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Evaluation Of Need And Feasibility Of Tuberculosis Screening In Buprenorphine Treatment Programs

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A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

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Declaration of Interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

Abstract:

Background: Buprenorphine's availability in primary care settings offers increased access to treatment and linkage to primary care for opioid-dependent patients. Currently, tuberculin skin testing (TST) is recommended for patients enrolling in methadone maintenance treatment (MMT), but not for those enrolling in buprenorphine maintenance treatment (BMT).

Objectives: To compare TST screening results in enrollees in BMT and MMT programs and assess the correlates of TST positivity among these subjects.

Methods: A cross-sectional analysis of a retrospective cohort study was conducted to compare concurrent TST results among contemporaneously matched groups of MMT and BMT patients in the same community.

Results: TST positivity was 9% in both MMT and BMT settings (p = .27). Increased TST positivity was associated with being Black (AOR = 3.53, CI = 1.28–9.77), Hispanic (AOR = 3.11, CI = 1.12–8.60), and having higher education (AOR= 3.01, CI = 1.20–7.53).

Conclusions: These results confirm a similarly high prevalence of TST positivity in opioid-dependent patients enrolling in MMT and BMT programs. Racial and ethnic health disparities remain associated with TST positivity, yet a relationship between higher education and tuberculosis requires further investigation.

Scientific significance: These data suggest the importance of incorporating TST screening in emerging BMT programs as a mechanism to provide increased detection and treatment of tuberculosis infection in opioid-dependent patient populations

Introduction

Substance Dependence

"Drug addiction," or more formally "substance dependence" as termed by the American Psychiatric Association, is defined as a "maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring any time in the same 12-month period: tolerance; withdrawal; increasing use (quantity and/or frequency) over time; persistent but unsuccessful intention to cut down on use; significant time occupied by habit; social, occupational and recreational activities suffer as a result; and/or usage is continued in spite of recognition of deleterious physical or psychological effects [1].

In the United States today it is estimated that approximately 2 million (range between 1.5 and 2.4 million) people are dependent upon opiate-containing substances [2, 3]. In addition to heroin, opioids of abuse range from natural opium to manufactured forms including codeine, fentanyl, hydrocodone, methadone, morphine, and oxycodone. Natural opium has been used recreationally for over five thousand years with Sumerian records of a "joy plant" dating back to ancient Mesopotamia in 3400 B.C. [4]. Since the Sumerians, opioids have been used continuously, both recreationally and clinically, in cultures around the world. Opioids can be taken through intravenous, intranasal or inhalation routes of administration and are regularly used for many clinical indications in addition to their potential for abuse.

Of the approximate 2 million opiate-dependent persons in the United States presently, approximately 900,000 are dependent on heroin [5]. Irrespective of the opiate or

administrative route of choice, opiate dependence is a significant problem in the United States today with enormous social and economic costs to society [6]. A National Institute of Justice study reported that over 60% of inmates in federal prisons in 2002 were incarcerated for crimes associated with illicit substances trade or usage [7]. In addition to the challenges posed in the legal and social realms by substance abuse, the financial costs are substantial: a 1994 study suggested that in New York City alone substance abuse cost tax payers over 20 billion dollars [8]. Since 1994 the number of substance users has increased, as has the cost. While the socioeconomic challenges associated with substance dependence are notable, they are, however, outside the scope of this paper. In this report we will discuss in greater detail specific concerns surrounding the implementation of substance dependence treatment programs and the policy implications necessary to optimize treatment for this marginalized population.

Health status of substance users

Substance dependence has significant impact on the health status of substance-dependent patients, including higher rates of infectious diseases, medical comorbidities, and mental illness [9-14].

Epidemiologically, individuals who use illicit substances, and particularly opioids, are at increased age-matched risk for associated infectious diseases. For example, many studies have shown substance users to have higher rates of human immunodeficiency virus (HIV)[10, 15]. While many opioids are used by patients with HIV, those that are injectable have contributed most to the transmission of HIV through needle-sharing practices involving blood-to-blood contact [5]. Currently, over one in three cases of HIV/AIDS in the United States are accounted for by injecting drug users (IDUs) or their

partners or children, and approximately 25% of new HIV cases annually in the United States are secondary to injecting drug use practices [10, 15]. In addition to high rates of HIV/AIDS, higher rates of tuberculosis have also been documented in this population, with both increased risk of *Mycobacterium tuberculosis* infection and tuberculosis disease [11, 16]. Increased risk for tuberculosis is due in part to the fact that it is a common opportunistic infection associated with HIV, and further that HIV markedly increases reactivation of latent tuberculosis infections [17]. Higher rates of tuberculosis are additionally caused by the impoverished and cramped living conditions many substance users live in; such living quarters can increase the risk of air-borne transmission of *Mycobacterium tuberculosis* causing infection and leading to disease [11]. Similarly, other research has shown that rates of viral hepatitis are increased in populations who use opioids through intravenous routes [12, 18]. There is a higher risk for transmission of both hepatitis B and hepatitis C viruses through blood-to-blood contact which frequently occurs through needle sharing in injecting drug use. Additionally, many patients who contract one form of viral hepatitis via intravenous drug abuse are co-infected with both hepatitis B and C, with some studies showing over 80% co-infection rates in this population [19].

In addition to the increased risk of infectious diseases, this population is also disproportionately affected by mental illness. Research demonstrates that mental illnesses such as depression, schizophrenia and bipolar disorder are increased in this population and can lead to higher risk-taking behavior, including substance use, injecting drug use, and high-risk sexual practices that may expose persons to sexually transmitted infections including HIV [13, 20].

Marginalization from health services

This disparity in general health status amongst substance users, and specifically those who use intravenous drugs, has been well documented yet remains largely unaddressed. In part, poor health status is due to a significant marginalization of these individuals from mainstream healthcare resources [21, 22]. This marginalization is multi-factorial, however in part occurs due to stigma against substance users both from the general public as well as health care providers [23, 24]. Despite significant evidence illustrating the benefits of substance abuse treatment modalities such as methadone [25], many health care practitioners continue to be uncomfortable treating active substance users. One study of primary care practitioners in New York City treating HIV patients revealed 55% were uncomfortable providing services to patients injecting drugs [26]. Other clinicians may be comfortable working with substance users however are wary of long-term maintenance treatment approaches (i.e. medication-assisted treatment – further discussed below) [27]. In the latter case, while care may be provided, it is frequently sub-optimal as the doctor-patient relationship is compromised by a lack of trust between parties and discomfort on the part of the clinician in dealing with this population [28].

Whether clinicians do or do not provide services to this population, in both cases practitioners often maintain that substance dependence is different from other diseases and understand substance dependency as a personal choice, and accordingly not a responsibility of the public health care system. The New York Academy of Medicine discusses how, "…much of the general public and those in the health care field have come to believe that drug dependence is essentially self-indulgent, voluntary behavior for which individuals should take personal responsibility [28]." Consequently public opinion

frequently maintains that substance dependence should be dealt with politically (i.e. keeping illicit substances off the street) and/or legally (i.e. punishing those who participate in the trade or use of such substances), but not medically. In parallel, there is reticence amongst health care providers to offer treatment to substance users as discussed. Furthermore, for some clinicians who do provide treatment to this population there is a harsher approach to medication non-compliance given the view that substance dependence is a fundamentally different type of disease than other chronic illnesses such as diabetes or HIV [29-32].

These perceptions are in contrast to a significant body of literature which understands substance dependence as a chronic illness influenced by biological, psychological and socioeconomic factors, not unlike other chronic illnesses such as HIV or diabetes. Multiple previous studies – including twin studies, cohort studies, and randomized control trials – have lead science to now purport that substance dependence must be conceptualized and treated as a non-curable, chronic disease. Twin studies have shown that there is a significant genetic component to substance dependence [33-35]. Additionally, we now know that there are typical neurostructural and neurochemical responses to substance use and dependence underlining the pathophysiologic nature of dependence [36, 37]. Finally, we know that social problems such as poverty, poor social support structures, or psychiatric co-morbidities portend a poor outcome of treatment with frequent non-compliance to treatment plans and relapse following discharge [38, 39]. While none of this evidence is sufficient to state that substance dependence is by definition a chronic illness, when held up against well-established literature of other

chronic diseases such as asthma, hypertension, or diabetes, there is a striking similarity between the etiology and correlates of treatment success [28].

More specifically, several key challenges exist in working with this population that complicate the ability of clinicians to provide effective and/or compassionate care. Due to an often chaotic set of life circumstances, many substance users have significant difficulty interacting with the health care system in a traditional fashion. For instance, many patients in this population have difficulty keeping set appointment times required at most health facilities and therefore frequently utilize emergency departments or drop-in clinics as a replacement for general primary care centers [40-43]. Secondly, high psychiatric co-morbidities can make these patients challenging and often frustrating to deal with [28]. The same mental illness burden also leads to challenges for such patients in accessing reliable and consistent primary care [13]. Finally, there is a dearth of effective medical and psychosocial outreach programs engaging this population to enter treatment in the traditional fashion, further exacerbating the tendency of this population to visit emergency departments with late-stage disease rather than accessing primary care services on a regular basis [44].

However, aside from the multiple factors making this population less likely to regularly access health resources, and irrespective of whether substance dependence should in fact be examined through the lens of a chronic illness, current public opinion, including that of many health care workers, has not yet adopted this perspective. This has lead to an increasing and continued stigmatization of this population which has only exacerbated the difficulty in effectively providing health services to such patients. In particular, it has lead to a lack of primary care practitioners willing to provide services for these patients,

and additionally has created an even greater perceived lack of health services given the dearth of information readily available to this population.

Medication-assisted treatment

Medication-assisted treatment, or a therapeutic modality for substance dependence in which medications are used in parallel with behavioral therapy, is the most effective treatment strategy in this population [45, 46]. Furthermore, it is an important strategy to address parallel and comorbid health issues for substance-dependent patients.

Medications such as methadone and buprenorphine – further described below – have been shown to provide several key benefits to this population. Primarily, these medications, especially when paired with behavioral therapeutic approaches are the most effective modality to address substance dependence [45, 46]. Secondarily, medication-assisted treatment modalities have been demonstrated as effective means to engage patients in treatment for associated conditions, including infectious diseases, mental health, and/or non-substance-dependence related medical comorbidities. A third critical benefit of medication-assisted treatment is that, in addition to acting as a foundation for increased patient health services engagement, it enhances adherence to treatments for associated conditions, including for instance, HIV and tuberculosis [45-48]. In this paper we will primarily discuss the two most effective medication-assisted treatments, methadone and buprenorphine.

Methadone: medication-assisted treatment for substance dependence

Methadone is a synthetic, full mu-opioid agonist, originally developed in 1939 in Germany in an effort to identify alternative opiates due to a nation-wide opium shortage.

In 1947 it was introduced in the United States by Eli Lily as an analgesic medication under the name of Dolophine. Since then it has become more well-known for its ability to treat opiate dependence when used as an opiate substitution therapy, or, a "medication-assisted treatment." In 1964 Vincent Dole and Marie Nyswander of Rockefeller University, first pioneered the use of methadone to treat heroin addiction. They initially treated 22 patients using methadone and were able to successfully show that patients treated with methadone in combination with psychosocial interventions stopped heroin usage and regained self-confidence and an ability to live typical family and work lives [49]. This study laid the foundation for the usage of methadone as a medication-assisted treatment; Dole later received the Lasker award for this work.

Since the 1960s the usage of methadone for opiate dependence has become much more well refined with methadone maintenance therapy now offered in outpatient settings throughout the world [24, 25]. Methadone maintenance treatment is a medication-assisted treatment and therefore patients typically take methadone for long, if not indefinite, periods of time following opiate dependence. In treatment programs patients receive daily doses under the regular supervision of a certified doctor with doses ranging significantly depending upon the individual. In the United States most programs initiate patients on a low dose and gradually increase daily dosage until symptoms of withdrawal and cravings for opiate use are well controlled. For most programs, patients are initially required to visit a clinic daily to receive their treatment. However, following a certain period of time – location and provider-dependent, and pending continued compliance and negative drug screening tests – patients are allowed to visit the clinic less frequently, taking some of their doses independently at home.

With now over 40 years of research examining the impact of methadone maintenance treatment there is evidence of multiple benefits resulting from treatment programs. First, methadone can successfully manage opiate dependence, especially when paired with additional psychosocial interventions [24, 25, 50]. Secondly, methadone programs have been shown to be a cost-effective intervention when examining their impact on public health as well as societal economic and financial statistics [51]. Methadone has also been shown to have ancillary beneficial effects including: reducing rates of prison recidivism [52]; decreasing transmission of infectious diseases including HIV, tuberculosis and viral hepatitis [53]; improving clinical compliance and treatment outcomes for chronic illnesses [30, 54]; enhancing general employment status and opportunities [55]; decreasing high-risk behaviors such as needle sharing and injecting [56] as well as overdoses from opiate abuse [57]; and, generally improving psychological and physical health status for patients enrolled in treatment programs [58].

Regulation of methadone treatment

Despite research demonstrating the marked benefits of methadone maintenance treatment, however, it remains a controversial issue, and access to methadone treatment is available in only a limited capacity due to stringent legal and clinical regulations for use. A brief discussion of the history of regulations surrounding methadone and other opiate-replacement therapies is instructive to understanding the current policy debates surrounding newer treatment modalities.

Prior to Dole and Nyswander's seminal work with methadone at Rockefeller in the early 1960s, prescribing opiates to opioid-dependent patients in the United States was difficult, if not impossible. In 1914 the Harrison Act along with a group of passionate anti-opioid

politicians began to limit the ability of clinicians to prescribe opiates to this population. In 1920, when the American Medical Association similarly condemned the practice, clinicians began to be formally prosecuted for offering opiate-replacement therapies. During much of this period Harry Anslinger was head of the Bureau of Narcotics – Ansligner purported that severe penalties for possession, use or sale of illicit substances would ultimately eliminate substance dependence. Similarly, he was not in favor of opiate-replacement therapies and lead efforts to stop clinicians from engaging in such practices [32].

Data from the Rockefeller studies came out in the setting of a harsh legal environment for substance users as well as the clinicians that aimed to treat them, however also at a time when sentiment for the treatment and "rehabilitation" of opiate-dependent patients was on the rise [59, 60]. Following Dole and Nyswander's data, multiple treatment centers sprang up throughout the country functioning mainly through Investigational New Drug (IND) certifications issued by the Food and Drug Administration. IND certification was important as it allowed centers to provide treatment in spite of the Bureau of Narcotics continued opinion that providing opiates to substance-dependent patients was illegal. While thousands of patients were enrolled in treatment in the first 10 years [2], government agencies maintained their opposition to the programs and many activist and patients-rights groups derided the practice as an inappropriate approach to the treatment of substance abuse [61]. During this time the FDA refused to qualify methadone as a legitimate form of therapy, thereby limiting the number of programs functioning under the label of "research." These limitations quickly lead to many opiate-dependent patients (largely heroin) being unable to enroll in treatment and generated long waiting lists for

programs [32]. In 1973 new Federal regulations were approved, and while originally intended to be revised regularly, between approval and 2001, were only amended twice. Most notably in the 1973 revisions was included the implementation of a physician accreditation process for the prescription of methadone. In 1974, Congress approved further oversight mechanisms for methadone treatment programs, placing much of the jurisdiction under the DEA [62].

Between the 1920s and 2003 the number of patients receiving methadone has increased from approximately 20,000 to 180,000; still only a significant minority of the opiate-dependent population in the United States. Throughout this time period efforts were made to revise and ease the FDA regulations however significant resistance was voiced by both the DEA as well as clinicians offering treatment [32]. Ultimately, while opinions are diverse, the regulatory environment during the 1970s, 80s, and 90s has largely been credited with limiting access to methadone treatment.

Buprenorphine – a new medication-assisted treatment

Buprenorphine is a partial-opiate agonist that was first noted to have potential clinical utility in 1978 [63]. At the time, buprenorphine was particularly interesting due to its potential to limit the adverse side effects associated with methadone toxicity in opiate-naïve individuals. Potential clinical use for substance dependence, and evidence for limited toxicity, was formally illustrated by the early 1990s [64-66]. In addition to data suggesting that buprenorphine could be an effective clinical treatment for opioid-dependence, the limited toxicity (due to its partial agonist properties and formulation) significantly decreased concerns for diversion of the medication as it largely limited the potential for overdoses seen frequently with methadone. This lead many clinicians and

scientists to believe that following FDA approval for the clinical use of buprenorphine, it might be exempted from many of the severe regulatory constraints that limited methadone treatment access.

Due in large part to the efforts of private pharmaceutical company Reckitt and Colman – who decided to market buprenorphine and in doing so take on the legal and political bureaucracy involved in the regulation of methadone – and accompanied by several key political allies, legislation was developed to ease the previous regulations for opiate-replacement therapies. The political lobbying was done with the express intention of establishing the legal framework necessary to expand the potential patient population for buprenorphine prior to Reckitt and Colman bringing the drug to market. Beginning in 1995, the legislation of the proposed Drug Addiction Treatment Act (DATA) – a rather minor amendment to the existing legislation – took more than 5 years to finally be passed by Congress. In 2000, President Clinton signed into law the DATA which offered clinicians the opportunity to obtain special training which would exempt them from obtaining DEA certification as well as allow them to offer buprenorphine treatment outside of federal methadone regulations [32].

On October 8th, 2002 buprenorphine was approved for the treatment of opiate-dependence making it the third such drug to gain certification (LAAM – levo-alpha-acetyl methadol, a similar compound to methadone – had been previously approved in 1993 by the FDA however was subsequently removed from both the European and US markets in 2001 and 2003 respectively). Buprenorphine is a partial opioid agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor [63]. As a result, buprenorphine blocks patients' ability to use exogenous opioids while at the same time

preventing withdrawal symptoms. Similarly, buprenorphine has a lesser potential for abuse or overdose and therefore risks of diversion are of less concern than those for methadone [66]. Because of these pharmacological properties, buprenorphine has been classified as a Schedule III medication whereas methadone is a Schedule II; this will enable its wider use clinically and aid in eliminating stringent regulatory barriers seen with methadone.

Previous research has shown that buprenorphine is an effective maintenance therapy in multiple dosage formulations – including daily or several times weekly – and is manufactured both singly as well as in a dual-formulation with naloxone to further prevent diversion efforts [67]. Multiple previous studies have shown effect with buprenorphine maintenance therapy in various settings including outpatient primary care clinics [23, 68] and other research suggests its use as a cost-effective public health measure [69].

Buprenorphine maintenance treatment involves three major phases – 1) induction, 2) stabilization, and 3) maintenance. In the induction phase patients are given a "test dose" which is typically observed at the treatment facility. This initial dose is usually 4mg and is given after a patient has been opiate-free for 12 to 24 hours and beginning to experience symptoms of opiate withdrawal. Following verification that the patient tolerates the initial test dose, dose titration is begun rapidly to a dose of 16mg typically by day number two. At this point the stabilization phase begins during which time the patient works with their clinician to achieve a dose at which they can greatly reduce or cease entirely opiate usage. Psychosocial counseling and behavioral interventions are an important part of the stabilization phase. Once the patient achieves a stable dosing

regimen and lack of continued cravings for opiate abuse the maintenance phase begins. During this phase the patient is maintained on their steady dose. The length of this phase is contingent upon patient performance and comfort, and also the judgment of the clinician. During the maintenance phase doses can continue to be adjusted and psychosocial and behavioral interventions are also often continued.

Extended release naltrexone – a new medication-assisted treatment

Naltrexone is a long-acting, full opioid-receptor antagonist utilized primarily in the treatment of alcohol and opioid dependence. Recent data [70] has shown a depot formulation of naltrexone as an effective treamtment modality for prevention of relapse in substance-dependent patients who have already undergone detoxification. Recently, Vivitrol, a depot, extended-release formulation of naltrexone, was approved in the United States for the treatment of opioid dependence; similar to buprenorphine, utilization of Vivitrol must follow detoxification from opioids.

Given naltrexone's pure opioid antagonist properties there are no regulatory barriers to offering treatment. Additionally, the depot formulation comes in a monthly dosage. Given these properties, there is hope that Vivitrol may further expand access to medication-assisted treatments in patients previously unable to access resources due to the regulations and challenges surrounding methadone and buprenorphine.

Tuberculosis screening in buprenorphine treatment programs

Despite significant increases in access to medication-assisted treamtment over the last 40 years, there remains significant stigma, regulatory barriers, and limited funding for such treatments. While the overall number of patients receiving treatment has increased,

currently in the United States, only 15–20% of opioid-dependent patients have access to maintenance treatment [71, 72]. It is estimated that only approximately 200,000 patients have access to methadone [73], while in 2009 only approximately 600,000 patients had access to buprenorphine[1].[74]. Currently depot naltrexone is too new to accurately estimate the number of patients on treatment.

Given the great gap in medication-assisted treatment available to this population, there is a significant need for increased drug treatment opportunities. In parallel, given the marginalization of this population from mainstream health care services, there is also need for enhanced primary care mechanisms to treat the medical co-morbidities of this population. By creating innovative strategies to treat substance dependence in a primary care setting public health practitioners have already expanded opportunities for these patients [25, 27, 68, 75, 76]. Further expansion of substance abuse treatment programs integrated with primary care services can address both the continued disparity in drug treatment as well as medical care available to this population [5].

Some treatment programs have begun to respond to this need by integrating primary care services with substance abuse treatment [23, 25, 27, 77-79]. These programs include screening and treatment of diseases commonly affecting substance users as well as induction and stabilization on medication-assisted treatments such as methadone and

[1] As of writing there are 20,180 buprenorphine-certified physicians in the United States. While no definitive numbers are yet available describing exactly how many patients have received/are receiving buprenorphine we know that during the 2009 year 640,000 individuals received a Suboxone/Subutex prescription, however length and number of refills of these prescriptions varied significantly. Through personal communication with Dr. Douglas Bruce of Yale University only "half or less [of these] are in 'active treatment'."

buprenorphine [27, 44, 80-82]. Further, such programs are situated and conducted in ways more amenable to the specific needs of this population [5, 27].

As previously discussed, a key component of health services for this population must address the increased prevalence of infectious diseases such as tuberculosis, HIV and viral hepatitis. In examining these programs with an eye towards tuberculosis control, methadone maintenance treatment programs in particular have successfully incorporated tuberculosis screening. Additionally, these programs also include further linkage to directly observed preventive therapy for those requiring tuberculosis treatment [81-84]. Methadone treatment guidelines in the United States, as well as recommendations from the World Health Organization and Center for Disease Control and Prevention support the continued usage of such programs as evidence-based and cost-effective [51, 82] means of detecting and treating tuberculosis among opioid-dependent patients [85, 86].

Because of buprenorphine's liberalized regulatory framework and its consequent availability to the primary-care practitioner, buprenorphine maintenance treatment has the potential to greatly increase the availability of opiate-replacement therapy to those currently without access. Further, if substance abuse treatment is coupled with primary care services, such expansion into the primary care setting also has the dual benefit of enhancing access for this population to ancillary services such as tuberculosis screening [87]. Regulations for methadone treatment programs, including recommendations for ancillary services offered, are well-founded after over 40 years of use in the clinical setting. However, as standards of care for buprenorphine treatment continue to evolve, policy recommendations for associated clinical services, such as tuberculosis screening via tuberculosis skin testing, do not yet exist, nor is there data to support or refute such

policies. Further, such programs are important to enhance treatment of both latent and active tuberculosis in this patient population and inform the development of further linkages to care for both isoniazid preventive therapies – for latent tuberculosis – as well as treatment programs for active infections including directly observed therapy programs. For this reason, we have examined the need and feasibility for implementation of a tuberculosis screening program in the setting of a buprenorphine treatment program. This research compares the prevalence of tuberculosis skin testing positivity among matched clients contemporaneously enrolled in buprenorphine and methadone treatment programs within inner-city New Haven, Connecticut. The treatment program described is the first mobile, community-based model for buprenorphine treatment and will also be discussed [88].

Statement of Purpose

While buprenorphine has been studied since the 1970s, strategies for optimizing buprenorphine maintenance treatment programs to provide associated primary care services for this population continue to be assessed and revised. This study will address the particular issue of tuberculosis screening in buprenorphine treatment programs.

While the correlation between opiate addiction and tuberculosis infection has been well documented, and there are established international guidelines for tuberculosis screening in methadone programs, there has been to date no published investigation on the feasibility and efficacy of tuberculosis screening incorporated into buprenorphine programs. Using the cohort of buprenorphine treatment patients here described, this study will compare positive rates of tuberculin skin testing to a contemporaneous and geographically similar matched cohort of methadone maintenance treatment patients.

Cohort averages as well as sub-group analysis will be described. Implications for the need and practicality of such tuberculosis screening in buprenorphine maintenance treatment programs will be discussed.

Hypotheses

1. The prevalence of positive tuberculin skin tests in a buprenorphine treatment program will be similar to a contemporaneous and matched cohort of methadone treatment patients.
2. It is possible to provide effective tuberculosis screening in the setting of a buprenorphine treatment program

Aims of Research

1. To evaluate the prevalence of positive tuberculin skin tests in contemporaneous, matched cohorts of buprenorphine and methadone maintenance treatment patients
2. To assess the feasibility of implementing a tuberculosis screening program in a buprenorphine maintenance treatment program

Methods

Study Design

A cross-sectional analysis of a retrospective cohort study was conducted to compare the prevalence of tuberculin skin test positivity between patients enrolled in the country's first mobile, community-based buprenorphine stabilization and induction program to contemporaneous patients enrolled in a nearby methadone maintenance treatment

program. Both treatment-derived study groups were from the city of New Haven, Connecticut and were matched across four criteria.

Ethical approval

This study was approved through the Yale University School of Medicine's Human Investigation Committee (HIC# 27630).

Site Descriptions

New Haven, Connecticut

New Haven is a moderate-sized, post-industrial, city of approximately 130,000 with a wide socioeconomic diversity. Yale University is located in New Haven, however New Haven is also home to significant populations of African American and Latino American populations. The "town-gown" relations between the former and latter are stark and socioeconomic, political and health inequities are significant. Unemployment and poverty, substance abuse (including a high degree of injecting drug use), HIV and mental illness have made a deep impact upon the city.

Community Health Care Van

The Community Health Care Van (CHCV) is a 36-foot mobile medical facility that provides health services in parallel to a needle-exchange program in New Haven, Connecticut. The CHCV provides health services five days per week throughout four neighborhoods in the New Haven area. While some areas of New Haven are quite affluent, the neighborhoods the CHCV serves are disproportionately affected by poverty, substance abuse, HIV, Hepatitis C, and mental illness. The CHCV provides a variety of basic treatment and preventive health services including basic medical care (as provided by a nurse practitioner/physician's assistant), screening for sexually transmitted infections, tuberculosis, and HIV, directly observed HIV therapy, referral to drug

treatment facilities and case management services, and buprenorphine induction and stabilization treatment for opioid-dependent patients. The CHCV operates with the express goal of offering health services to marginalized populations within the New Haven area in a manner which enables patients to effectively access these services. The focus of this research is in particular on the CHCV's provision of buprenorphine induction and stabilization services and the concurrent screening for tuberculosis in this population [44, 89].

The CHCV was first developed in 1991 when it operated out of an 18-foot van and provided services only one day per week. Services expanded to two days per week in 1994, offering HIV counseling and testing, social work referrals and acute medical care. The van expanded to its current form in 1996 and now has two examination rooms and one counseling room. Service provision has been continually expanded both in scope and in number of days offered since 1996. Clinical care and medications donated through affiliated programs are provided free of charge to uninsured patients and all patients are offered referral services to local and regional health facilities as indicated [88, 89]. The clientele of the CHCV are diverse yet all from particularly disadvantaged and underserved backgrounds. Over 35% are previous or current injecting drug users, approximately 70% are unemployed, 27% reported previous or current commercial sex work, and 26% had been in jail or prison in the 6 months prior to CHCV engagement [89].

Key components of the CHCV's buprenorphine treatment program include rapid initiation of opioid-replacement therapy, surveillance for associated infectious diseases and/or psychiatric co-morbidities, and street-level case management services. An

additional critical component of the CHCV program is its harm reduction approach to complicated patients with multiple health and psychosocial co-morbidities. With particular regard to the buprenorphine treatment program, if patients are effectively taking their buprenorphine and engaging in parallel psychosocial and behavioral counseling, other high-risk behaviors such as continued illicit substance abuse (e.g. crack cocaine) are tolerated and not addressed punitively (e.g. discharge from the buprenorphine program or judgement/stigmatization from health care providers at the CHCV). Such harm-reduction techniques have been well established as effective means of treating substance abuse and retaining patients in active engagement with health providers. This approach helps to maintain patients engaged in health services and counseling creating an environment in which further behavioral modification and general health improvement may occur [28].

While such an approach has proven effective in enhancing the provision of health services to this marginalized population, it also entails certain challenges in implementation. This patient population frequently has difficulty in maintaining set appointments thus requiring significant flexibility in staffing and time allocation for counseling sessions. The CHCV program was developed with the intention of ensuring therapeutic encounters at the time the patient presented for treatment, in direct contrast to the standard health care system which is centered on clinician-set appointments. This operations model requires staff to be flexible to see patients that they have not previously seen, at times they had not expected patients to arrive, yet also ensures patients are engaged in health services in a manner that their challenging life circumstances can accommodate. All staff accordingly are connected via cell phones and able to

communicate with other counselors and health care providers and are additionally co-located within the same mobile unit to allow one staff member to assist another when patients unexpectedly arrive and/or require more attention than typically expected. Providing health services in this fashion is time-intensive and costly, however by adopting a harm-reduction approach the CHCV has effectively provided health services to a population previously marginalized from the health care system and ultimately enhanced the health status of this population [27, 44, 89].

Buprenorphine Maintenance Treatment Subjects

Buprenorphine treatment subjects were derived from Project BEST – Buprenorphine Entry into Substance abuse Treatment – which is the first mobile, community-based, buprenorphine induction and stabilization program in the United States [44]. Project BEST operates out of the CHCV as described above and is funded by the Substance Abuse and Mental Health Services Agency (SAMHSA). All patients enrolling in Project BEST underwent induction and treatment in accordance with Treatment Improvement Protocol 40 guide-lines [90].

Criteria for inclusion in buprenorphine treatment included:

1. fulfilling DSM-IV criteria for opioid dependence;
2. no previous uncontrolled benzodiazepine abuse;
3. hepatic transaminase values less than five times the upper limit of normal; and
4. a negative pregnancy test for women of child-bearing age.

Induction to Project BEST consisted of a standardized protocol over a two-day period. On the first day patients received 8mg divided into two doses over 1 to 2 hours, and 16mg on the second day. In addition to buprenorphine patients also received evidence-based drug treatment counseling. Manualized counseling included an initial four weeks of motivational enhancement therapy and an additional eight weeks of cognitive

behavioral therapy [91]. Patients enrolled in the program also received weekly urine immunoassay tests for opiates, cocaine, THC, methadone and/or benzodiazepines. Following the initial 12 weeks of treatment patients returned for urine toxicology and counseling at a frequency determined by the clinician, per the patient's perceived stability and progress in the program [88].

Project BEST utilized a single pharmacy for all buprenorphine provision. Early in treatment patients were prescribed only one-week supplies of buprenorphine which was intended to last from one counseling appointment to the next. Prescriptions were written for a one-week bottle with 3 refills however patients were required to show up to counseling sessions in order to fill the refill. The latter was accomplished by never providing patients with an actual prescription but instead a voucher. This voucher required that both the patient and the counselor sign it at the time of the counseling session, and also emboss it with a program seal. The pharmacy ensured that only vouchers – and never prescriptions – that were doubly signed and embossed, were filled. Through this mechanism Project BEST was able to ensure that all buprenorphine treatment was accompanied by a minimum of 12 weeks counseling as patients began the program [88].

In addition to buprenorphine maintenance treatment, all Project BEST enrollees are routinely screened for HIV, tuberculosis, hepatitis B and C, and sexually transmitted diseases [44, 92]. Hepatitis B vaccination is also provided for eligible participants [93]. All Project BEST participants also undergo health surveys to collect relevant information about their past and current health status, substance abuse behavior, socioeconomic and demographic information. These surveys include the Addiction Severity Index (ASI)

[94], the Structured Clinical Interview for DSM-IV (SCID) [95], the CHCV Short and Long forms, and the Project BEST Supplemental Survey [88], and are conducted at induction as well as periodically thereafter. In addition to the surveys documented, subjects enrolled in Project BEST provided informed consent to access all medical records from one year prior to induction to five years following enrollment.

Methadone Maintenance Treatment Subjects

To investigate the concurrent prevalence of tuberculosis among methadone maintenance patients in the area, characteristics from Project BEST participants were matched to methadone patients enrolled at The APT Foundation in New Haven, Connecticut. The APT Foundation (http://www.aptfoundation.org/) runs New Haven's largest (2,000 patients) methadone maintenance treatment program and has been providing treatment to substance users for over 40 years. Through their methadone treatment program, all APT Foundation clients are routinely screened for tuberculosis and mental illness. Additional screening for hepatitis B and C is performed if deemed clinically appropriate, and HIV testing is voluntary. Finally, all entrants to The APT Foundation's methadone maintenance treatment program provide informed consent for medical chart review extraction involving de-identified data.

Inclusion criteria for methadone maintenance treatment at The APT Foundation includes 1) adults over the age of 21 years old, 2) fulfillment of DSM-IV criteria for opiate addiction of greater than one year in duration, and 3) one previous treatment failure. Pregnant women under 21 years old are admitted on a case-by-case basis at the discretion of clinicians. The APT Foundation serves a wide catchment area including cities surrounding New Haven such as Milford, Old Saybrook and Wallingford [96].

Definitions

In collecting data from Project BEST and The APT Foundation, medical record formatting was distinct between the two groups, and therefore, reconciliation of selected variables is required. The level of previous education was categorized differently in the two study groups – for Project BEST patients, the number of months of education was reported, with 144 months being equivalent to having completed a high-school education. Conversely however, for APT Foundation patients education data was recorded only by the number of years of education completed. Secondly, to assess the substance of abuse preferred by each patient, data from both groups was compiled according to whether patients had reported a given substance as their primary, secondary, or tertiary substance of choice. Substances that were listed but not classified as primary, secondary, or tertiary, were not included in data analysis. Last, to evaluate the psychiatric co-morbidities of patients, including previous and current treatment histories, all enrollees were defined to have an *a priori* diagnosis of substance abuse. Additional psychiatric co-morbidities were defined if, in addition to their substance abuse treatment, patients were also engaged in outpatient psychiatric care, with or without prescription medications, prior to buprenorphine or methadone maintenance treatment enrollment. This psychiatric outpatient data was reported through the Addiction Severity Index survey for Project BEST clients and through a standardized admission form for all patients at The APT Foundation.

Data Sources

Data for Project BEST buprenorphine and APT Foundation methadone maintenance treatment subjects were compared for enrollees from January 1st, 2005 to June 30th, 2007. Subjects from Project BEST were matched to clients at The APT Foundation on four

criteria including age, gender, race, and previous history of crack or cocaine use. Utilizing these criteria allowed for the evaluation of factors previously associated with tuberculin skin test positivity [97, 98] in comparing patients in Project BEST buprenorphine treatment to those in The APT Foundation's methadone program. Chart review was performed by author RS on 190 patients from the buprenorphine and methadone treatment matched groups using a uniform data extraction instrument. The data extraction instrument was developed using the Teleform software package [99] enabling hand-written chart-review data to be easily translated into Microsoft Excel databases for analysis. Clinical data, including previous and enrollment tuberculin skin test results, was extracted retrospectively via chart review in accordance with HIC #27630. All data was subsequently uploaded to databases stored at The Yale AIDS Program at 135 College St, Suite 323, where it was kept under password protection in accordance with HIC #27630 protocol.

Tuberculin skin test results were unavailable for 15 subjects in the Project BEST cohort and 19 in The APT Foundation cohort due to insufficient record keeping at the study sites. These subjects were excluded from the final data analysis and are not exhibited in the results tables. Ultimately data collection resulted in 175 and 171 subjects in the Project BEST and The APT Foundation study groups, respectively. To account for the missing tuberculin skin testing data, each group was reassessed. This re-evaluation verified that characteristics set by the original matching criteria were retained. No statistically significant differences were found in this re-evaluation.

Data Analysis

The prevalence of tuberculin skin test positivity and comparison of demographic and substance use characteristics were compared between buprenorphine and methadone treatment study groups using two-sided chi-square tests (alpha = .05). Bivariate associations with the primary outcome (tuberculin skin test positivity) were calculated to determine variables that could be included into the final multiple logistic regression model for predicting skin test positivity. The Akaike information criterion (AIC) was used to assess model fit – a lower AIC value indicates a better balance of parsimony and clarification of variance. A p-value <0.20 was used to enter and leave the regression model. The two-sided Wald's test (alpha = .05) was used to assess significance of each of the variables. All statistical analyses were performed at The Yale AIDS Program using SAS, version 9.1.3 (SAS Institute, Cary, NC).

Results

The demographic and health characteristics of the two comparison groups, described in Table 1, did not differ statistically. Though the two groups did not differ on the primary outcome (9% in both groups were tuberculin skin test positive), the buprenorphine treatment group contained twice as many (6% vs. 3%) "new" positive skin test results, with the opposite found in the methadone treatment group where twice as many (6% vs. 3%) were "previously detected" positive skin tests. Thus, 10 (62.5%) of the 16 buprenorphine treatment subjects and 5 (33.3%) of the 15 methadone treatment subjects had "new" positive skin test results and trended toward significance (p = .10).

TABLE 1
Demographic characteristics of study populations.

Characteristic	Buprenorphine Maintenance Treatment ($N = 175$)	Methadone Maintenance Treatment ($N = 171$)	P-value
Mean Age (years)	36 ± 10	36 ± 11	.94
Gender	$N = 174$	$N = 171$	.08
Male	129 (74%)	112 (66%)	
Female	45 (26%)	59 (34%)	
Race			1.00
Black	29 (17%)	28 (16%)	
Hispanic	33 (19%)	32 (19%)	
White	113 (64%)	111 (65%)	
Cocaine/Crack Use	$N = 168$	$N = 171$	.39
Yes	123 (73%)	118 (69%)	
No	45 (27%)	53 (31%)	
High-School Education	$N = 158$	$N = 170$	.07
No	115 (73%)	138 (81%)	
Yes	43 (27%)	32 (19%)	
Psychiatric Comorbidity			.71
Substance use Disorder only	112 (64%)	112 (66%)	
Comorbid mental Illness	63 (36%)	58 (34%)	
TST Status*			.27
Negative	159 (91%)	156 (91%)	
New positive	10 (6%)	5 (3%)	
Previous positive	6 (3%)	10 (6%)	

Sample size is complete except where otherwise noted.
P-value calculated from chi-square test (p less than or equal to .05 is considered significant).
*P-value using Fisher's exact test.

Though not significant, there was a trend toward higher levels of education in the buprenorphine treatment group with 27% having completed education beyond high school compared to 19% in the methadone treatment group (p =.07). Over a third of all patients in both groups (36% of buprenorphine vs. 34% of methadone treatment) met criteria for an Axis I disorder, thus qualifying as having a co-morbid mental illness in addition to opioid-dependence.

There were, however, significant differences between the two groups in their reported substance use preferences (Table 2). Enrollees in buprenorphine treatment were statistically more likely to report secondary preferences for alcohol (30% vs. 8%, p < .0001) and benzodiazepines (8% vs. 3%, p = .038) than their methadone treatment counterparts, while the latter expressed higher preferences for heroin (91% vs. 71%, p <

.0001) and cocaine (69% vs. 26%, p < .0001).

TABLE 2
Substance of abuse characteristics of study populations.

Substance identified as primary, secondary, or tertiary preferred substance of abuse	Buprenorphine Maintenance Treatment ($N = 175$)	Methadone Maintenance Treatment ($N = 171$)	Chi-Square p-value
Alcohol	30%	8%	<.0001
Benzodiazepines	8%	3%	.038
Cocaine/crack	26%	69%	<.0001
Heroin	71%	91%	<.0001
Prescription Opiates	39%	32%	.127
Marijuana	15%	16%	.810

Unadjusted and adjusted analyses are presented in Table 3. Unadjusted analysis illustrated a significant association between tuberculin skin test positivity and black race (OR = 2.72). The adjusted analysis indicated statistically significant higher associations between skin test positivity and blacks (AOR = 3.53, 95% CI = 1.28–9.77), Hispanics (AOR = 3.11, 95% CI = 1.12–8.60) and higher education status (AOR = 3.01, CI = 1.20–7.53). All other associations were non-significant.

TABLE 3
Correlates of positive tuberculin skin test using multiple logistic regression*.

Characteristic	TST Positive ($N = 31$)	Bivariate model ($N = 346$)		Multivariate model ($N = 346$)	
		OR (95% CI)	p-value	AOR (95% CI)	p-value
Study Group					
Methadone Maintenance Treatment (MMT)	15	.96 (.46–2.00)	.9	1.11 (.5–2.48)	.79
Buprenorphine Maintenance Treatment (BMT)	16	Referent		Referent	
Age (years)	–	1.03 (.99–1.07)	.09	1.02 (.98–1.07)	.25
Gender					
Male	26	Referent	–	Referent	–
Female	5	.42 (.16–1.13)	.08	.47 (.15–1.51)	.21
Race/Ethnicity					
White	12	Referent	–	Referent	–
Black	10	2.72 (1.20–6.13)	.016	3.53 (1.28–9.77)	.015
Hispanic	9	1.892 (.83–4.33)	.13	3.11 (1.12–8.60)	.029
Cocaine Use					
No	8	Referent	–	Out of model	–
Yes	23	1.28 (.55–2.96)	.57	Out of model	–
Completed High School					
No	Referent	–	–	Referent	–
Yes	10	1.79 (.80–4.02)	.16	3.01 (1.20–7.53)	.018
Psychiatric Comorbidity					
Substance use Disorder only	24	Referent	–	Referent	–
Comorbid Mental illness	7	.51 (.21–1.23)	.13	.58 (.22–1.54)	.27
Use of substance in 6 months prior to treatment entry					
Heroin	26/281	1.22 (.45–3.32)	.69	Out of model	–
Methadone	3/57	.52 (.15–1.77)	.29	Out of model	–
Other opiates	5/80	.62 (.23–1.66)	.34	Out of model	–
Crack	9/94	1.11 (.49–2.50)	.81	Out of model	–
Cocaine	7/69	1.19 (.49–2.89)	.70	Out of model	–
Crack/Cocaine combined	15/158	1.13 (.54–2.36)	.75	Out of model	–
Marijuana	3/53	.57 (.17–1.94)	.37	Out of model	–
Alcohol	8/66	1.54 (.64–3.62)	.32	Out of model	–

*Patient enrollment status in BMT vs. MMT was forced into the final model.
Note: p-value of .2 was used to determine variables allowed to enter the final multivariate model.

Discussion

The purpose of this study was to evaluate the prevalence of tuberculin skin test positivity in a buprenorphine treatment group as compared to a similar and contemporaneous methadone treatment cohort. Buprenorphine is a relatively new treatment modality for opiate-dependent patients and accordingly best practices surrounding the implementation

of such programs are not fully understood. Given the pre-existing guidelines that all methadone treatment patients should be screened for tuberculosis, yet the lack of evidence supporting or refuting similar guidelines for buprenorphine treatment programs, the data from our study can be used to inform policy and the guidelines surrounding substance abuse treatment programs.

To our knowledge, this is the first study examining the prevalence of tuberculin skin test positivity in a group of patients receiving buprenorphine treatment. Data from this study illustrate a similar prevalence of 9% in new enrollees in both methadone and buprenorphine maintenance treatment programs in the same community. In light of the current recommendations that all clients entering methadone treatment programs be screened for tuberculosis, our findings suggest that similar screening practices are warranted for patients initiating buprenorphine treatment.

In particular, such screening is important as buprenorphine may be reaching a different target of opioid-dependent patients in community settings as evidenced in our study by the differing poly-substance use profiles. Though not reaching statistical significance, the trend that the buprenorphine program identified more "new" positive skin tests requires further investigation, and again suggests that buprenorphine may be reaching a group of opioid-dependent patients with different risk profiles. Data found in our study suggesting differing characteristics between methadone and buprenorphine treatment patients is consistent with previous research [77]. Nonetheless, irrespective of the different sociodemographic and/or risk profiles highlighted by this and previous data, similar prevalence of skin test positivity still suggests that buprenorphine enrollees also require tuberculosis screening at entrance.

Similar to previous studies, these findings additionally suggest higher positive tuberculosis prevalence among racial and ethnic minorities – specifically blacks and Hispanics [100]. Such results highlight the different health risks of people of color in the United States and confirm not only the need for identifying those at highest risk for tuberculosis, but ensuring that they are screened and prophylactically treated. Paradoxically in this study, higher education, often a marker of higher socioeconomic status, was associated with a positive tuberculin skin test. To our knowledge, this has not been previously demonstrated among treatment-seeking opioid-dependent populations. A potential explanation of this result is that those with higher levels of education who were skin test positive were those that had formerly worked within congregate settings, such as nursing homes, hospitals or even prisons, where tuberculin skin test conversions would be expected. An alternative explanation of these data could be that those Hispanics with higher education were not U.S.-born, but came to the United States in search of financial opportunities and had been previously exposed to tuberculosis within their home or endemic within their country. Given a higher previous educational history we could conjecture that such persons were more able to immigrate to the United States in search of more gainful employment opportunities. We assessed the latter relationship, however, and there was no significant interaction. Further studies are warranted to more accurately characterize this population, to confirm or refute our findings, and to better establish the relationship between higher education and tuberculin skin test positivity.

Of note, our study offers implications for the development of enhanced linkages to tuberculosis treatment strategies for the buprenorphine patient population. Previously it has been shown that isoniazid treatment offered in parallel to methadone maintenance

therapy programs is both effective [101] and cost-effective [102], with innovative treatment models enhancing adherence [103, 104]. In part, this is due to the increased structured environment that methadone treatment programs offer with consistent and regular follow-up enabling parallel directly observed isoniazid therapy. However, in contrast, due to the more rapid rate at which buprenorphine maintenance treatment patients receive at-home medication privileges, such consistent structure is typically not available. Thus, in parallel to implementing screening programs for tuberculosis with buprenorphine maintenance treatment, consideration should also be paid to alternative interventions to ensure adequate treatment success on tuberculosis treatment. Previous strategies to enhance adherence [103, 104] may be instructive yet further research will be required to optimize treatment success. Notably, our data also offers potential implications in the international arena. While medication-assisted treatments are limited, if not non-existent, in many countries outside of the United States, increasingly other nations are developing substance-dependence treatment programs utilizing medication-assisted therapies. Data from developed country models such as the long-standing programs in the UK [105] have offered critical insight on the development of newer programs in countries such as Malaysia or the Ukraine. Both of the latter examples have significant HIV epidemics largely fueled by injecting drug use, and therefore the implementation of safe, effective and cost-effective substance-dependence programs will be critical to their public health systems [106, 107]. Our data offers an important insight for such programs, especially those in which medication-assisted treatment will address large burdens of HIV and associated conditions such as tuberculosis. Further data from studies such as our own will help to inform these best-practices and thereby enhance the

evidence base for developing programs. By adopting tuberculosis screening in parallel with the implementation of methadone and/or buprenorphine maintenance treatment programs, public health investments in newly developing programs will be more effective and cost-effective.

Notably, this study has several important limitations. The sample size of the buprenorphine treatment program, while growing, remains relatively small. Furthermore, recommendations stemming from these data are specific to the New Haven community context, and given the paucity of existing buprenorphine treatment programs, it is as yet unclear to what extent our data are generalizeable to the larger opioid-dependent patient population. Additionally, the CHCV is a particular buprenorphine setting that may further limit the degree of generalizability of our data. Finally, with particular regard to analysis of psychiatric co-morbidities, we recognize survey data as utilized in this study are less reliable than validated diagnostic indices. As a result, we suspect that we have likely underestimated the overall burden of psychopathology in our study groups.

Despite these limitations, these data provide preliminary but compelling support for incorporating tuberculosis screening into buprenorphine treatment programs. Such inclusion provides increased potential for detection of latent tuberculosis and enhances access to onsite primary care services for an already marginalized patient population. Increased detection of latent tuberculosis may, therefore, result in increased access to treatment due to engagement in continuity of care. This is particularly true because of buprenorphine's availability within the primary care setting where regular tuberculin skin test screening would facilitate linkage to treatment. Finally, our experience

implementing this screening program has illustrated that it is a practical model that can be considered for other buprenorphine treatment programs.

As research continues to define standards of care for buprenorphine maintenance treatment, other mechanisms to ensure increased access to primary care services for opioid-dependent patients, in particular targeting those co-morbidities known to exist in this population, should remain a priority.

References

1. *American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. 2000, Washington, DC, : American Psychiatric Association.
2. Kreek, M.J. and F.J. Vocci, *History and current status of opioid maintenance treatments: blending conference session.* J Subst Abuse Treat, 2002. **23**(2): p. 93-105.
3. Fiellin, D.A. and P.G. O'Connor, *Clinical practice. Office-based treatment of opioid-dependent patients.* N Engl J Med, 2002. **347**(11): p. 817-23.
4. *Opioids.com*. Accessed October 8th, 2010]; Available from: http://www.opioids.com/timeline/index.html.
5. Altice, F.L., et al., *The potential role of buprenorphine in the treatment of opioid dependence in HIV-infected individuals and in HIV infection prevention.* Clin Infect Dis, 2006. **43 Suppl 4**: p. S178-83.
6. Horgan, C., *Substance Abuse: The Nation's Number One Health Problem - Key Indicators for Policy Update*, ed. S.I.f.H. Policy. 2001, Brandeis University; Princeton, NJ: The Robert Wood Johnson Foundation.
7. *Behind Bars: Substance abuse and America's prison population*. 1998, National Center for Addiction and Substance Abuse at Columbia University: New York, NY.
8. *Substance Abuse and Urban America: Its Impact on An American City, New York*. 1996, Center on Addiction and Substance Abuse (CASA)
9. Altice, F.L., et al., *Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs.* Lancet. **376**(9738): p. 367-87.
10. CDC, *Advancing HIV prevention: new strategies for a changing epidemic--United States, 2003.* MMWR, 2003. **52**(15): p. 329-332.
11. Reichman, L.B., C.P. Felton, and J.R. Edsall, *Drug dependence, a possible new risk factor for tuberculosis disease.* Arch Intern Med, 1979. **139**(3): p. 337-9.
12. Backmund, M., et al., *Factors associated with exposure to hepatitis B virus in injection drug users.* Drug Alcohol Depend, 2006. **84**(2): p. 154-9.
13. Kosten, T.R., B.J. Rounsaville, and H.D. Kleber, *DSM-III personality disorders in opiate addicts.* Compr Psychiatry, 1982. **23**(6): p. 572-81.
14. Rounsaville, B.J., et al., *Diagnosis and symptoms of depression in opiate addicts. Course and relationship to treatment outcome.* Arch Gen Psychiatry, 1982. **39**(2): p. 151-156.
15. CDC, *HIV Diagnoses Among Injection-Drug Users in States with HIV Surveillance --- 25 States, 1994--2000.* MMWR, 2003. **52**(27): p. 634-636.
16. Friedman, L.N., et al., *Tuberculosis screening in alcoholics and drug addicts.* Am Rev Respir Dis, 1987. **136**(5): p. 1188-92.
17. Selwyn, P.A., et al., *A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection.* N Engl J Med, 1989. **320**(9): p. 545-50.
18. Novick, D.M., *The impact of hepatitis C virus infection on methadone maintenance treatment.* Mt Sinai J Med, 2000. **67**(5-6): p. 437-443.
19. Zeldis, J.B., et al., *Seroepidemiology of viral infections among intravenous drug users in northern California.* West J Med, 1992. **156**(1): p. 30-5.
20. Rounsaville, B.J., et al., *Diagnosis and symptoms of depression in opiate addicts. Course and relationship to treatment outcome.* Arch Gen Psychiatry, 1982. **39**(2): p. 151-6.

21. Kerr, T., et al., *Factors associated with methadone maintenance therapy use among a cohort of polysubstance using injection drug users in Vancouver.* Drug Alcohol Depend, 2005.
22. Ding, L., et al., *Predictors and consequences of negative physician attitudes toward HIV-infected injection drug users.* Arch Intern Med, 2005. **165**(6): p. 618-23.
23. Fiellin, D.A., et al., *Treatment of heroin dependence with buprenorphine in primary care.* Am J Drug Alcohol Abuse, 2002. **28**(2): p. 231-241.
24. Gossop, M., et al., *Methadone treatment for opiate dependent patients in general practice and specialist clinic settings: Outcomes at 2-year follow-up.* J Subst Abuse Treat, 2003. **24**(4): p. 313-321.
25. Fiellin, D.A., et al., *Methadone maintenance in primary care: a randomized controlled trial.* Jama, 2001. **286**(14): p. 1724-31.
26. Gerbert, B., et al., *Primary care physicians and AIDS. Attitudinal and structural barriers to care.* Jama, 1991. **266**(20): p. 2837-42.
27. Basu, S., et al., *Models for integrating buprenorphine therapy into the primary HIV care setting.* Clin Infect Dis, 2006. **42**(5): p. 716-21.
28. *Manual for Primary Care Providers: Effectively Caring for Active Substance Users*. 2002, New York, NY: The New York Academy of Medicine.
29. Crystal, S., et al., *Initiation and continuation of newer antiretroviral treatments among Medicaid recipients with AIDS.* J Gen Intern Med, 2001. **16**(12): p. 850-859.
30. Hsu, L.C., et al., *Predictors of use of highly active antiretroviral therapy (HAART) among persons with AIDS in San Francisco, 1996-1999.* Journal of acquired immune deficiency syndromes (1999), 2001. **28**(4): p. 345-350.
31. Davids, E. and M. Gastpar, *Buprenorphine in the treatment of opioid dependence.* European Neuropsychopharmacology, 2004. **14**(3): p. 209-216.
32. Jaffe, J.H. and C. O'Keeffe, *From morphine clinics to buprenorphine: regulating opioid agonist treatment of addiction in the United States.* Drug and alcohol dependence, 2003. **70**(2, Supplement 1): p. S3-S11.
33. Tsuang, M.T., et al., *Genetic influences on DSM-III-R drug abuse and dependence: a study of 3,372 twin pairs.* Am J Med Genet, 1996. **67**(5): p. 473-7.
34. Kendler, K.S. and C.A. Prescott, *Cannabis use, abuse, and dependence in a population-based sample of female twins.* Am J Psychiatry, 1998. **155**(8): p. 1016-22.
35. van den Bree, M.B., et al., *Genetic and environmental influences on drug use and abuse/dependence in male and female twins.* Drug Alcohol Depend, 1998. **52**(3): p. 231-41.
36. Koob, G.F. and F.E. Bloom, *Cellular and molecular mechanisms of drug dependence.* Science, 1988. **242**(4879): p. 715-23.
37. Wise, R.A. and M.A. Bozarth, *Brain substrates for reinforcement and drug self-administration.* Prog Neuropsychopharmacol, 1981. **5**(5-6): p. 467-74.
38. McLellan, A.T., et al., *Similarity of outcome predictors across opiate, cocaine, and alcohol treatments: role of treatment services.* J Consult Clin Psychol, 1994. **62**(6): p. 1141-1158.
39. Schaub, A.F., A. Steiner, and W. Vetter, *Compliance to treatment.* Clin Exp Hypertens, 1993. **15**(6): p. 1121-30.
40. Solomon, L., et al., *Utilization of health services in a cohort of intravenous drug users with known HIV-1 serostatus.* Am J Public Health, 1991. **81**(10): p. 1285-90.
41. Markson, L.E., et al., *Repeated emergency department use by HIV-infected persons: effect of clinic accessibility and expertise in HIV care.* J Acquir Immune Defic Syndr Hum Retrovirol, 1998. **17**(1): p. 35-41.

42. Palepu, A., et al., *The social determinants of emergency department and hospital use by injection drug users in Canada.* J Urban Health, 1999. **76**(4): p. 409-18.
43. French, M.T., et al., *Chronic illicit drug use, health services utilization and the cost of medical care.* Soc Sci Med, 2000. **50**(12): p. 1703-13.
44. Sullivan, L.E., et al., *Initial strategies for integrating buprenorphine into HIV care settings in the United States.* Clin Infect Dis, 2006. **43 Suppl 4**: p. S191-6.
45. Amato, L., et al., *Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification.* Cochrane Database Syst Rev, 2008(4): p. CD005031.
46. Mattick, R.P., et al., *Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence.* Cochrane Database Syst Rev, 2009(3): p. CD002209.
47. Bruce, R.D., T.F. Kresina, and E.F. McCance-Katz, *Medication-assisted treatment and HIV/AIDS: aspects in treating HIV-infected drug users.* AIDS. **24**(3): p. 331-40.
48. Spire, B., G.M. Lucas, and M.P. Carrieri, *Adherence to HIV treatment among IDUs and the role of opioid substitution treatment (OST).* Int J Drug Policy, 2007. **18**(4): p. 262-70.
49. Dole, V.P., M.E. Nyswander, and M.J. Kreek, *Narcotic blockade. 1966.* J Psychoactive Drugs, 1991. **23**(2): p. following 232.
50. Krambeer, L.L., et al., *Methadone therapy for opioid dependence.* Am Fam Physician, 2001. **63**(12): p. 2404-10.
51. Barnett, P.G. and S.S. Hui, *The cost-effectiveness of methadone maintenance.* Mt Sinai J Med, 2000. **67**(5-6): p. 365-74.
52. Keen, J., et al., *Can methadone maintenance for heroin-dependent patients retained in general practice reduce criminal conviction rates and time spent in prison?* Br J Gen Pract, 2000. **50**(450): p. 48-9.
53. Yoast, R., et al., *Report of the Council on Scientific Affairs: methadone maintenance and needle-exchange programs to reduce the medical and public health consequences of drug abuse.* J Addict Dis, 2001. **20**(2): p. 15-40.
54. Bouhnik, A.D., et al., *Nonadherence among HIV-infected injecting drug users: the impact of social instability.* J Acquir Immune Defic Syndr, 2002. **31 Suppl 3**: p. S149-53.
55. Weinrich, M. and M. Stuart, *Provision of methadone treatment in primary care medical practices: review of the Scottish experience and implications for US policy.* JAMA, 2000. **283**(10): p. 1343-8.
56. Gossop, M., et al., *Reduced injection risk and sexual risk behaviours after drug misuse treatment: results from the National Treatment Outcome Research Study.* AIDS Care, 2002. **14**(1): p. 77-93.
57. Mattick, R.P., et al., *Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence.* Cochrane Database Syst Rev, 2002(4): p. CD002207.
58. Sorensen, J.L. and A.L. Copeland, *Drug abuse treatment as an HIV prevention strategy: a review.* Drug Alcohol Depend, 2000. **59**(1): p. 17-31.
59. Glasscote, R., Sussex, J.N., Jaffe, J.H., Ball, J., Brill, L., *The treatment of drug abuse-programs, problems, prospects*. 1972, American Psychiatric Association: Washington DC.
60. Gerstein, D.R., Harwood, H.J. , ed. Treating Drug Problems. Vol. 1. 1990, Institute of Medicine, National Academy Press: Washington DC.
61. Jaffe, J.H., *The maintenance option and the Special Action Office for Drug Abuse Prevention.* Psychiatr. Ann, 1975. **5**(12): p. 42.
62. Fiellin, D.A. and P.G. O'Connor, *New federal initiatives to enhance the medical treatment of opioid dependence.* Ann Intern Med, 2002. **137**(8): p. 688-92.

63. Jasinski, D.R., J.S. Pevnick, and J.D. Griffith, *Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction.* Arch Gen Psychiatry, 1978. **35**(4): p. 501-516.
64. Johnson, R.E., J.H. Jaffe, and P.J. Fudala, *A controlled trial of buprenorphine treatment for opioid dependence.* Jama, 1992. **267**(20): p. 2750-2755.
65. Ling, W., et al., *A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence.* Arch Gen Psychiatry, 1996. **53**(5): p. 401-407.
66. Walsh, S.L., et al., *Clinical pharmacology of buprenorphine: ceiling effects at high doses.* Clin Pharmacol Ther, 1994. **55**(5): p. 569-80.
67. Ball J, R.A., *The Effectiveness of Methadone Maintenance Treatment*. 1991, New York, NY: Springer-Verlag Inc.
68. Fiellin, D.A. and P.G. O'Connor, *Clinical practice. Office-based treatment of opioid-dependent patients.* N Engl J Med, 2002. **347**(11): p. 817-823.
69. Barnett, P.G., G.S. Zaric, and M.L. Brandeau, *The cost-effectiveness of buprenorphine maintenance therapy for opiate addiction in the United States.* Addiction, 2001. **96**(9): p. 1267-1278.
70. Krupitsky, E.M., Illeperuma, A., Gastfriend, D. R., & Silverman, B. L. *Efficacy and Safety of Extended Release Naltrexone (NTX-XR) for the Treatment of Opioid Dependence*. Paper presented at the American Psychiatric Association May 22-24, 2010. New Orleans, LA.
71. Amato, L., et al., *Methadone at tapered doses for the management of opioid withdrawal.* Cochrane Database Syst Rev, 2005(3): p. CD003409.
72. Mattick, R.P., et al., *Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence.* Cochrane Database Syst Rev, 2008(2): p. CD002207.
73. *Drug Court Fact Sheet: Methadone Maintenance and Other Pharmacotherapeutic Interventions in the Treatment of Opioid Dependence*. 2010, American Association for the Treatment of Opioid Dependence.
74. Bruce, R.D. 2010: New Haven.
75. Fiellin, D.A., R.A. Rosenheck, and T.R. Kosten, *Office-based treatment for opioid dependence: reaching new patient populations.* Am J Psychiatry, 2001. **158**(8): p. 1200-1204.
76. Khalsa, J., et al., *Buprenorphine and HIV Primary Care: New Opportunities for Integrated Treatment.* Clin Infect Dis, 2006. **43 Suppl 4**: p. S169-72.
77. Sullivan, L.E., et al., *The practice of office-based buprenorphine treatment of opioid dependence: is it associated with new patients entering into treatment?* Drug Alcohol Depend, 2005. **79**(1): p. 113-6.
78. Weisner, C., et al., *Integrating primary medical care with addiction treatment: a randomized controlled trial.* JAMA, 2001. **286**(14): p. 1715-23.
79. Friedmann, P.D., et al., *Medical and psychosocial services in drug abuse treatment: do stronger linkages promote client utilization?* Health Serv Res, 2000. **35**(2): p. 443-65.
80. Brassard, P., et al., *Yield of tuberculin screening among injection drug users.* Int J Tuberc Lung Dis, 2004. **8**(8): p. 988-93.
81. Scholten, J.N., et al., *Effectiveness of isoniazid treatment for latent tuberculosis infection among human immunodeficiency virus (HIV)-infected and HIV-uninfected injection drug users in methadone programs.* Clin Infect Dis, 2003. **37**(12): p. 1686-92.
82. Snyder, D.C., et al., *Tuberculosis prevention in methadone maintenance clinics. Effectiveness and cost-effectiveness.* Am J Respir Crit Care Med, 1999. **160**(1): p. 178-85.

83. Kunins, H.V., et al., *Validity of a self-reported history of a positive tuberculin skin test. A prospective study of drug users.* J Gen Intern Med, 2004. **19**(10): p. 1039-44.
84. Gourevitch, M.N., et al., *Successful adherence to observed prophylaxis and treatment of tuberculosis among drug users in a methadone program.* J Addict Dis, 1996. **15**(1): p. 93-104.
85. *Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society.* MMWR Recomm Rep, 2000. **49**(RR-6): p. 1-51.
86. WHO, *Policy guidelines for collaborative TB and HIV services for injecting and other drug users: An integrated approach*. 2008.
87. Bridge, T.P., et al., *Safety and health policy considerations related to the use of buprenorphine/naloxone as an office-based treatment for opiate dependence.* Drug Alcohol Depend, 2003. **70**(2S): p. S79-S85.
88. BruceRD, *Development of a Novel Buprenorphine Induction and Stabilization Program: Program Description and Lessons Learned from a Mobile Health Care Program (unpublished)*.
89. Pollack, H.A., et al., *The impact of needle exchange-based health services on emergency department use.* J Gen Intern Med, 2002. **17**(5): p. 341-8.
90. Treatment, C.f.S.A., *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction Treatment Improvement Protocol (TIP) Series 40*, D.P.N.S. 04-3939, Editor. 2004, Substance Abuse and Mental Health Services Administration: Rockville, MD.
91. Copenhaver, M.M., R.D. Bruce, and F.L. Altice, *Behavioral counseling content for optimizing the use of buprenorphine for treatment of opioid dependence in community-based settings: a review of the empirical evidence.* Am J Drug Alcohol Abuse, 2007. **33**(5): p. 643-54.
92. Liebman, J., M. Pat Lamberti, and F. Altice, *Effectiveness of a mobile medical van in providing screening services for STDs and HIV.* Public Health Nurs, 2002. **19**(5): p. 345-353.
93. Altice, F.L., et al., *Adherence to hepatitis B virus vaccination at syringe exchange sites.* J Urban Health, 2005. **82**(1): p. 151-61.
94. McLellan AT, K.H., Metzger D, et al, *The Fifth Edition of the Addiction Severity Index.* J Subst Abuse 1992(9): p. 199-213.
95. First MB, S.R., Gibbon M, Williams J, *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P)* 2002, New York: Biometrics Research, New York State Psychiatric Institute.
96. *The APT Foundation*. Accessed October 8th, 2010]; Available from: http://www.aptfoundation.org/methadone.htm.
97. Carbonara, S., et al., *Correlates of Mycobacterium tuberculosis infection in a prison population.* Eur Respir J, 2005. **25**(6): p. 1070-6.
98. Howard, A.A., et al., *Crack cocaine use and other risk factors for tuberculin positivity in drug users.* Clin Infect Dis, 2002. **35**(10): p. 1183-90.
99. *Cardiff - Teleform*. Accessed October 8th, 2010]; Available from: http://www.cardiff.com/products/teleform/.
100. *Trends in tuberculosis--United States, 2008.* MMWR Morb Mortal Wkly Rep, 2009. **58**(10): p. 249-53.
101. Gourevitch, M.N., et al., *Effectiveness of isoniazid chemoprophylaxis for HIV-infected drug users at high risk for active tuberculosis.* AIDS, 1999. **13**(15): p. 2069-74.

102. Gourevitch, M.N., et al., *Cost-effectiveness of directly observed chemoprophylaxis of tuberculosis among drug users at high risk for tuberculosis.* Int J Tuberc Lung Dis, 1998. **2**(7): p. 531-40.
103. Elk, R., et al., *Compliance with tuberculosis treatment in methadone-maintained patients: behavioral interventions.* J Subst Abuse Treat, 1993. **10**(4): p. 371-82.
104. O'Connor, P.G., et al., *Tuberculosis chemoprophylaxis using a liquid isoniazid-methadone admixture for drug users in methadone maintenance.* Addiction, 1999. **94**(7): p. 1071-5.
105. Strang, J., et al., *Impact of supervision of methadone consumption on deaths related to methadone overdose (1993-2008): analyses using OD4 index in England and Scotland.* BMJ. **341**: p. c4851.
106. Noordin, N.M., et al., *Substitution treatment in Malaysia.* Lancet, 2008. **372**(9644): p. 1149-50.
107. Bruce, R.D., et al., *HIV treatment access and scale-up for delivery of opiate substitution therapy with buprenorphine for IDUs in Ukraine--programme description and policy implications.* Int J Drug Policy, 2007. **18**(4): p. 326-8.