)	(effect, effective &/or effectiveness)	(1 & 2) and (3 & 4)	(5 & 7)	(6 & 8)
<b>Search Terms</b>	BUPRENORPHINE + NALOXONE	detoxification	opiates	(opiate\$ or opioid\$ or heroin\$ or narcot\$ or prescript\$)	(substance abuse or substance use or addiction)	(effect, effective &/or effectiveness)	(1 & 2) and (3 & 4)	(5 & 7)	(6 & 8)
<b>Search Terms</b>	BUPRENORPHINE + NALOXONE	maintenance	opiates	(opiate\$ or opioid\$ or heroin\$ or narcot\$ or prescript\$)	(substance abuse or substance use or addiction)	(effect, effective &/or effectiveness)	(1 & 2) and (3 & 4)	(5 & 7)	(6 & 8)
<b>Search Terms</b>	NALTREXONE (oral)	detoxification	opiates	(opiate\$ or opioid\$ or heroin\$ or narcot\$ or prescript\$)	(substance abuse or substance use or addiction)	(effect, effective &/or effectiveness)	(1 & 2) and (3 & 4)	(5 & 7)	(6 & 8)

				prescript\$)					
<b>Search Terms</b>	NALTREXONE (oral)	maintenance	opioids	(opiate\$ or opioid\$ or heroin\$ or narcot\$ or prescript\$)	(substance abuse or substance use or addiction)	(effect, effective &/or effectiveness)	(1 & 2) and (3 & 4)	(5 & 7)	(6 & 8)
<b>Search Terms</b>	NALTREXONE (extended release)	maintenance	opioids	(opiate\$ or opioid\$ or heroin\$ or narcot\$ or prescript\$)	(substance abuse or substance use or addiction)	(effect, effective &/or effectiveness)	(1 & 2) and (3 & 4)	(5 & 7)	(6 & 8)
<b>Search Terms</b>	NALTREXONE (extended release)	maintenance	opioids	(opiate\$ or opioid\$ or heroin\$ or narcot\$ or prescript\$)	(substance abuse or substance use or addiction)	(effect, effective &/or effectiveness)	(1 & 2) and (3 & 4)	(5 & 7)	(6 & 8)

### ***Inclusion Criteria***

We will include all articles and reports in which the stated objectives of the research pertain to any sort of attempt to evaluate the effectiveness of our target medications (methadone, buprenorphine, buprenorphine plus naloxone, naltrexone, naltrexone XR) used to treat opioid addiction.

A target medication could be considered effective if its outcome measures display an improvement over those of a clinically comparable group. The most common outcome measures used in medication effectiveness studies are reductions in use or abstinence, but other outcome measures (see Effectiveness Review Outline) will be included if there is a distinct difference between an experimental group and a matched comparison group.

We will *exclude* non-empirical articles; specifically, we will exclude literature reviews and commentary (however, we will use these articles to search for additional empirical studies not previously discovered in searches outlined above). Dr. Alanis-Hirsch will perform pre-screening of titles and abstracts identified from the searches and will exclude any irrelevant articles. One other team member will review the titles and abstracts of articles determined to be ineligible to ensure agreement on the determination.

Other exclusions include studies of off-label use of the target medications and use of the target medications for conditions other than opioid addiction.

The review will be limited to the years 2008-2013, a period just over five years.

### ***Coding***

We will construct a database of articles which includes the following fields and codes created to: (1) track the methods used to locate the studies; (2) identify the scope and objectives of the studies; (3) categorize the nature and quality of the studies; and (4) classify the findings from the studies. All coding will be conducted by Dr. Alanis-Hirsch, and a random sample of ten articles/reports will be coded by another team member.

**Identifier:** Numeric unique identifier for each published and unpublished report.

**First Author:** Text field containing the last name and initials for the first author (in APA format).

**Authors Total:** Total number of authors including the first author.

**Publication Year:** Four-digit year of publication or dissemination date if unpublished.

**Title:** Text field containing the title of the article/report (APA format).

**Source:** Numeric field indicating the source of the article/report:

- 1=PsychINFO (only)
- 2=PubMed (only)
- 3=References in previously identified materials (only)
- 4=Online (only)
- 5=Other source (only)
- 6=Multiple sources

**Source Describe:** Text field describing the source if Other or Multiple sources indicated in Source

**Medication:** Numeric field indicating the type of medication investigated

- 1=Methadone (only)
- 2=Buprenorphine (only)
- 3=Buprenorphine plus naloxone (only)
- 3=Naltrexone (only)
- 4=Naltrexone XR (only)
- 5=Other (only)
- 6=Multiple

**Medication Describe:** Text field describing the medication(s) studied if Other or Multiple indicated in Medication.

**Outcome Variables:** Numeric field indicating the type of outcome measure reported.

- 1=Dropouts: number of participants abandoning treatment
- 2=Use of opiate during treatment: Number of participants with opiate positive urinalysis during treatment
- 3=Use of opiate at follow-up after treatment: number of participants with opiate positive urinalysis during the treatment
- 4=Compliance: clinic absences during the treatment
- 5=Engagement in further treatment: engaging in further treatment such as 12-step group participation
- 6=Use of other drugs
- 7=Psychosocial improvements: number of participants experiencing improvements in family relationships, social difficulties, employment
- 8=Other

**Outcome Describe:** Text field describing the outcome measure if Other is indicated in outcome variables.

**Manuscript Type:** Numeric field indicating the type of manuscript:

- 1=Journal article
- 2=Unpublished report
- 3=Online resource
- 4=Other

**Journal:** Text field containing the name of the journal in which the article was published (this field should be blank for all types of manuscripts other than journals).

**Study Design:** Numeric field indicating the design of empirical study conducted. Our coding scheme will be based on the Scientific Methods Scale of Sherman et al. (1997; 2002) which was also employed by Welsh and Farrington (2000) and McDougall et al. (2008). This hierarchical scale is scored from 1, low, to 5, high, and its core criteria are as follows:

- 1=Reporting of a correlation coefficient denoting the strength of the relationship between, for example, a particular sentencing option and its effectiveness at preventing re-offending at a given point in time.
- 2=Reporting of a comparison group present but this might lack comparability to the target group. Alternatively, where no comparison group is present, before and after measures, of, for example, offending behavior have been obtained for the target group.
- 3=Reporting of a controlled experimental design with comparable target and control groups present, for example, one group of offenders sentenced to imprisonment with a particular treatment intervention and a comparable group of offenders sentenced to imprisonment only, with pre-post comparisons being made and experimental-control comparisons on (a) specific variable/s.
- 4=Reporting of a controlled experimental design, as in 3 above, but with additional controlling for other variables that might pose a threat to the interpretation of results. Examples of controlling extraneous variables may include, but are not limited to, the use of statistical procedures or matching of individuals.
- 5=Reporting of a fully randomized experimental design in which target and control groups consist of randomly assigned individuals and appropriate measures are taken to test for the effects of the sentencing option.
- 6=Other

**Study Type Describe:** Text field describing the design for *Other* types of studies to include non-randomized study methods.

**Objectives:** Text field summarizing objectives of the manuscript.

**Sample Characteristics:** Text field describing age, sex, ethnicity/racial, number of individuals studied.

**Data Type:** Numeric field indicating the source of data:

- 1=Self report (only)
- 2=Biological (only)
- 3=Chart review (only)
- 4=Billing records (only)
- 5=Collateral report (only)
- 7=Other (only)
- 8=Multiple

**Data Type Describe:** Text field describing the type of data if *Other* or *Multiple* indicated in Data Type.

*Statistical Procedures and Conventions*

The results of the review will be discussed and a narrative summary of the findings will be presented



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## PART 2

# **Economic Evaluation of Pharmacotherapies for the Treatment of Opioid Disorders: A Systematic Review**

This review was developed with support from the American Society of Addiction Medicine and the National Institute on Drug Addiction

## Executive Summary

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**Aims:** Substance use disorders, in general, and opioid dependence, in particular, are prevalent and costly. Effective medications are available to treat opioid dependence, but they are underutilized, in part due to economic considerations. We undertook a systematic evaluation of the cost-effectiveness, cost-offset and cost-utility literature relevant to three FDA-approved opioid dependence treatment medications to help decision makers determine whether medications for the treatment of opioid disorders might add sufficient value to justify their costs. The three medications reviewed were: methadone, buprenorphine (Subutex® and Suboxone®) and, naltrexone (Revia® and Vivitrol®).

**Methods:** A comprehensive and systematic literature search following Campbell Collaboration guidelines was conducted of all research articles published in English on these three medications, with no time period stipulations. From this larger search, the present report extracted, evaluated and summarized all articles and reports in which the stated objectives of the research pertained to any evaluation of the effectiveness of medications used to treat opioid addiction in relation to costs associated with using them. We excluded non-empirical articles; such as commentaries. Included studies were coded to identify their scope and objectives, categorize the nature and quality of the studies, and summarize findings from those studies.

**Results:** Our search strategy located 362 unique articles/reports pertaining to economic evaluations of medications for opioid dependence. Although no Cochrane or Campbell Reviews were found, our search located four relatively recent systematic reviews pertaining to economic evaluations of various medications for opioid dependence, all published in 2006 or 2007.

In summary, methadone maintenance treatment ranges in costs from just over \$6,000 per year to over \$12,000 per year depending upon the nature and frequency of counseling and social services provided. Various studies have seen clinically and statistically significant reductions in opioid use and opioid use-related incidence of infectious diseases and crimes with averted costs ranging from two to four times the costs of methadone per year. There are few enduring clinical benefits from methadone detoxification and thus very low cost-effectiveness or cost-offset from this short term treatment.

Far fewer cost-effectiveness studies have thus far been completed on buprenorphine. In general buprenorphine-naloxone (Suboxone) medication costs are approximately five times more than methadone (~\$3.50 - \$5.00 per dose versus ~\$0.50 - \$1.50 per dose); the administration costs are approximately comparable though in very different settings (dedicated methadone clinic versus office setting) and the clinical effects on reductions of opioid use and opioid use-related health and social problems are quite comparable. An Australian Treatment Outcome Study (ATOS; Ross et al., 2003; Shanahan et al., 2003) showed that two-year opioid abstinence rates were projected to cost \$5,000 in Australian dollars (AUD) for either buprenorphine or methadone maintenance, \$11,000 AUD for residential rehabilitation and \$52,000 AUD for prison.

Still fewer economic evaluations of oral or, particularly, injectable naltrexone have been completed. There is no doubt about the clinical effectiveness of naltrexone in eliminating opioid

use but very poor patient retention rates for the oral medication and high costs of the injectable medication compromise definitive economic conclusions about this medication at this time.

This review has been hampered by lack of standard clinical outcome measures and evaluation time points (during or following treatment). Many studies in this field have attempted to make contact with the cost-effectiveness literature from the broader healthcare field using Quality Adjusted Life Years (QALY) as a primary measure; but it is not clear that this is an appropriate or desirable indication of clinical or economic value in the opioid dependence field.

**Conclusions:** Three conclusions are possible from this review:

1. The three pharmacotherapies have all shown clear clinical evidence of effectiveness in reducing opioid use and opioid use-related symptoms of withdrawal and craving as well as risk of infectious diseases and crime – during the time of active medication but not following medication cessation.
2. Methadone medication costs are the least expensive (\$30 - \$40 per monthly dose) but can only be administered in a licensed methadone maintenance clinic. Buprenorphine-naloxone medication costs are next most expensive of the three (\$140 - \$160 per monthly dose) and can be administered by specially trained generalist physicians in a range of clinical settings. Oral naltrexone is also inexpensive (~\$60 per monthly dose) but patient retention has been problematic making outcome estimations less reliable. Injectable, extended release naltrexone is only recently available, is much more expensive (~\$700 per monthly dose) and shows the potential for sustained retention of patients (IMS, 2010).
3. All three medications are underutilized in the treatment of opioid addiction (McGovern et al., 2004; Knudsen et al., 2011; Abraham et al., 2013).

## Introduction and Background

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### **Measures of Effectiveness**

Prior to a review of the effectiveness and cost-effectiveness of these medications it is important to establish some primary outcomes that represent realistic expectations of each medication. For many decades it was thought that withdrawal was the major and perhaps only driving force maintaining abuse and addiction; and in turn, that once that withdrawal had been effectively managed, there should be no driving force to maintain continued drug seeking. It is now known that the processes by which irregular, voluntary, euphoria-driven opioid “use” becomes regular, compulsive, withdrawal-avoiding “addiction” are many, varied and still only partially understood. Suffice it to say for this report that mechanisms of gene expression, prolonged changes in brain function in the areas of cognition, motivation and inhibition; and a myriad of changes in social and family relationships are just some of the many direct and indirect sequelae of opioid addiction that result from prior opioid use but also promote future use. In this regard, none of the medications discussed here can be considered an effective treatment for opioid dependence by itself – all medications are expected to be used as part of more comprehensive treatment strategies that usually include counseling, social supports and behavioral change strategies. With this as background, we now suggest four key outcomes that are expectable from an “effective” medication to treat opioid addiction – at least during the active course of medication.

**Withdrawal Symptoms:** Persistent, intensive, high-frequency use of opioids is reliably associated with many physical, emotional and social problems. Some of these problems (e.g. withdrawal, craving, constipation, etc.) are a rapid and direct consequence of the opioid use; and in turn, it is reasonable to expect that effective opioid treatment medications should be able to reduce or eliminate these direct physiological symptoms and thereby lead to physiological stabilization and relatively normal function. Withdrawal and craving have been reliably measured by several standard questionnaires and by recording of physiological signs.

**Patient Retention:** Because each of the medications is considered part of a more comprehensive treatment strategy one of the expectations of “effective” pharmacotherapy for opioid dependence is that patients should find problematic symptom relief from the prescribed medication and thus should engage in and remain actively participating in the rest of the available constellation of therapeutic components of comprehensive care. Patient retention is typically measured as a function of the proportion of intended patient visits actually attended in a fixed time period (e.g. past 30 days).

**Reduction of Opioid Use:** The cardinal measure of effectiveness for any opioid addiction treatment medication has been reduction of opioid use, typically measured by urine drug screening and self-report. The presumed mechanisms by which this expected outcome should occur differ for the medications discussed (reduction of withdrawal and craving symptoms, prevention of euphoric effect, etc.) but all are expected to produce significant reductions in frequency and amount of opioid use.

**Reduction of Opioid-Related Health and Social Problems:** As indicated, there are typically a constellation of health and social problems associated with prolonged opioid use. Some of these are directly and proximally associated with the opioid use, such as the health

risks of infectious diseases (HIV, Hepatitis, TB) associated with unsafe injection and needle sharing. Some other related problems are indirectly and distally related to opioid use such as return to or initiation of employment, reduction or elimination of criminal acts, improved mood and physical health, and improved family and social relationships. These important and highly desirable outcomes typically require a combination of reduced opioid use as well as the acquisition or re-acquisition of new behavioral patterns. Most of these outcomes are measured by self-report but most can be validated (pay stubs, crime records).

### ***State of extant research on the effectiveness of these therapies***

Numerous studies have examined the efficacy and effectiveness of these medications, particularly methadone. So many, in fact, that the Drug and Alcohol group in the Cochrane Collaboration has published 14 systematic reviews on various aspects of medication-assisted treatment for opioid addiction, covering several different populations. Taken together, these systematic reviews provide strong evidence for the effectiveness of methadone maintenance in reducing withdrawal and craving for opioids, retaining patient participation in treatment, reducing opioid use and use-related risk of infectious disease during the course of the medication (Faggiano et al., 2003; Mattick et al., 2009) – but not following termination of the medication, as through detoxification. The evidence is more variable regarding the effectiveness of methadone in reducing non-opioid drug use or improving employment; due largely to variations in the patient population studied and the clinical approach of the treatment program.

Buprenorphine has only been available for prescription since 2000 and thus there are fewer studies. Nonetheless, the available literature suggests virtually identical clinical outcomes (Amato et al., 2011; Gowing et al., 2011; Mattick et al., 2008). This is interesting because while buprenorphine has many of the same pharmacological properties as methadone, it has been available in private office and general clinical medical settings, and thus has reached a much different population of opioid dependent patients. Again, buprenorphine has been shown to be effective in reducing withdrawal and craving for opioids, retaining patient participation in treatment, and reducing opioid use and use-related risk of infectious disease during the course of the medication (Faggiano et al., 2003; Mattick et al., 2009) – but not following termination of the medication. As with methadone, the literature is quite mixed with regard to reducing non-opioid drug use, improving employment and reducing crime.

There has been much less effectiveness research with oral naltrexone and even less with extended release injectable naltrexone (Lobmaier et al., 2008; Minozzi et al., 2011). Oral naltrexone can only be prescribed following opioid detoxification so relief of withdrawal symptoms is not a meaningful outcome. Both forms of naltrexone essentially eliminate opioid use, but again this reduction of use does not reliably extend following termination of the medication. Oral naltrexone has not been effective in retaining patients, drop-out rates have been greater than 50% in most studies and usually within one month of prescription initiation. The extended release, injectable form of naltrexone has only been approved since 2010 but there is indication of much better patient retention: more than 50% of patients prescribed one 30-day injection return for additional injections. The few studies of this form of naltrexone do not yet provide clear evidence for improvement in addiction-related health and social problems. Future studies are needed to collect data on a broader range of health outcomes and from heterogeneous practice settings (Amato et al., 2005).

### ***The usefulness of economic evaluations***

Despite strong evidence that all three of these pharmacotherapies are effective in reducing opioid use and in some additional addiction-related problems, use of these medications in substance abuse treatment in the US remains modest at best (Ducharme et al., 2006; SAMHSA, 2011; Knudsen et al., 2011). This may be due in part to the costs of medications themselves, to the required medical care necessary to support proper prescribing, and/or to inadequate clinical value added to justify these costs. Thus, economic evaluation is a technique that can aid decision makers to determine whether medications for the treatment of opioid addiction add sufficient value to justify their costs (French & Drummond, 2005; O'Brien., 1995). Formally, an economic evaluation refers to the comparative analysis of alternative clinical courses of action in terms of both their costs and consequences (Drummond et al., 1997). There are different types of economic evaluations that generally fall into categories of cost-effectiveness and cost-benefit analysis.

### ***Cost Analysis***

An essential aspect of both cost-effectiveness and cost-benefit research is cost-analysis (Drummond et al., 1997). Ideally, cost-analyses not only provide monetary estimates of the direct and indirect costs of a particular intervention under study, but also information on the amount of resources (e.g., labor, facility, supplies) used in providing the intervention. The latter information is often used to identify critical cost components of the intervention and to assess whether costs are affected by changes in key assumptions (Bray & Zarkin, 2006). In addition to being the first step in a cost-effectiveness and cost-benefit analysis, cost studies can also be used to compare the relative costs of one intervention or medication to another or to monetize savings from implementing a particular intervention.

In general, cost data can be collected from a number of different viewpoints (e.g. costs to patient, costs to a health system, costs to a government or non-government payer, or overall social costs) (Drummond et. al 1997, Gold et al. 1996). The societal perspective is understandably the broadest perspective and counts all expended resources regardless of who is responsible for bearing the cost. Approaches to measuring costs can also vary along a spectrum of specificity. Micro-costing involves a detailed inventory and measurement of resources used while gross-costing involves the use of estimates. For example, the cost of an intervention using micro-costing measures the individual costs of each treatment component in an intervention, while gross-costing it might use the average total cost of a treatment episode or visit (Luce et al., 1996).

### ***Cost-effectiveness analysis***

According to Gold et al. (1996), cost-effectiveness analysis involves estimating the ratio of the difference in costs between two alternatives (net costs) divided by the difference in the health outcomes (net effectiveness). It is essentially the incremental price of obtaining a unit health effect (e.g. 10% reduction in days of opioid use in the past month) from a given health intervention (e.g. counseling plus methadone) when compared to an alternative (e.g. counseling alone). Costs for interventions are estimated in monetary units, such as the dollar. The effect of the intervention can be any clinical or policy-relevant outcome that is collected for all interventions under consideration.

A variant of cost-effectiveness analysis is cost-utility analysis in which the effects of the intervention are expressed as 'utilities'. The best known utility measure is the 'quality adjusted life year' or QALY. QALYs assign a quality-of life weight to each additional year of life generated by a treatment, with a weight of 1.0 indicating perfect health and a weight of 0 indicating death. In this case, competing interventions are compared in terms of cost per utility (cost per QALY).

When the intervention under study is both more effective and less costly than the alternative, it is said to dominate the alternative. When this occurs, there is no need to calculate a cost-effectiveness ratio. Cost-effectiveness ratios are useful, however, when the intervention under study is both more effective but also more costly than the alternative; or when an intervention is less effective but also less costly than the alternative (Gold et al, 1996).

The decision about whether an intervention is cost-effective is often influenced by the values of different intervention stakeholders, however, some attempts have been made to provide guidelines for standardizing recommendations about cost-effectiveness. For example, interventions that produce a QALY for \$50,000 or less in the US are considered a bargain, whereas those that require \$100,000 or more are considered unaffordable. There has been substantial debate among economists and policy makers about the fairness and impartiality of this general rule (Braithwaite et al., 2008; Hirth et al., 2000; Ubel et al., 2003; Laufer, 2005; Murray et al., 2000). Also in the case of addiction research, there is question whether the QALY is an appropriate or attractive measure at all.

### ***Cost-benefit analysis***

In contrast to cost-effectiveness analysis, cost-benefit analysis converts all outcomes to a monetary equivalent (Drummond et al., 1997). As a result, the dollar value of the benefits of the intervention can be directly compared with the dollar value of the intervention's costs. Two common methods for comparing benefits and costs include calculating net benefits (costs are subtracted from benefits) and benefit-cost ratios (benefits are expressed as a percent of program costs). A related type of analysis is the cost-offset analysis in which future costs or cost-savings are examined. Because cost-benefit analyses combine multiple outcomes into a single measure and allow direct comparison of costs to benefits, they often provide clearer guidance than cost-effectiveness analyses on which treatment programs should be adopted - namely, those programs whose benefits exceed their costs. Cost-effectiveness analyses can provide a ranking of competing alternatives but not information on the extrinsic value any single intervention independent of the alternatives (Bray & Zarkin, 2006).

### ***Economic modeling studies***

Economic evaluations can be carried out within a variety of different study designs - clinical trials, prospective cohort studies, database studies, as well as decision-analytical modeling. Decision-analytical modeling has been widely used in the investigation cost-effectiveness in healthcare, and although modeling might be low in validity due to limited capacity of simulating the manifold complexities of the real world, it remains an important and essential aspect of economic evaluation (Xin, 2000). Part of the reason why decision-analytic modeling techniques are so prevalent is due to the many benefits that these techniques can provide: extending the results of clinical trials to project cost-effectiveness for longer follow-up

periods, extrapolating intermediate clinical endpoints to final outcomes, and simulating head-to-head comparative effectiveness of treatments when the treatments themselves have been tested in separate trials (Xin, 2000; Briggs and Schulpher, 1998).

***Purpose and scope of this review***

Given the scope and magnitude of the problems associated with opioid dependence, and evidence for the effectiveness of medications for it, the objective of this study was to systematically gather, evaluate, and summarize empirical research on the cost-effectiveness of pharmacotherapies (e.g., methadone, buprenorphine, naltrexone) in the treatment of opioid addiction to guide healthcare payers and policy makers in decisions about expanding the use of these medications. In addition to summarizing the literature and key findings, the review also offers comment on the quality of the economic evaluations conducted to date with suggestions for future research to strengthen this literature and fill critical gaps.



## Methods

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This review was conducted by searching electronic bibliographic databases (e.g., PsychINFO and PubMed) using search terms and established selection criteria as well as by reviewing citations in published studies. In addition to searching electronic databases for published reports, we followed Campbell Collaboration guidelines and searched for unpublished reports and international publications using web-based search engines (e.g., Google and Google Scholar). Examination of the extant reviews conducted by the Cochrane Alcohol and Drug Group revealed that no systematic reviews had been done by this group pertaining to the cost-effectiveness of pharmacotherapies for the treatment of opioid addiction. Further, no protocols for this type of review have been registered. The Campbell Collaboration does not have a coordinating group for alcohol and drugs, so a key word search was conducted to determine whether any reviews or protocols in the Campbell library contained the term “cost”. This search resulted in two reviews, neither pertaining to opioid addiction.

Abstracts and reports from web-based searches were reviewed for preliminary inclusion, and a random sample of the abstracts were re-viewed by another reviewer to ensure that all potentially relevant studies were coded and analyzed. Details regarding our search and inclusion criteria as well as our coding and analytic procedures are provided below. The review protocol can be found in the appendices (see Appendix 5).

### ***Search criteria***

In the PsychINFO data base, we used the terms cost-benefit, cost-effectiveness, and cost-offset in conjunction with terms methadone, buprenorphine, and naltrexone, which resulted in a total of nine distinct searches. All searches looked for specified terms in all fields (e.g., title, abstract, text, etc.), and limited results to journal articles. This approach was used to maximize the number of articles and reports retrieved, and no publication date limits were applied to the searches. Another nine searches using similar criteria were conducted in PubMed. In addition to these databases, we also conducted similar searches in Google and Google Scholar. Finally, references in prominent literature reviews were examined to find any additional studies not previously identified in the aforementioned searches.

### ***Inclusion criteria***

We included all articles and reports in which the stated objectives of the research pertained to any evaluation of the effectiveness of medications used to treat opioid addiction in relation to costs associated with using them. We *excluded* non-empirical articles such as commentaries (however, we did use these articles to search for additional empirical studies not previously discovered in searches outlined above). One member of the research team carried out pre-screening of titles and abstracts identified from the database searches; while another, independent member of the team reviewed the titles and abstracts of a random 10% of articles to ensure that hardcopies of all possible articles and reports were included for coding.

### ***Coding and data analysis***

We constructed a database to: (1) track the methods used to locate the studies; (2) identify the scope and objectives of the studies; (3) categorize the nature and quality of the studies; and (4) classify the findings from the studies. Regarding the scope and objectives, we coded characteristics of the sample being studied, the type of medication being investigated, and the type of economic evaluation conducted. For the purposes of coding the type of economic evaluation employed, we used a hierarchical coding scheme used by McDougall and colleagues (2008) to categorize different types of economic information collected in which cost-studies were anchored at the bottom and complete cost-benefit studies were set at the top.

Regarding the nature and quality of studies, we created a numeric field to capture key features of the effectiveness component of the study. Our coding scheme was based on the Scientific Methods Scale of Sherman et al. (1997; 2002). This hierarchical scale was scored from 1-5. At the lower end of the scale, a value of 1 indicated a correlational study and, at the highest end of the scale, a value of 5 indicated a fully randomized experimental design in which appropriate measures were taken to test for the effects of the intervention. To capture the key characteristics of the economic evaluation, we coded salient features of the costing, modeling, and analytic techniques employed using guidelines for authors and peer-reviewers of economic evaluations submitted to the British Medical Journal (Drummond & Jefferson, 1996). The source of data used in the study was coded as were details on the types of outcomes studied, how they were measured, and what was found about them. We also coded author-noted study limitations and “key” findings. Frequencies examined the distribution of categorical variables and content analysis was performed to identify patterns and differences among coded studies.

## Results

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### **Search Results**

The nine PsychINFO searches netted a total 112 unique articles to be reviewed for preliminary eligibility; the nine PubMed searches netted a total 121 unique articles. The search engine Google Scholar was also used. Because these searches were not limited to journal articles, they turned up many more results (typically 10,000 hits or more). Results from these searches were sorted according to relevance and only the first 10 pages of results were reviewed. These searches netted an additional 92 unique and previously unidentified articles/reports (most of these were literature reviews or reports summarizing findings from others' empirical work). Finally, bibliographies from prominent literature reviews published on the cost-effectiveness of medications for the treatment of opioid disorders were reviewed in order to ensure that no other published or unpublished reports had been missed. This process netted an additional 37 unique and previously identified reports.

In total, our search strategy located 362 unique articles/reports pertaining to economic evaluations of medications for opioid dependence.

### **Included Articles/Reports**

Of the 362 articles/reports located, only 36% (n=130) were flagged as preliminarily eligible for coding and analysis. Those considered *ineligible* were; literature reviews or commentaries about published empirical studies 31% (n=111), lacking sufficient econometrics 16% (n=58), or lacked sufficient effectiveness components 8% (n=30). Thirty-three other articles (9%) were excluded for other reasons, including only looking at MAT for alcohol abuse/dependence, examining opioid MAT medications for pain, using non-human subjects, being a case study, or being published in a non-English language journal (see **Figure 1**). Inter-rater agreement on these inclusion/exclusion decisions was validated by comparison of independent ratings of a 10% sample of flagged articles (78% agreement).

As noted above, no Cochrane or Campbell systematic reviews were conducted on the cost-effectiveness of pharmacotherapies for the treatment of opioid addiction. However, our literature search located four relatively recent and comprehensive "systematic" reviews of economic evaluations of medications for opioid dependence (Adi et al., 2007; Connock et al., 2007; Doran, 2007; Simoens et al., 2006). A summary of the findings from these four reviews is provided below (a table highlighting key aspects of these systematic reviews is included in the appendices--see **Appendix 1**).

### **Summary and critique of prior systematic reviews**

The objectives of the systematic reviews by Simoens et al. (2006) and Doran et al. (2007) were: to review, synthesize, and appraise the evidence on economic evaluations of treatment for opioid addiction. The primary difference between these two reviews, however, was that the Doran review looked more broadly at economic evaluations of "interventions for illicit opioid dependence" and the review by Simoens and colleagues looked more narrowly at studies of the pharmaco-economics of community maintenance for opioid dependence. The Connock et al. (2007) review focused specifically on methadone and buprenorphine. However, in

addition to including a review of extant economic evaluations, this work also included a systematic review of the clinical effectiveness literature and a decision tree with Monte Carlo simulation model to assess the cost-effectiveness of methadone and buprenorphine maintenance therapies. The Adi et al. (2007) review was primarily a systematic review of the effectiveness of oral naltrexone and an economic simulation study based on those findings from that review. However, the author did attempt to locate existing economic evaluations of oral naltrexone and found none (Adi et al., 2007, p. xii).

In terms of review quality, the Doran review cast the widest net in terms of search strategy (no language or publication year limits were applied to the searches), but the Simoens review, although focusing just on studies published between 1995 and 2005, employed more search terms and involved more databases. All contained some sort of exclusionary criteria for studies that did not examine treatments for opioid dependence, and the Simoens and Connock reviews excluded studies that did not compare one treatment to another. These two reviews were also clearer about how they appraised the quality of the economic evaluation methods used. Despite identifying several hundreds of articles and reports, the Connock review analyzed 11 studies and the Simoens review analyzed 18 studies. The Doran review considered findings from 24 studies examining the costs and effectiveness of pharmacotherapies were summarized. A total of six studies were included in the reviews by Doran, Simoens, and Connock and another nine studies were included in at least two of these reviews, suggesting a good deal of overlap in the studies examined.

Simoens and colleagues concluded that there was sufficient evidence of the pharmacoeconomic value of methadone and that cost-benefit studies from community maintenance programs showed net benefits. Connock and colleagues noted that no studies assessing the cost-effectiveness of buprenorphine maintenance compared with no treatment. Both the Simoens and Connock reviews commented on studies comparing methadone and buprenorphine. Simoens et al. (2006) concluded that “findings on the cost-effectiveness/cost-utility of buprenorphine as compared with methadone are inconclusive” (p.38).

All of these systematic reviews noted limitations of studies examining economic aspects of treatment for opioid addiction, including restricted range of costs and consequences considered, failing to identify the sub-groups of subjects or the clinical conditions within the studied programs. Many studies failed to consider the impact of program factors (setting, providers, provision of additional medical and psychosocial services) on the economic value of treatment programs. Finally, most of the research was restricted to studies done within North-America. Connock et al. (2007) concluded that, although the studies they examined were considered to be of high quality, “none used all of the appropriate parameters, effectiveness data, perspectives and comparators required to make their results generalizable to the NHS [National Health Services] and PSS [Personal Social Services] context” (p.37).

### ***Summary of characteristics and findings from economic evaluations published after 2006***

Given the quality and comprehensiveness of these reviews and that they were all published around 2007, we excluded all articles and reports for coding that were published prior to 2007 (n=108). An additional two articles published after 2007 were found to contain insufficient effectiveness components to be considered either cost-effectiveness or cost-benefit

studies and were also excluded. **Table 1** displays, 20 articles and two of these (Adi et al., 2007; Connock et al., 2007) were comprehensive systematic reviews of economic evaluations. The majority of the studies were economic evaluations of methadone. A total of four studies (Bell et al., 2007; Kaur et al., 2008; Polsky et al., 2010; Schackman et al., 2012) were economic evaluations of buprenorphine (monotherapy or buprenorphine-naloxone combination therapy), and only one examined oral naltrexone (Adi et al., 2007). Four studies conducted economic evaluations comparing multiple types of medications for opioid dependence (Connock et al., 2007; Geitona et al., 2012; Moore et al., 2007; Ruger et al., 2012). The majority of studies (55%) were economic evaluations of methadone and half (50%) were published in the past 2 years. Approximately 35% of the studies were conducted in North American and 20% in South East Asia. All employed cost-effectiveness techniques and over half (55%) could be characterized as cost-utility analyses. Approximately 40% of the studies employed analytic decision models and simulation techniques, and 20% were randomized controlled trials. Characteristics and findings from these studies are summarized below by type of medication studied.

### ***Characteristics and findings from methadone studies***

A total of 11 studies examined the pharmaco-economics of methadone maintenance therapy (MMT). Most (n=7) were published in 2011 or 2012; and most were done in North America (n=4) or Southeast Asia (n=3). All studies were cost-effectiveness studies, with the majority (n=7) implementing cost-utility analyses. Nearly half (n=5) implemented decision analytic designs and simulation modeling, and only one implemented a randomized controlled trial (RCT). Four of the studies examined the cost-effectiveness of MMT or MMT versus other sorts of treatment, five studies examined the cost-effectiveness of MMT as an HIV prevention and treatment strategy, and two examined ways to increase the cost-effectiveness of MMT. **Table 2** (pg. 80) summarizes the characteristics and key findings from these studies

**Table 1. Summary of Studies Conducted after 2006 by Medication Type (N=20)**

	Total (N=20)		Methadone (N=11)		Buprenorphine (N=4)		Naltrexone (N=1)		Multiple* (N=4)	
	n	%	n	%	n	%	n	%	n	%
<b>Year Published</b>										
2012	9	45.0	6	54.5	1	25.0	0	0.0	2	50.0
2011	1	5.0	1	9.1	0	0.0	0	0.0	0	0.0
2010	3	15.0	2	18.2	1	25.0	0	0.0	0	0.0
2009	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2008	2	10.0	1	9.1	1	25.0	0	0.0	0	0.0
2007	5	25.0	1	9.1	1	25.0	1	100.0	2	50.0
<b>Geographic Region Represented</b>										
Asia	1	5.0	1	9.1	0	0.0	0	0.0	0	0.0
Europe	3	15.0	2	18.2	0	0.0	0	0.0	1	25.0
North America	7	35.0	4	36.4	3	75.0	0	0.0	0	0.0
South East Asia	4	20.0	3	27.3	0	0.0	0	0.0	1	25.0
South Pacific	2	10.0	0	0.0	1	25.0	0	0.0	1	25.0
Global	3	15.0	1	9.1	0	0.0	1	100.0	1	25.0
<b>Type of Economic Evaluation</b>										
Cost-Effectiveness	9	45.0	4	36.4	2	50.0	0	0.0	3	75.0
Cost-Utility	11	55.0	7	63.6	2	50.0	1	100.0	1	25.0
Cost-Benefit	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
<b>Study Design</b>										
Descriptive/Correlational	2	10.0	1	9.1	1	25.0	0	0.0	0	0.0
Quasi-experimental	5	25.0	3	27.3	0	0.0	0	0.0	2	50.0
Experimental	1	5.0	1	9.1	0	0.0	0	0.0	0	0.0
Randomized Trial	4	20.0	1	9.1	2	50.0	0	0.0	1	25.0
Modeling Study	8	40.0	6	54.5	1	25.0	1	100.0	1	25.0

\*One study examined methadone or buprenorphine, another study compared methadone and buprenorphine monotherapy to buprenorphine-naloxone combination therapy, another studied buprenorphine, naloxone, and placebo, and the other compared methadone, buprenorphine, and no treatment.

### **Cost-effectiveness studies**

Of the four studies published after 2006, only one study (Vanagas et al., 2010) was a simple prospective, cost-effectiveness study of MMT. This is likely due to the wealth of research already pointing to the cost-effectiveness of MMT (Connock et al., 2007; Doran, 2007; Simoens et al., 2006). In this study, 3- and 6-month follow-up assessments showed that MMT significantly improved components of quality of life (QoL) in the 102 opiate dependent patients recruited into the study. However, these authors found that MMT was not as cost-effective in Lithuania as other studies have found it to be, although the authors note that no threshold value of acceptable cost-utility rates has been established in Lithuania.

Three studies compared the cost-effectiveness of MMT to other treatments for opioid dependence. Nosyk et al. (2012) constructed a decision-analytic, semi-Markov cohort model to compare the cost-effectiveness of diacetylmorphine (medically prescribed heroin) to MMT for opioid dependence refractory to treatment using data from the North American Opiate Medication Initiative (Oviedo-Joekes et al., 2009). These authors found that diacetylmorphine dominated over methadone in each of the time horizons analyzed (1-, 5-, 10-year and lifetime). Over the lifetime horizon, people receiving methadone gained 7.46 discounted QALYs and generated a societal cost of \$1.14 million while those who received diacetylmorphine gained 7.92 discounted QALYs and generated a societal cost of \$1.10 million.

Stephen et al. (2011) developed an analytic model to compare the cost-effectiveness of MMT and deep brain stimulation (DBS). These authors found that a trial of DBS was less expensive (\$81,000) than untreated (or relapsed) heroin dependence (\$100,000), but more expensive than MMT (\$58,000) and concluded that a theoretical course of DBS would need a success rate of 36.5% to match MMT and a success rate of 49% to be more cost-effective.

Basu et al., (2008) examined the social costs of robbery using fixed-effects negative binomial regression to examine incidence rate reductions (IRR) in armed robbery for different treatment modalities studied (hospital short-term inpatient, residential short-term inpatient, residential, long-term inpatient, outpatient MMT, outpatient non-MMT) using the National Treatment Improvement Evaluation Study (NTIES) data (Gerstein et al., 1997) and published data on willingness to pay to avoid robbery (Cohen et al., 2004). These authors found that treatment modalities were associated with large and statistically significant reductions in robbery; the average number of self-reported robberies declined from 0.83/client/year pre-entry to 0.12/client/year following SAT ( $p < 0.001$ ). Additionally, these authors also found that under worst-case assumptions, monetized valuations of reductions in armed robbery associated with outpatient methadone and residential SAT exceeded economic costs of these interventions.

**Table 2. Characteristics and Key Findings of Economic Evaluations of Methadone for Treatment of Opioid Dependence (N=11)**

Studies	Objective	Design	Participants	Key Findings
<i>Cost-effectiveness and Comparative Cost-Effectiveness Studies (n=4)</i>				
Vanagas et al., 2010 (Lithuania)	<ul style="list-style-type: none"> <li>To analyze the cost-utility of six-month methadone maintenance treatment program in a Lithuanian primary health care setting.</li> </ul>	<ul style="list-style-type: none"> <li>Prospective design collecting data at baseline, 3- and 6-month follow-ups using the WHO QOL-BREF and the DATCAP.</li> </ul>	<ul style="list-style-type: none"> <li>102 opioid dependent individuals enrolled in outpatient MMT clinics within primary care settings in Lithuania.</li> </ul>	<ul style="list-style-type: none"> <li>Results highlighted that 6-month methadone maintenance program was effective in terms of QoL improvement with WHO QOL-BREF measures, but the program was less effective in terms of cost per QALY;</li> <li>Cost per QALY was 34,368 EUR.</li> </ul>
Nosyk et al., 2012 (Canada)	<ul style="list-style-type: none"> <li>To compared the cost-effectiveness of diacetylmorphine (heroin) and MMT for chronic opioid dependence refractory to treatment.</li> </ul>	<ul style="list-style-type: none"> <li>A decision analytic, semi-Markov cohort model was used;</li> <li>Incremental cost-effectiveness ratios (interpreted as incremental cost per QALY gained) were calculated to compare diacetylmorphine and methadone over 1-, 5-, 10-year and lifetime horizons.</li> </ul>	<ul style="list-style-type: none"> <li>Parameters and outcomes were extrapolated from the North American Opiate Medication Initiative trial (Oviedo-Joekes et al., 2009) and supplemented with administrative data for the province of British Columbia.</li> </ul>	<ul style="list-style-type: none"> <li>Diacetylmorphine was found to be a dominant strategy over MMT in each of the time horizons;</li> <li>Over a lifetime horizon, people receiving methadone gained 7.46 discounted QALYs and generated a societal cost of \$1.14 million while those who received Diacetylmorphine gained 7.92 discounted QALYs and generated a societal cost of \$1.10 million.</li> </ul>
Stephen et al., 2012	<ul style="list-style-type: none"> <li>To determine the threshold at which a theoretical course of deep brain stimulation (DBS) would provide the same quality of life (QoL) and cost-effectiveness for heroin dependence as methadone maintenance treatment (MMT).</li> </ul>	<ul style="list-style-type: none"> <li>A decision analytical model was developed to estimate and compare costs and outcomes of MMT and DBS for heroin dependence.</li> <li>The model projected costs and quality-adjusted life years (QALYs) during a 6-month course of treatment.</li> <li>Data for the model were derived from a critical review of published reports.</li> </ul>	<ul style="list-style-type: none"> <li>An aggregate of 1191 patients from 15 trials administering 6 months of MMT and 2937 patients from 45 trials of DBS for movement disorders.</li> </ul>	<ul style="list-style-type: none"> <li>Sixty-six per cent of patients completed MMT, but only 47% of them had opiate-free urine samples, resulting in an average QoL of 0.7148 (0.3574 QALYs over 6 months).</li> <li>A trial of DBS is less expensive (\$81 000) than untreated (or relapsed) heroin dependence (\$100 000), but more expensive than MMT (\$58 000).</li> <li>A theoretical course of DBS would need a success rate of 36.5% to match MMT, but a success rate of 49% to be cost-effective.</li> </ul>
Basu et al., 2008 (USA)	<ul style="list-style-type: none"> <li>To examined pre-post differences in self-reported robbery among clients in five residential and outpatient SAT modalities (hospital short-term inpatient, residential short-term inpatient, residential; longterm inpatient, outpatient MMT, outpatient non-MMT).</li> </ul>	<ul style="list-style-type: none"> <li>Secondary data analysis using fixed-effects negative binomial regression to examine incidence rate reductions (IRR) in armed robbery. Published data on willingness to pay to avoid robbery were used to determine the social valuation of these effects.</li> </ul>	<ul style="list-style-type: none"> <li>Client outcome and treatment cost data from the National Treatment Improvement Evaluation Study (NTIES; Gerstein et al., 1997).</li> </ul>	<ul style="list-style-type: none"> <li>All SAT modalities were associated with large and statistically significant reductions in robbery. The average number of self-reported robberies declined from 0.83/client/year pre-entry to 0.12/client/year following SAT (p&lt;0.001);</li> <li>Under worst-case assumptions, monetized valuations of reductions in armed robbery associated with outpatient methadone and residential SAT exceeded economic costs of these interventions.</li> </ul>
				<b>Table continues...</b>



Table 2. (Continued)				
Studies	Objective	Design	Participants	Key Findings
<i>Cost-effectiveness MMT as an HIV prevention and treatment strategy (n=5)</i>				
Xing et al., 2012 (China)	<ul style="list-style-type: none"> <li>To analyze the cost and cost-effectiveness of methadone maintenance treatment (MMT) to prevent the spread of HIV in Dehong prefecture, Yunnan province, China.</li> </ul>	<ul style="list-style-type: none"> <li>Cost-effectiveness analyses of MMT were conducted using patient outcomes and process data retrospectively collected between July 2005 to December 2007;</li> <li>Estimates of the number of HIV infections prevented were calculated using incidence rates from cohort studies and retrospective studies.</li> </ul>	<ul style="list-style-type: none"> <li>1257 injection drug users in 5 MMT clinics in 5 counties representing 6.28% of all registered drug users.</li> </ul>	<ul style="list-style-type: none"> <li>The cost for each participant treated in MMT clinics was about \$9.1-16.7/month;</li> <li>MMT averted 8.4-87.2 HIV infections with a cost-effectiveness of \$2509.3-\$4609.3 per HIV infection averted, suggesting that it is a cost-effective intervention for reducing HIV transmission among injection drug users.</li> </ul>
Wammes et al., 2012 (Indonesia)	<ul style="list-style-type: none"> <li>To examine the costs and cost-effectiveness of expanding MMT in Indonesia from a societal perspective.</li> </ul>	<ul style="list-style-type: none"> <li>The Asian Epidemic Model (AEM) and Resource Needs Model (RNM) were used to evaluate the long-term population-level preventive impact of MMT in West Java;</li> <li>Intervention costs and the number of incident HIV cases in the intervention scenario were compared with current practice to establish the cost per infection averted by expanding MMT.</li> </ul>	<ul style="list-style-type: none"> <li>Population parameters were based on the AEM for West Java Province.</li> </ul>	<ul style="list-style-type: none"> <li>Expanding MMT from 5% coverage to 40% coverage in 2019 would avert approximately 2400 HIV infections, at a cost of approximately US\$7000 per HIV infection averted;</li> <li>Use of alternative assumptions did not change the finding that expanding MMT is cost-effective.</li> </ul>
Alistar et al., 2011 (Ukraine)	<ul style="list-style-type: none"> <li>To estimate the effectiveness and cost-effectiveness of strategies for expanding MMT and ART in mixed HIV epidemics using the Ukraine as a case study.</li> </ul>	<ul style="list-style-type: none"> <li>A dynamic compartmental model of the HIV epidemic in a population of non-IDUs, IDUs using opiates, and IDUs on methadone substitution therapy, stratified by HIV status was developed;</li> <li>Interventions expanding methadone substitution therapy, increasing access to ART, or both were considered;</li> <li>Health care costs, quality-adjusted life years (QALYs), HIV prevalence, infections averted, and incremental cost-effectiveness were examined.</li> </ul>	<ul style="list-style-type: none"> <li>The model was parameterized using Ukraine country-level data and calibrated against current HIV trends in Ukraine.</li> </ul>	<ul style="list-style-type: none"> <li>Without incremental interventions, HIV prevalence reached 67.2% (IDUs) and 0.88% (non-IDUs) after 20 years.</li> <li>Offering MMT to 25% of IDUs reduced prevalence most effectively (to 53.1% IDUs, 0.80% non-IDUs), and was most cost-effective, averting 4,700 infections and adding 76,000 QALYs compared with no intervention at US\$530/QALY gained.</li> </ul>
Tran et al., 2012a (Vietnam)	<ul style="list-style-type: none"> <li>To evaluate the incremental cost-effectiveness of MMT for HIV-positive drug users in Vietnam from the perspective of health service providers.</li> </ul>	<ul style="list-style-type: none"> <li>Patients were assessed at baseline, three, six and nine months;</li> <li>Quality-adjusted life years (QALYs) were modeled from changes in health-related quality of life of patients using the modified World Health Organization Quality of Life Brief Version (WHOQOL-BREF);</li> <li>Costs of MMT services were analyzed and converted to the year 2009.</li> </ul>	<ul style="list-style-type: none"> <li>370 HIV-positive drug users from 6 MMT clinics across several districts in Vietnam.</li> </ul>	<ul style="list-style-type: none"> <li>Over 9 months, MMT substantially improved QALYs of HIV/AIDS patients (0.076 QALY [0.066-0.084]);</li> <li>For one QALY gained, the MMT program would cost US\$3745.3, approximately 3.2 times Vietnam GDP per capita in 2009, an incremental cost effectiveness ratio indicating cost-effectiveness based on thresholds established in developed countries and used by the World Health Organization (WHO).</li> </ul>
Tran et al., 2012b (Vietnam)	<ul style="list-style-type: none"> <li>To evaluate the cost-effectiveness of integrating methadone maintenance treatment (MMT) with antiretroviral treatment (ART) for HIV-positive drug users in Vietnam.</li> </ul>	<ul style="list-style-type: none"> <li>A decision analytical model was developed to compare cost effectiveness (quantified in QALYs) and incremental cost effectiveness of three HIV/AIDS treatment strategies: (1) only ART, (2) providing ART and MMT in separated sites (ART-MMT), and (3) integrating ART and MMT with direct administration (DAART-MMT);</li> <li>The model was parameterized using empirical data on costs and outcomes extracted from the MMT and ART cohort studies in Vietnam, and international published sources.</li> <li>Probabilistic sensitivity analysis was conducted to examine the model's robustness.</li> </ul>	<ul style="list-style-type: none"> <li>Patient outcome data from MMT and ART cohort studies (see Tran et al., 2012c).</li> </ul>	<ul style="list-style-type: none"> <li>Compared to the ART strategy, providing MMT for HIV-positive drug users in either stand-alone sites or in an integrated model, such as DAART-MMT, incurred higher costs but significantly better outcomes;</li> <li>The incremental cost-effectiveness ratio for DAART-MMT and ART-MMT versus ART strategy was 569.4 and 1227.8, approximately 0.51 and 1.10 times GDP per capita/QALY indicating that providing MMT along with ART for HIV positive drug users is a cost-effective intervention in Vietnam.</li> </ul>
				Table continues...

Table 2. (Continued)				
Studies	Objective	Design	Participants	Key Findings
<i>Improving the cost-effectiveness of MMT (n=2)</i>				
Barnett et al., 2010 (USA)	<ul style="list-style-type: none"> <li>To identify the cost of compliance with treatment guidelines, whether these costs are offset by a decrease in other health care costs, and the impact of guideline concordance on mortality and other outcomes.</li> </ul>	<ul style="list-style-type: none"> <li>Prospective design whereby program staff were surveyed and consenting new patients from highly concordant (n=164) and less-concordant Veterans Affairs (VA) MMT programs (n= 91) were assessed at baseline and 6- and 12-month after enrollment to determine costs.</li> </ul>	<ul style="list-style-type: none"> <li>255 clients participating in the Medical Opiate Substitution Treatment Study (MOST; Humpreys et al., 2008; Trafton et al., 2007).</li> </ul>	<ul style="list-style-type: none"> <li>Treatment at highly staffed, guideline concordant sites cost \$10,252, which is significantly more than the \$6,476 cost at less-concordant programs;</li> <li>Opioid substitution therapy was effective at reducing heroin use, especially at sites that were highly concordant with treatment guidelines;</li> <li>Annual mortality was 3.0% and did not differ by type of care;</li> <li>Preference-based quality of life significantly improved only at highly concordant sites.</li> </ul>
Sindelar et al., 2007 (USA)	<ul style="list-style-type: none"> <li>To determine if prize-based contingency management (CM), which has been shown to improve treatment outcomes over usual care (UC) MMT alone, is cost-effective.</li> </ul>	<ul style="list-style-type: none"> <li>Cost-effectiveness analyses of a randomized controlled trial (RCT) of prize-based CM using patient outcomes and resource utilization data;</li> <li>Cost data collected from clinics participating in the effectiveness study.</li> </ul>	<ul style="list-style-type: none"> <li>Six methadone maintenance community clinics participating in the NIDA Clinical Trials Network (CTN). The study sample consisted of 388 participants: 190 in the UC MMT condition and 198 in the CM condition (see Peirce et al., 2006).</li> </ul>	<ul style="list-style-type: none"> <li>Compared to UC MMT, the incremental cost of using prize-based CM to lengthen the longest duration of abstinence by 1 week was \$141;</li> <li>The incremental cost to obtain an additional stimulant-negative urine sample was \$70.</li> </ul>

### **Cost-effectiveness MMT as an HIV prevention and treatment strategy**

Five of the economic evaluations published after 2006 examined the cost-effectiveness of MMT as an HIV prevention and treatment strategy among opiate-dependent injection drug users: one in China (Xing et al., 2012), one in Indonesia (Wammes et al., 2012), and one in the Ukraine (Alistar et al., 2011). In their pre-post comparison group study in China, Xing et al. (2012) found that the cost for each participant treated in MMT clinics was about \$9.1-16.7/month and the intervention averted 8.4-87.2 HIV infections with a cost-effectiveness of \$2,509 - \$4,609 per HIV infection averted.

Wammes et al. (2012) used the Asian Epidemic Model (AEM) and Resource Needs Model (RNM) to evaluate the long-term population-level preventative impact of MMT in West Java and found that expanding MMT from 5% coverage in 2012 to 40% coverage in 2019 would avert approximately 2400 HIV infections, at a cost of approximately US \$7,000 each, making it very cost-effective by WHO standards (Laufer, 2005; Murray et al., 2000; WHO, 2003). In their study, Alistar et al., (2012) developed a dynamic compartmental model of the HIV epidemic in a population of non-IDUs, IDUs using opiates, and IDUs on methadone substitution therapy, stratified by HIV status, and populated it with data from the Ukraine. When considering interventions aimed at expanding MMT, increasing access to anti-retroviral therapy (ART), or both, they concluded that MMT was a highly cost-effective option for the growing mixed HIV epidemic in Ukraine and that a strategy expanding both MMT and ART was very cost-effective by World Health Organization (WHO) criteria.

Two studies conducted in Vietnam examined the cost-effectiveness of MMT to improve outcomes among HIV-positive opioid-dependent individuals. In one study, Tran and colleagues (2012a) evaluated the incremental cost-effectiveness of MMT for HIV-positive drug users in Vietnam from the perspective of health service providers. These authors found that, over nine months, MMT substantially improved QALYs of HIV/AIDS patients (0.076 QALY); for one QALY

gained, the MMT program would cost US \$3,745, approximately 3.2 times Vietnam GDP per capita in 2009, indicating cost-effectiveness based on WHO criteria. In a related study examining the cost-effectiveness of integrating MMT with ART for HIV-positive drug users in Vietnam, Tran et al., (2012b) found that, compared to the ART strategy, providing MMT for HIV-positive drug users in either stand-alone sites or in an integrated model, such as MMT with direct-administration ART (DAART-MMT), incurred higher costs but significantly better outcomes. Base-case analysis showed that the cost-effectiveness ratio of ART, DAART-MMT, and ART–MMT strategies was US \$1,358, \$1,118, and \$1,327 per QALY respectively; equivalent to 1.22, 1.00, and 1.19 times GDP per capita in Vietnam.

### ***Improving the cost-effectiveness of MMT***

The remaining two MMT cost-effectiveness studies published after 2006 examined the cost-effectiveness of interventions to increase the cost-effectiveness of MMT. In their study, Barnett et al., (2010) examined compliance with MMT treatment guidelines, whether these costs associated with compliance were offset by a decrease in other health care costs, and the impact of guideline concordance on mortality and other outcomes (Humphreys et al., 2008; Trafton et al., 2007). These authors found that treatment at highly staffed and guideline-concordant sites cost \$10,252, which is significantly more than the \$6,476 cost at less-concordant programs. However, they also found that opioid substitution therapy was more effective at reducing heroin use at sites that were highly concordant with treatment guidelines. Annual mortality was 3.0%, not different based on level of guideline concordance, but quality of life measures were more improved at highly concordant sites.

Sindelar et al., (2007) conducted a cost-effectiveness analysis of prize-based contingency-management (CM) using data from a RCT assigning participants to MMT and a condition in which those in MMT whose random urine drug screens were negative drew from a prize bowl (Peirce et al., 2006). These authors found that the incremental cost of using prize-based CM to lengthen the longest duration of abstinence by 1 week was \$141, and the incremental cost to obtain an additional stimulant-negative urine sample was \$70.

In summary, a total of 11 studies were published on the pharmaco-economics of methadone maintenance therapy (MMT) since 2006. Although the focus of these studies differed, on the whole, they provided further evidence for the effectiveness and cost-effectiveness of methadone for the reducing opioid use but not non-opioid use. Several of these studies examined the cost-effectiveness of methadone as an HIV prevention and treatment strategy and all showed that MMT is cost-effective at reducing new infections and lowering costs among drug users with HIV. Research on interventions to increase the cost-effectiveness of MMT is emerging, but more research is needed in this area.

### ***Characteristics and findings from buprenorphine and naltrexone studies***

**Table 3** (page 85) highlights the characteristics and key findings from economic evaluations that examined buprenorphine (n=4), naltrexone (n=1), and multiple medications simultaneously (n=4). One study examined methadone or buprenorphine (Moore et al., 2007), another study compared methadone and buprenorphine monotherapy to buprenorphine-naloxone (bup/nx) combination therapy (Geitona et al., 2012), another studied buprenorphine,

naltrexone, and placebo (Ruger et al., 2012), and the final study compared methadone, buprenorphine, and no treatment (Connock et al., 2007).

**Table 3. Characteristics and Key Findings of Economic Evaluations of Buprenorphine, Naloxone, and Multiple Medications (N=9)**

Studies	Objective	Design	Participants	Key Findings
<i>Buprenorphine Naloxone (bup/nx) Studies (n=4)</i>				
Kaur et al., 2008 (USA)	<ul style="list-style-type: none"> <li>To determine: (1) the length and cost of therapy with oral buprenorphine-naloxone (bup-nx), and (2) the cost avoidance for opioid dependence as measured by opioid utilization and opioid drug cost obtained from pharmacy claim records.</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective analysis of claims data from a New Jersey managed care organization with pharmacy benefits;</li> <li>Outcome measures included the number of opioid pharmacy claims, daily dose, days supply, and cost defined as opioid ingredient cost. Member cost share and net plan cost (after subtraction of member cost share) were also measured.</li> </ul>	<ul style="list-style-type: none"> <li>Participants (N=84) were continuously enrolled from 10/11/2004-9/30/2006, (b) had their first bup/nx pharmacy claim during the fixed 6-month initiation period (4/1/2005, through 9/30/2005), and (c) had at least 1 opioid pharmacy claim in the 6-month pre-period preceding the 6-month initiation period.</li> </ul>	<ul style="list-style-type: none"> <li>Utilization of opioids decreased by 18.8%, from 1.49 opioid pharmacy claims per patient per month (PPPM) in the pre period to 1.21 claims PPPM in the post period (P = 0.031);</li> <li>Excluding the cost of the buprenorphine-naloxone, actual opioid drug cost decreased 66.5% from \$213.74 PPPM pre period to \$71.65 PPPM post period (P = 0.047).</li> </ul>
Schackman et al., 2012 (USA)	<ul style="list-style-type: none"> <li>To evaluate the cost-effectiveness of longterm office-based bup/nx treatment for clinically stable opioid-dependent patients compared to no treatment.</li> </ul>	<ul style="list-style-type: none"> <li>A decision analytic model was developed to simulate a hypothetical cohort of clinically stable opioid-dependent individuals using data from a cohort study that collected treatment retention, opioid use, and treatment costs, and available data on quality-of-life (QoL) weights.</li> </ul>	<ul style="list-style-type: none"> <li>Clinically stable opioid-dependent patients who completed 6 months of office-based bup/nx treatment (N=53; see Fiellin et al., 2006)</li> </ul>	<ul style="list-style-type: none"> <li>Office-based bup/nx had a CE ratio of \$35,100/QALY compared to no treatment after 24 months, with 64% probability of being &lt;\$100,000/QALY in probabilistic sensitivity analysis;</li> <li>With a 50% bup/nx price reduction the CE ratio is \$23,000/QALY with 69% probability of being &lt;\$100,000/QALY.</li> </ul>
Polsky et al., 2010 (USA)	<ul style="list-style-type: none"> <li>To estimate cost, net social cost and cost-effectiveness in a clinical trial of extended bup-nx treatment versus brief detoxification treatment in opioid-dependent youth.</li> </ul>	<ul style="list-style-type: none"> <li>Randomized control trial of youth randomly assigned to 12 weeks of bup/nx or a 14-day bup/nx taper (detox);</li> <li>Outcome measures included opioid-free urines and the patient's quality of life and social consequences related to addiction and its treatment;</li> <li>Costs were evaluated from a variety of perspectives and calculated by summing across units of service and their unit prices.</li> </ul>	<ul style="list-style-type: none"> <li>152 youth (15-21) recruited from six community-based outpatient substance abuse treatment programs between July 2003 and December 2006.</li> </ul>	<ul style="list-style-type: none"> <li>The cost-effectiveness ratio of bup/nx relative to detox was \$1,376 in terms of 1-year direct medical cost per QALY and \$25,049 in terms of outpatient treatment program cost per QALY;</li> <li>The acceptability curve suggests that the cost-effectiveness ratio of bup/nx relative to detox has an 86% chance of being accepted as cost-effective for a threshold of \$100,000 per QALY.</li> </ul>
Bell et al., 2007 (Australia)	<ul style="list-style-type: none"> <li>To compare the effectiveness and cost-effectiveness of unobserved vs observed dosing of patients seeking treatment of heroin dependence.</li> </ul>	<ul style="list-style-type: none"> <li>Participants were randomly assigned to observed or unobserved bup/nx dosing for 3 months.</li> <li>Primary outcomes were retention in treatment and heroin use at 3 months. Costs of treatment were measured (in Australian dollars, AU\$) and cost effectiveness.</li> <li>Secondary outcomes included quality of life, psychological symptoms and use of non-opioid drugs.</li> </ul>	<ul style="list-style-type: none"> <li>Participants were 119 heroin users seeking treatment at specialist outpatient drug treatment centers in Australia.</li> </ul>	<ul style="list-style-type: none"> <li>Reductions in days of heroin use in the preceding month, from baseline to 3 months, did not differ significantly; 18.5 days and 22.0 days, respectively.</li> <li>The mean cost for the unobserved group was AU \$1,663 per treatment episode, significantly less than the mean cost for the observed group at AU \$2,138;</li> <li>Treatment with close clinical monitoring, but no observation of dosing, was significantly cheaper and therefore significantly more cost-effective.</li> </ul>
<i>Naltrexone (Oral) Studies (n=1)</i>				
Adi et al., 2007	<ul style="list-style-type: none"> <li>To investigate the cost-effectiveness of naltrexone for relapse prevention in detoxified formerly opioid-dependent individuals.</li> </ul>	<ul style="list-style-type: none"> <li>De novo cost-utility analysis using a decision analytic model and a Monte Carlo simulation to compare naltrexone and an adjunctive therapy to no naltrexone;</li> <li>The model estimates costs, from the perspective of the UK NHS and Personal Social Services (PSS), and outcomes in terms of QALYs for 12 months for both strategies.</li> </ul>	<ul style="list-style-type: none"> <li>Parameter estimates came from published empirical studies examining the effectiveness of naltrexone.</li> </ul>	<ul style="list-style-type: none"> <li>Naltrexone with psychosocial therapy is more expensive but more effective than placebo with psychosocial therapy alone, giving an incremental cost-effectiveness ratio (ICER) of £42,500 per QALY gained.</li> <li>Serious concerns over interpretation of the results were raised based on this model because of its extreme sensitivity to the smallest changes in the parameter values, which are in themselves highly uncertain due to little research on this topic.</li> </ul>
				Table continues...

Table 3. (Continued)				
Studies	Objective	Design	Participants	Key Findings
<i>Multiple Medication Studies (n=4)</i>				
Moore et al., 2007 (Australia)	<ul style="list-style-type: none"> <li>To compare the costs and consequences of three interventions for reducing heroin dependency: pharmacotherapy (methadone or buprenorphine) maintenance, residential rehabilitation and prison.</li> </ul>	<ul style="list-style-type: none"> <li>Cost-consequence analysis providing disaggregated results and outcomes to costs ratios using data from the Australian Outcomes Study.</li> </ul>	<ul style="list-style-type: none"> <li>Parameters were drawn from the Australian Treatment Outcome Study (ATOS) conducted between 2001 and 2003 across three states of Australia--Victoria, New South Wales and South Australia (see Ross et al., 2003; Shanahan et al., 2003)</li> </ul>	<ul style="list-style-type: none"> <li>If post-program abstinence rates are sustained for 2 years, then for an average heroin user, the cost of averting a year of heroin use is approximately AUD \$5,000 for pharmacotherapy maintenance, AUD\$11,000 for residential rehabilitation and AUD\$52,000 for prison. A hybrid model of pharmacotherapy and prison would be the most cost-effective.</li> </ul>
Connock et al., 2007	<ul style="list-style-type: none"> <li>To assess the cost-effectiveness of methadone maintenance therapy (MMT) or buprenorphine maintenance therapy (BMT) compared with alternative therapies or no treatment for opioid dependence.</li> </ul>	<ul style="list-style-type: none"> <li>A decision tree with Monte Carlo simulation was used to assess the cost-effectiveness of BMT compared with MMT or no treatment; The model was designed to estimate costs, from the perspective of the NHS and PSS, and outcomes in terms of QALYs for 12 months for the three strategies.</li> </ul>	<ul style="list-style-type: none"> <li>Parameter estimates were drawn from a systematic review of the literature and utilities from the the Peninsula Technology Assessment Group (PenTAG).</li> </ul>	<ul style="list-style-type: none"> <li>Both MMT and BMT were found to cost-effective strategies compared with no drug therapy; Although MMT was dominant in comparison with BMT from the perspectives of both the NHS/PSS and society (inclusion of the CIS costs), the difference in QALYs was very small.</li> </ul>
Geitona et al., 2012 (Greece)	<ul style="list-style-type: none"> <li>To evaluate the outcomes and costs associated with opioid substitution therapies (OSTs) in Greece.</li> </ul>	<ul style="list-style-type: none"> <li>Cost-minimization analyses and cost-effectiveness analyses were performed to compare methadone and buprenorphine monotherapy with buprenorphine-naloxone (bup-nx); A budget-impact analysis was carried out to estimate the potential economic savings that could be gained from the expansion of OST programmes in Greece.</li> </ul>	<ul style="list-style-type: none"> <li>The study population was drawn from OKANA and included all the 4,046 opioid users participating in OST programmes; of these, 2,138 were treated with methadone and 1,908 with buprenorphine (data for 2008).</li> </ul>	<ul style="list-style-type: none"> <li>Analyses of cost effectiveness demonstrated that bup-nx was the dominant therapy in terms of mortality avoidance and completion of treatment; Compared with methadone, bup-nx reduced the mean cost by 49%, raised the percentage of participants who completed their treatment, and reduced the percentage of deaths; Budget impact analysis demonstrated that switching to buprenorphine-naloxone treatment would result in significant savings, cut the length of waiting lists, and allow greater access to OST in Greece.</li> </ul>
Ruger et al., 2012 (Malaysia)	<ul style="list-style-type: none"> <li>To study the cost-effectiveness of buprenorphine (monotherapy), naltrexone, and placebo interventions for heroin dependence in Malaysia</li> </ul>	<ul style="list-style-type: none"> <li>Randomized, double-blind, placebo-controlled clinical trial in Malaysia (2003–2005); Cost-effectiveness ratios of three treatments for heroin dependence were estimated used a microcosting methodology to determine fixed, variable, and societal costs of each intervention.</li> </ul>	<ul style="list-style-type: none"> <li>126 patients enrolled receiving counseling and buprenorphine, naltrexone, or placebo for treatment of heroin dependence (see Schottenfeld et al., 2008).</li> </ul>	<ul style="list-style-type: none"> <li>Buprenorphine was more effective and more costly than naltrexone for all primary and most secondary outcomes; Incremental cost-effectiveness ratios were below \$50 for primary outcomes, mostly below \$350 for secondary outcomes; Naltrexone was dominated by placebo for all secondary outcomes at almost all endpoints; Incremental treatment costs were driven mainly by medication costs, especially the price of buprenorphine.</li> </ul>

### **Characteristics and findings from buprenorphine (bup/nx) studies**

As mentioned earlier, buprenorphine is currently available in two forms: buprenorphine monotherapy which contains only buprenorphine hydrochloride and buprenorphine-naloxone

(bup/nx) combination therapy which includes naloxone to guard against diversion and injection use. All of the economic evaluations conducted on buprenorphine after 2006 examined buprenorphine-naloxone (bup/nx) combination therapy. In their study, Kaur et al (2008) examined the cost of bup/nx therapy and cost-avoidance for opioid dependence using data obtained from pharmacy claim records. These authors found that use of opioids significantly decreased by 18.8%, from 1.49 opioid pharmacy claims per patient per month (PPPM) in the pre-period to 1.21 claims PPPM in the post-period. After excluding the cost of the bup-nx, the actual opioid drug cost significantly decreased 66.5% from \$213.74 PPPM pre-period to \$71.65 PPPM post-period, however there were no drug cost savings in the follow-up period when the actual cost of the bup-nx therapy was included.

Studies by Schackman et al. (2011) and Polsky et al. (2010) more directly examined the cost-effectiveness of bup/nx maintenance therapy. In their study of clinically stable opioid-dependent patients who completed 6 months of office-based bup/nx treatment, Schackman et al. (2011) found that continued office-based bup/nx had a cost-effectiveness ratio of \$35,100/QALY compared to no treatment after 24 months. Studying adolescents recruited from community-based substance abuse treatment programs and randomly assigned to 12 weeks of bup/nx or to a 14-day bup/nx detoxification, Polsky et al., (2010) found that the cost-effectiveness ratio of bup/nx relative to detox was \$1,376 for 1-year direct medical cost per QALY and \$25,049 for out-patient treatment program cost per QALY, leading them to conclude that extended bup/nx treatment relative to brief detoxification was cost effective in the US healthcare system for the outpatient treatment of opioid-dependent youth.

A study by Bell et al. (2007) examined a way in which the effectiveness of bup/nx treatment could be improved, namely by observed dosing of patients. In their study of adult heroin users in outpatient treatment centers in Austria, these authors found that reductions in days of heroin use from baseline to follow-up, did not differ significantly among individual assigned to the observed versus the unobserved groups and that the mean cost for the unobserved group was AU \$1,663 per treatment episode, significantly less than the mean cost for the observed group at AU \$2,138, suggesting that close clinical monitoring but no observed dosing might be a more cost-effective strategy.

### ***Characteristics and findings from naltrexone studies***

As mentioned earlier, naltrexone comes in two formulations: oral and extended-release injectable. Our search located only one economic evaluation of naltrexone published after 2006, and this study examined oral naltrexone. This study (Adi et al., 2007) also included a systematic review of the economic evaluations on naltrexone and found that none existed. The economic evaluation conducted by Adi and colleagues involved a cost-utility analysis using a decision-analytic model and a Monte Carlo simulation to compare naltrexone and an adjunctive therapy versus the same therapy without naltrexone. These authors found that naltrexone with psychosocial therapy was more expensive but more effective than placebo with psychosocial therapy alone, giving an incremental cost-effectiveness ratio (ICER) of £42,500 per QALY gained. Despite the promise of these findings, however, the authors expressed serious concerns over interpretation of the results based on this model because of its extreme sensitivity to the smallest changes in the parameter values, which are in themselves highly uncertain due to little research on this topic.

### ***Characteristics and findings from multiple medication studies***

Our search located four studies that examined the comparative effectiveness of multiple medications for opioid dependence. The study conducted by Moore et al., (2007) compared the costs and consequences of three interventions: residential rehabilitation, prison, and pharmacotherapy (either methadone or buprenorphine maintenance therapy). Using data from the Australian Treatment Outcome Study (ATOS; Ross et al., 2003; Shanahan et al., 2003), these authors found that, if post-program abstinence rates were sustained for 2 years, the cost of averting a year of heroin use was approximately \$5,000 in Australian dollars (AUD) for pharmacotherapy maintenance, AUD\$ 11,000 for residential rehabilitation and AUD \$52,000 for prison. The authors concluded that a hybrid model of pharmacotherapy (with the option of prison for non-completers) would be the most cost-effective model.

Connock et al. (2007) used a decision-tree model with a Monte Carlo simulation to assess the cost-effectiveness of buprenorphine maintenance therapy (BMT) compared with methadone maintenance therapy (MMT) or to no treatment. The model used parameter estimates available in the published literature. These authors found that both MMT and BMT were cost-effective compared with no treatment. They also found that, although MMT was dominant in comparison with BMT from the perspectives of both the National Health Service and society (including criminal justice costs), the difference in QALYs was very small.

In their economic evaluation comparing methadone and buprenorphine monotherapy to buprenorphine-naloxone (bup-nx) in Greece, Geitona et al. (2012) found that bup-nx was the dominant therapy in terms of mortality avoidance and completion of treatment. Compared with methadone, bup-nx reduced mean cost of care by 49%, raised the percentage of participants who completed their treatment, and reduced the percentage of deaths.

In the only economic evaluation examining the comparative effectiveness of naltrexone to buprenorphine, Ruger et al. (2012) found that buprenorphine was more effective but also more costly than naltrexone for all primary and most secondary outcomes. However, incremental cost-effectiveness ratios were below \$50 for primary outcomes, mostly below \$350 for secondary outcomes which led the authors to conclude that buprenorphine was more cost-effective than naltrexone in Malaysia.

In sum, our search located nine economic evaluations on buprenorphine, naltrexone, and multiple pharmacotherapies compared to one another. Studies examining the cost-effectiveness and comparative cost-effectiveness of buprenorphine are encouraging, providing evidence for the cost-effectiveness of buprenorphine maintenance treatment- especially compared with no drug treatment (Connock et al., 2007). Buprenorphine was also more cost effective as a long-term treatment for adults (Schackman et al., 2012), and for adolescents and young adults (Polsky et al., 2010). One Malaysian study showed it was more cost-effective than naltrexone (Ruger et al., 2012). Although we located one economic evaluation of oral naltrexone (Adi et al., 2007), the authors who conducted this study expressed concerns over interpretation of the results based on the model's extreme sensitivity to small changes in the parameter values due to little research on this topic. We found no economic evaluations of injectable extended-release naltrexone.



### ***Characteristics of economic evaluations***

Beyond the low number of economic studies of these medications, prior reviewers of this research area commented on limitations regarding the range of costs, benefits, and consequences studied, the lack of identification of subgroups for and conditions under which treatments had the most economic benefit, and the extent to which studies addressed the transferability of their findings to other settings, contexts, and geographic areas (Doran, 2007; Simoens et al., 2006) both. Doran also noted a particular void in the literature regarding the extent to which psychosocial interventions work in conjunction with pharmacotherapies, and Simoens noted that modelling studies are critically dependent on the quality validity of their parameter estimates. Although many of these critiques still apply to economic evaluations conducted after 2006, the more recent studies have examined additional costs and consequences/effects of opioid addiction (e.g., HIV transmission) and expanded the number of studies conducted in countries outside North America. Additionally, although modeling studies will necessarily be limited based on model assumptions and parameters utilized, all economic evaluations reviewed that employed these techniques attempted to deal with model uncertainties in some way or another (primarily through sensitivity analyses varying model parameters).

One key feature of note in the economic evaluations published after 2006 is that *none* of the studies employed cost-benefit analyses. As mentioned earlier, cost-benefit analysis converts all gains or outcomes to a monetary equivalent (Drummond et al., 1997). In other words, the value of the health benefit from the intervention under study is expressed in terms of dollars just as the costs are. This economic evaluation method yields a very simple decision rule for determining whether the intervention should be adopted: undertake the intervention if the benefits exceed the costs. In many respects, it is not surprising that no cost-benefit studies were located, given some of the inherent challenges involved in conducting cost-benefit analyses. For example, it is often challenging to estimate dollar values for outcomes because many clinical outcomes are intangible or cannot be (or are not easily) expressed in dollars and benefits from a particular intervention may not manifest until several years after the invention has been implemented (Bray & Zarkin, 2006).

One potentially promising approach to valuing the benefits of clinical interventions is the willingness to pay approach. In economics, willingness to pay is the maximum amount a person would be willing to pay, sacrifice or exchange in order to receive a good or to avoid something undesired. Although some economists urge skepticism in adoption of willingness to pay methods primarily due to error in measuring it (see Cookson, 2003), Zarkin and colleagues (2000) were able to use these methods to demonstrate the societal benefit of drug abuse treatment in a hypothetical cost-benefit study in Brooklyn, NY and Greensboro County, NC. Basu and colleagues (2008) also incorporated these methods into their cost-effectiveness study of drug abuse treatment to monetize the outcome of reduced crime. These methods may be particularly useful in the economic evaluations of different medications for opiate dependence due to their ability to value intangible costs.

In summary, a number of limitations on studies of economic evaluations of medications for opioid dependence noted in prior systematic reviews are still relevant, despite advances in the number of studies conducted outside North American and those examining the costs and outcomes of opioid medications in relation to HIV transmission. Although many of the studies

employing modeling techniques incorporated sensitivity analyses, economic evaluations undertaken as part of a randomized controlled-trial were in the minority. None of the studies conducted after 2006 employed formal cost-benefit analysis. The study conducted by Basu et al., (2008) incorporated willingness to pay estimates from another study to monetize the outcome of reduced crime, but clearly more work can be undertaken in this area to facilitate cost-benefit analyses of medications for opioid dependence.

## Discussion

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Effective medications are available to treat opioid dependence, but they are underutilized (See Knudsen et al., 2011). Economic evaluations are useful in helping decision makers determine whether medications for the treatment of opioid disorders might add sufficient value to justify their costs and could provide evidence to support the more widespread use of medications for opioid dependence. As such, the objective of this review was to gather, evaluate, and summarize empirical economic evaluations of medications (e.g., methadone, buprenorphine and naltrexone) for the treatment of opioid dependence.

Our systematic literature search located 362 unique articles/reports pertaining to economic evaluations of medications for opioid dependence. Although no Cochran or Campbell Reviews were found, our search located four relatively recent systematic reviews pertaining to economic evaluations of various medications for opioid dependence, all published in 2006 or 2007. These reviews supported the pharmaco-economic value of methadone, pointed to a dearth of economic evaluations of buprenorphine and naltrexone, and highlighted a number of different methodological shortcomings of the studies reviewed.

A total of 20 studies published after 2006 were coded and analyzed. The majority of these studies (55%) were also economic evaluations of methadone but, there were also studies of buprenorphine. Approximately 20% of these more recent studies were conducted in South East Asia; and all employed cost-effectiveness techniques. Approximately 40% of the studies employed analytic decision models and other modeling techniques; 20% were randomized controlled trials. And although many limitations noted in prior studies still apply to these more recent studies, more studies published since 2006 examined HIV transmission outcomes.

Economic evaluations of methadone published after 2006 continue to provide support for its cost-effectiveness as a HIV prevention and treatment strategy among opioid users. Our search located nine economic evaluations on buprenorphine, naltrexone, and multiple pharmacotherapies compared to one another. There are still comparably fewer economic evaluations of buprenorphine than methadone but all studies reviewed showed clear evidence of buprenorphine's cost-effectiveness. Although we located one economic evaluation of oral naltrexone, the authors who conducted this study expressed concerns over interpretation of the results based on the model's extreme sensitivity to small changes in the parameter values due to little research on this topic. A systematic review of the effectiveness of oral naltrexone for the treatment of opioid dependence suggested that evidence for it was not strong (Minozzi et al, 2011), and a systematic review of injectable naltrexone pointed to a dearth of studies on this topic (Lobmaier et al., 2008). The injectable form of naltrexone was only FDA approved in 2010, which may explain why no economic evaluations have been conducted on it to date. Despite the absence of cost-effectiveness and cost-benefit analysis, formative cost-analysis work has been conducted and appears promising and additional research is warranted. Economic evaluations may be particularly useful in helping determine the benefits of this medication, particularly if willingness to pay methods are incorporated into the evaluation.

# APPENDIX 1

## RECENT SYSTEMATIC REVIEWS OF ECONOMIC EVALUATION FOR OPIOID DEPENDENCE MEDICATIONS

Table A. Recent Systematic Literature Reviews on the Pharmaco-Economics of Opioid Treatment					
Author(s)	Date	Search Strategy	Inclusion/Exclusion Criteria	Studies Included	Conclusions
Adi et al.	2007	<ul style="list-style-type: none"> <li>•Bibliographic databases were searched from database inception to September 2005;</li> <li>•Details regarding the search strategy for effectiveness studies provided but not provided for economic evaluations;</li> <li>•No existing economic evaluations were identified.</li> </ul>			
Connock et al.	2007	<ul style="list-style-type: none"> <li>•A comprehensive search for literature on the cost and cost-effectiveness of methadone and buprenorphine for opiate dependent drug users was conducted;</li> <li>•Bibliographic databases included: MEDLINE (Ovid) 1966 – 2005 week 1, EMBASE (Ovid) 1980–August 2005, Cochrane Library (NHS EED and DARE) (Wiley Internet interface) 2005 Issue 3, HEED database August 2005;</li> <li>•Searches also included industry submissions and internet sites of national economic units.</li> </ul>	<ul style="list-style-type: none"> <li>•Studies were included if they met the following criteria regarding the following parameters: Study design–Cost–consequence analysis, cost–benefit analysis, cost–effectiveness analysis, cost–utility analysis, cost studies (UK only), quality of life studies;</li> <li>Population–People who are dependent on opioids; Intervention–Buprenorphine or methadone employed in MT irrespective of dose; Comparator–Any comparator regime used in MT (including no therapy or placebo) or the intervention drug used in withdrawal/detoxification therapy; Outcome–Quality of life estimates, cost estimates, cost-effectiveness;</li> <li>•Of the 28 papers identified, 11 reached the final stage of review.</li> </ul>	<ul style="list-style-type: none"> <li>•Barnett, 1999;</li> <li>•Barnett et al., 2001;</li> <li>•Dijkgraaf et al., 2005;</li> <li>•Doran et al., 2003;</li> <li>•Goldschmidt, 1976;</li> <li>•Harris et al., 2005;</li> <li>•Masson et al., 2004;</li> <li>•Sheerin et al., 2004;</li> <li>•Zaric et al., 2000a;</li> <li>•Zaric et al., 2000b;</li> <li>•Zarkin et al., 2005.</li> </ul>	<ul style="list-style-type: none"> <li>•Although most of the included papers were considered to be of high quality, none used all of the appropriate parameters, effectiveness data, perspectives and comparators required to make their results generalisable to the NHS and PSS context;</li> <li>•Only one study, compared the cost-effectiveness of MMT with drug-free treatment and this study found MMT to be a cost-effective treatment; There were two studies that compared the cost-effectiveness of BMT directly with MMT that were appropriate for policy questions of the current report;</li> <li>•No studies assessing the cost-effectiveness of BMT compared with no drug therapy were found;</li> <li>•One study showed MMT to be more costly than MDT but to be more effective in preventing opiate abuse.</li> </ul>
Doran	2007	<ul style="list-style-type: none"> <li>•A "sensitive" approach was used in order to maximize articles retrieved (no language or publication year limits were applied to searches);</li> <li>•A combination of subject heading search terms were used in the categories of: (1) opiates, opiate use, and the treatment of opioid dependence, and (2) cost analysis and economic evaluation;</li> <li>•Databases included: Ovid (1966-2006), Cochrane Database of Systematic Reviews (Issue 2, 2006), NHS Economic Evaluation Library (via Cochrane), Cochrane Central Register of Controlled Clinical Trials (Issue 2, 2006), Web of Science (1900-2007), EMBASE (1990-2007), PsycINFO (1840-2007).</li> </ul>	<ul style="list-style-type: none"> <li>•1,289 articles were located with the search strategy described;</li> <li>•1,030 articles were excluded for the following reasons: (1) they examined alcohol and/or cocaine dependence rather than opiate dependence, (2) they were a letter to the editor or commentary;</li> <li>•259 articles were considered "relevant" and 8 literature review were located and 24 studies were summarized that examined costs and effectiveness of pharmacotherapies.</li> </ul>	<ul style="list-style-type: none"> <li>•Avants et al., 1999;</li> <li>•Bammer et al., 2003;</li> <li>•Barnett, 1999;</li> <li>•Barnett et al., 2001;</li> <li>•Daley et al., 2000;</li> <li>•Dijkgraaf et al., 2005;</li> <li>•Doran et al., 2003;</li> <li>•Doran et al., 2005;</li> <li>•Gerstein et al., 1994;</li> <li>•Godfrey et al., 2004;</li> <li>•Gossop et al., 2001;</li> <li>•Harris et al., 2005;</li> <li>•Harwood et al., 1998;</li> <li>•Healey et al., 2003;</li> <li>•Hubbard et al., 1989;</li> <li>•Kraft et al., 1997;</li> <li>•Mattick et al., 2001;</li> <li>•McLellan et al., 1993;</li> <li>•Miller et al., 2004;</li> <li>•Rosenheck &amp; Kosten, 2001;</li> <li>•Sigmond &amp; Stitzer, 2005;</li> <li>•Strang et al., 2000;</li> <li>•Warren et al., 2006;</li> <li>•Zaric et al., 2000a.</li> </ul>	<ul style="list-style-type: none"> <li>•Most economic evaluations of treatment options for opioid dependence are limited in terms of the range of costs and benefits considered;</li> <li>•None of the economic evaluations discussed the transferability of results to other settings or contexts;</li> <li>•There is a need for better-designed economic evaluations comparing the cost-effectiveness of drug treatment modalities and by particular sub-groups;</li> <li>•A particular void in the literature is the extent that psychosocial interventions work in conjunction with pharmacotherapies.</li> </ul>
Simoens et al.	2006	<ul style="list-style-type: none"> <li>•The review focused on studies published between 1995 and 2005 and only English-language studies were considered for practical reasons;</li> <li>•Search terms included 'opiate', 'heroin', 'dependence', 'substance abuse', 'community maintenance', 'economic evaluation', 'cost-effectiveness analysis', 'cost-utility analysis', 'cost-benefit analysis' alone and in combination with each other;</li> <li>•Studies to be reviewed were identified by searching the following databases: MEDLINE, EMBASE, Bath Information and Data Services, National Health Service Economic Evaluation Database, Cochrane Library, EconLit, Social Science and Citation Index, Cumulative Index of Nursing and Allied Health Medicine, PSYCHINFO, and Health Management Information Consortium.</li> </ul>	<ul style="list-style-type: none"> <li>•Studies had to exhibit the two defining characteristics of an economic evaluation: they compared at least two alternatives in terms of both costs and consequences;</li> <li>•Studies also had to compare different maintenance strategies, or contrasted maintenance treatment with non-maintenance treatment or no treatment, or compared individuals before treatment to after treatment;</li> <li>•The literature search generated a total of 105 articles;</li> <li>•Articles were excluded from the review for the following reasons: alcohol and/or cocaine dependence rather than opiate dependence, comparison of community detoxification programmes, analysis of a single intervention without a comparator, absence of data on both costs and consequences, analysis of inpatient services;</li> <li>•18 economic evaluations of community maintenance for opiate dependence met eligibility criteria.</li> </ul>	<ul style="list-style-type: none"> <li>•Avants et al. 1999;</li> <li>•Barnett, 1999;</li> <li>•Barnett et al., 2001;</li> <li>•Dijkgraaf et al., 2005;</li> <li>•Doran et al., 2003;</li> <li>•Flynn et al., 2003;</li> <li>•Godfrey et al., 2004;</li> <li>•Gossop et al., 2001;</li> <li>•Harris et al., 2005;</li> <li>•Healey et al., 2003;</li> <li>•Kraft et al., 1997;</li> <li>•Koenig et al., 1999;</li> <li>•Masson et al., 2004;</li> <li>•Miller et al., 2004;</li> <li>•Nordlund et al., 2004;</li> <li>•Rosenheck &amp; Kosten, 2001;</li> <li>•Strang et al., 2000;</li> <li>•Zaric et al., 2000a.</li> </ul>	<ul style="list-style-type: none"> <li>•Studies assessing the cost effectiveness/cost- utility of particular maintenance programmes were rare, but there is some evidence that methadone maintenance in the U.S. has a cost-utility ratio under US\$ 50,000 per QALY gained, the threshold that some analysts use to judge pharmaco-economic value;</li> <li>•The few cost-benefit studies showed positive net benefits from community maintenance programmes;</li> <li>•Findings on the cost-effectiveness/cost-utility of buprenorphine as compared with methadone are inconclusive;</li> <li>•Evidence is emerging of the pharmaco-economic value of prescribing heroin to opiate dependent subjects;</li> <li>•Economic evaluations suffered from a number of methodological limitations: (1) results of studies employing modelling approaches critically depended on the quality and validity of estimates of model parameters, (2) Most economic evaluations were limited in the range of costs and consequences considered, (3) Cost–benefit analyses rarely examined health benefits and studies based on a before-and-after comparison were not able to consider the impact of treatment on mortality of opiate-dependent subjects, (4) Economic evaluations have failed to identify the sub-groups of subjects and the conditions under which community maintenance for opiate dependence has the highest economic value, (5) studies did not generally consider the impact of programme factors (setting, providers, provision of additional medical and psychosocial services) on the economic value of community maintenance programmes, (6) the international literature on the pharmaco-economic profile of community maintenance for opiate dependence was dominated by North-American studies.</li> </ul>

## APPENDIX 2

### Review Protocol – Pharmacotherapies Cost-Effectiveness Literature Review

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#### **Background**

Substance use, in general, and opioid dependence, in particular, is both prevalent and costly. Effective medications are available to treat opioid dependence, but they are comparatively underutilized. Economic evaluations are useful in helping decision makers determine whether medications for the treatment of opioid disorders might add sufficient value to justify their costs and could provide evidence to support the more widespread use of medications for opioid dependence. The objective of this study was to systematically gather, evaluate, and summarize empirical economic evaluations of medications (e.g., methadone, buprenorphine, naltrexone) for the treatment of opioid disorders.

#### **Objectives**

The objective for this systematic review is to gather, evaluate, and summarize empirical research on the cost-effectiveness of pharmacotherapies (e.g., methadone, buprenorphine, naltrexone, XR naltrexone) in the treatment of opioid disorders.

#### **Methods**

A systematic literature review will be conducted by searching electronic bibliographic databases (e.g., PsychINFO and PubMed) using search terms and established selection criteria as well as by reviewing citations in published studies. In addition to searching electronic databases for published reports, we will follow Campbell Collaboration guidelines and search for unpublished reports and international publications as well using web-based search engines (e.g., Google and Google Scholar). To ensure that this systematic review constitutes a significant innovation to the field, prior to conducting this review, we will identify and evaluate the scope and quality of any prior systematic reviews conducted by the Cochrane or Campbell Collaborations to tailor our review to fill all critical gaps.

#### **Search Criteria**

In the PsychINFO data base, we will use the terms cost benefit, cost effectiveness, and cost offset in conjunction with terms methadone, buprenorphine, and naltrexone, which will result in a total of nine distinct searches. All searches will look for specified terms in all fields (e.g., title, abstract, text, etc.), and results will be limited to journal articles. A similar set of searches will be conducted in PubMed. In addition to these databases, we will also conduct similar searches in Google and Google Scholar. Finally, references in all articles and reports found through these search criteria (regardless of the type of article) will be reviewed to find any additional studies not previously identified in the aforementioned searches.

#### **Inclusion Criteria**

We will include all articles and reports in which the stated objectives of the research pertain to any sort of attempt to evaluate the effectiveness of medications used to treat opioid addiction in relation to costs associated with using them.

A particular opioid pharmacotherapy could be considered economically efficient if its monetary benefits exceed its monetary costs. The most succinct measure of economic efficiency is a benefit-cost ratio

which is a measure of the benefit derived from the investment of a single monetary unit. The review will include studies which either report this ratio or which enable a calculation of it. Cost-effectiveness studies provide cost information of an option, and outcomes in non-monetary terms. The most usual outcome measures used in cost-effectiveness studies are reductions in use or abstinence. These studies will be included as well as studies specifically examine cost-offset or costs saved by implementing a particular pharmacotherapy.

We will *exclude* non-empirical articles; specifically, we will exclude literature reviews and commentary (however, we will use these articles to search for addition empirical studies not previously discovered in searches outlined above). Dr. Mericle will carry out pre-screening of titles and abstracts identified from the database searches. One other team member will review the titles and abstracts of 10% of the abstracts determined to be ineligible to make sure that hardcopies of all possible articles and reports are included for coding.

### **Coding**

We will construct a database of articles which includes the following fields and codes created to: (1) track the methods used to locate the studies; (2) identify the scope and objectives of the studies; (3) categorize the nature and quality of the studies; and (4) classify the findings from the studies. All coding will be conducted by Dr. Mericle.

**Identifier:** Numeric unique identifier for each published and unpublished report.

**First Author:** Text field containing the last name and initials for the first author (in APA format).

**Authors Total:** Total number of authors including the first author.

**Publication Year:** Four-digit year of publication or dissemination date if unpublished.

**Title:** Text field containing the title of the article/report (APA format).

**Source:** Numeric field indicating the source of the article/report:

1=PsychINFO (only)

2=PubMed (only)

3=References in previously identified materials (only)

4=Online (only)

5=Other source (only)

6=Multiple sources

**Source Describe:** Text field describing the source if Other or Multiple sources indicated in Source

**County:** Text field identifying the County in which the study was conducted.

**Region:** Numeric identifier of the geographic region in which the study was conducted.

- 1=Asia (e.g., Japan, China, India)
- 2=Europe (e.g., Western and Eastern European Countries)
- 3=North America (e.g., USA and Canada)
- 7=South America (includes Central America)
- 4=South East Asia (e.g., Indonesia, Malaysia, Vietnam)
- 5=South Pacific (Australia, New Zealand)
- 6=Global

**Medication:** Numeric field indicating the type of medication investigated

- 1=Methadone (only)
- 2=Buprenorphine (only)
- 3=Naltrexone (only)
- 4=XR Naltrexone (only)
- 5=Other (only)
- 6=Multiple

**Medication Describe:** Text field describing the medication(s) studied if Other or Multiple indicated in Medication.

**Econometrics:** Numeric field indicating the nature of economic analyses conducted. For the purposes of coding the nature of econometrics studied, we will use the hierarchical coding scheme used by McDougall and colleagues (2008) in their systematic review of the benefits and cost-benefits and cost effectiveness of judicial sentencing to categorize different types of economic information collected.

- 1=Cost studies: Relevant costs (or averted costs) are fully assessed in monetary terms.
- 2=Cost-effectiveness studies: Relevant costs (or averted program costs) and effectiveness measures are included, but the effectiveness measures are not monetized.
- 3=Partial cost-benefit analysis: A cost-benefit ratio is included in the study, but costs and benefits are incomplete; hence, there is lack of confidence in the direction of the ratio.
- 4=Valid cost-benefit analysis: A cost-benefit ratio is included, with sufficient costs and benefits information to rate a valid analysis with confidence in the direction of the ratio.
- 5=Complete cost-benefit analysis: A cost-benefit ratio is included based on calculation of all appropriate costs and benefits, giving a complete analysis with confidence in the direction and the size of the ratio.
- 6=Other

**Econometrics Describe:** Text field describing the econometrics if Other is indicated in Econometrics.

**Cost-Utility Indicator:** 0=No/1=Yes indicator of cost-effectiveness analyses that include measurement of effectiveness in terms of health utilities of some sort.

**Manuscript Type:** Numeric field indicating the type of manuscript:

- 1=Journal article
- 2=Unpublished report
- 3=Online resource
- 4=Other

**Journal:** Text field containing the name of the journal in which the article was published (this field should be blank for all types of manuscripts other than journals).

**Study Design:** Numeric field indicating the design of empirical study conducted. Our coding scheme will be based on the Scientific Methods Scale of Sherman et al. (1997; 2002) which was also employed by Welsh and Farrington (2000) and McDougall et al. (2008). This hierarchical scale is scored from 1, low, to 5, high, and its core criteria are as follows:

- 1=Reporting of a correlation coefficient denoting the strength of the relationship between, for example, a particular sentencing option and its effectiveness at preventing re-offending at a given point in time.
- 2=Reporting of a comparison group present but this might lack comparability to the target group. Alternatively, where no comparison group is present, before and after measures, of, for example, offending behavior have been obtained for the target group.
- 3=Reporting of a controlled experimental design with comparable target and control groups present, for example, one group of offenders sentenced to imprisonment with a particular treatment intervention and a comparable group of offenders sentenced to imprisonment only, with pre-post comparisons being made and experimental-control comparisons on (a) specific variable/s
- 4=Reporting of a controlled experimental design, as in 3 above, but with additional controlling for other variables that might pose a threat to the interpretation of results. Examples of controlling extraneous variables may include, but are not limited to, the use of statistical procedures or matching of individuals.
- 5=Reporting of a fully randomized experimental design in which target and control groups consist of randomly assigned individuals and appropriate measures are taken to test for the effects of the sentencing option.
- 6=Other



**Modelling Study Indicator:** 0=No/1=Yes indicator noting with decision-analytic/ simulation designs were employed.

**Study Type Describe:** Text field describing the design for Other types of studies.

**Objectives:** Text field summarizing objectives of the manuscript.

**Sample Characteristics:** Text field describing age, sex, ethnicity/racial, number of individuals studied.

**Data Type:** Numeric field indicating the source of data:

1=Self report (only)

2=Biological (only)

3=Chart review (only)

4=Billing records (only)

5=Collateral report (only)

7=Other (only)

8=Multiple

**Data Type Describe:** Text field describing the type of data if Other or Multiple indicated in Data Type.

The following variables are Yes/No Indicators and accompanying descriptors for the following (more than one can be studied):

**Substance Abuse:** 0=No; 1=Yes

**Substance Abuse Description:** Text describing the measure

**Substance Abuse Results:** Text describing the results

**Criminal Justice:** 0=No; 1=Yes

**Criminal Justice Description:** Text describing the measure

**Criminal Justice Results:** Text describing results

**Psychosocial:** 0=No; 1=Yes

**Psychosocial Description:** Text describing the measure

**Psychosocial Results:** Text describing results

**Health:** 0=No; 1=Yes

**Health Description:** Text describing the measure

**Health Results:** Text describing results

**QOL:** 0=No; 1=Yes

**QOL Description:** Text describing the measure

**QOL Results:** Text describing results

**Service Use:** 0=No; 1=Yes

**Service Use Description:** Text describing the measure

**Service Use Results:** Text describing results

**Costs:** 0=No; 1=Yes

**Costs Description:** Text describing the measure

**Cost Results:** Text describing results

**Other Measures:** 0=No; 1=Yes

**Other Measures Description:** Text describing the measure

**Other Measures Results:** Text describing results

**Statistical Analyses:** Text describing type and nature of statistical analyses conducted

**Limitations:** Text describing limitations noted.

### ***Statistical Procedures and Conventions***

The results of the review will be discussed and a narrative summary of the findings will be presented. We will use descriptive statistical techniques to summarize relevant characteristics of the studies collected.

### ***Time Frame***

Searches will be conducted between 2/1/2013 and 4/1/2013.

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