The Science and Practice of Medication-Assisted Treatments for Opioid Dependence

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This paper briefly reviews the evolution of opioid addiction treatment from humanitarian to scientific and evidence-based, the evidence bases supporting major medication-assisted treatments and adjunctive psychosocial techniques, as well as challenges faced by clinicians and treatment providers seeking to provide those treatments. Attitudes, politics, policy, and financial issues are discussed.

Keywords opioid addiction, methadone, buprenorphine, heroin, diamorphine, history

INTRODUCTION

Humans have been using and misusing psychoactive substances for millennia, and it is likely that addiction has existed just as long. Addiction has been conceptualized in different ways throughout history: moral weakness, defect, inebriety, insanity, crime, social problem, and more recently, a chronic but treatable disease. All of these reflect society’s subtle—and not so subtle—perceptions about the nature and etiology of substance use, misuse, and addiction. Not surprisingly, global drug and user-related policies and treatment trends have paralleled and reflected these evolving views in many cultures globally and historically.

References to opium as an analgesic appear in ancient Mesopotamian medical texts ca. 3rd millennium BC. Traders brought opium to India and China in the eighth century AD (Dwarkanath, 1965; Fort, 1965) and to all of Europe between the 10th and 13th centuries. Beginning in the 16th century, manuscripts describing tolerance and addiction were written in Turkey, Egypt, Germany, and England. Opium addiction was particularly severe in China, where opium dens flourished during the 17th century and later (Brownstein, 1993). Opium use was also a widespread problem in 19th century England (Berridge, 1982; DeQuincey, 1821). While the practice of smoking opium spread to the USA in the 1870s, its association with the Chinese hindered its popularity there (Musto, 1987b).

Morphine was isolated from opium in 1806 (Sertürner, 1806) but was not widely used as an analgesic until the development of the hypodermic needle in 1853 (Aragon-Poce et al., 2002); the term “hypodermic” was coined in describing the optimal way to inject it (Davenport-Hines, 2004). Morphine became a mainstay in American medicine during the Civil War and also gained popularity in Europe. While opium was the drug of choice for minorities and the economically disadvantaged, morphine was viewed as medicinal and suitable for all classes. Unlike opium, no stigma was associated with morphine, and its use became a pastime in Europe and the USA.

By the time morphine’s addictive potential became known to the medical community, dependence was widespread. As a result, scientists began searching for a non-addictive pharmacological cure for opioid addiction (Aragon-Poce et al., 2002; White, 1998).

British chemist C.R. Wright (1874) synthesized diacetylmorphine by combining morphine with acetic acid, but the compound did not become popular until German Chemist F. Hoffmann re-synthesized it in 1897, and Bayer Pharmaceuticals marketed it under the name “Heroin.” This name is derived from the German “heroisch,” which means heroic or strong (Haubrich, 2003). Heroin was promoted as a non habit-forming over-the-counter cough suppressant and cure for morphine addiction. However, heroin was soon found to be even more habit forming than morphine. By 1910, heroin had replaced morphine and opium as the primary illicit drug in the USA, in part due to the ban imposed by the Smoking Opium Exclusion Act of 1909. It was also used widely in Europe (Aragon-Poce et al., 2002; Davenport-Hines, 2004). Opium in patent medicines, the use of morphine by Civil War veterans, and the use of heroin to treat a wide variety of ailments...
led to high rates of opioid dependence in early 20th century America (Marshall, 1911; Musto, 1991; Terry & Pellens, 1928). Legislation was soon passed to address this problem. The Harrison Narcotics Act, 1914, in the USA, banned the purchase of heroin without a prescription, and the Heroin Act of 1924 banned its manufacture, distribution, and sale. Despite these efforts, heroin use flourished throughout the 20th century in American cities, especially New York. Although heroin use began among upper middle class Whites, there was a sudden increase in heroin use among urban African Americans and Latinos shortly after World War II. By the 1960s, heroin use spread to the suburbs, and the number of US users rose from 50,000 to 500,000 between 1960 and 1970 (Aragón-Poche et al., 2002).

Governments worldwide have made multiple attempts to control opioid production and consumption (Angarola, 1990). The three most important treaties influencing current international policy include the 1961 Single Convention on Narcotic Drugs, the 1971 Convention on Psychotropic Substances, and the 1988 Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances. The 1961 Convention combined the multiple international agreements that existed at the time into a single treaty (Shapiro, 1994). It was expanded to include not only plant-based substances like coca and opium, but also drugs with similar effects to those specified in the treaty (United Nations, 1961). In 1971, the Convention on Psychotropic Substances extended the 1961 treaty to cover new psychoactive substances, including amphetamines, hypnotics, and hallucinogens (United Nations, 1971). Most potent analgesics are still controlled under the 1961 Convention, while some are controlled as psychotropic substances under the 1971 Convention (WHO, 2003).

In an effort to reduce the illicit availability of drugs by increasing global law enforcement, the UN drafted a third treaty, the Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, in 1988 (Gilmore, 1991; United Nations, 1988). The provisions of the 1988 Convention emphasized international cooperation and targeted criminal activity associated with drug trafficking (United Nations International Drug Control Program, 2000). For these treaties to be effective, however, individual governments must apply the provisions of the treaties in their respective laws (Rexed, Edmondson, Khan, & Samson, 1984). Different countries use their own national regulatory systems and classifications for drug restriction levels (WHO, 2003). In accordance with the 1961 Convention, the U.S. Congress enacted the Controlled Substances Act, which created five Schedules (I, II, III, IV, and V) of drugs, with Schedule I being under the most restriction and Schedule V being under the least restriction. Under the Controlled Substances Act, opium, morphine, and methadone are Schedule II drugs. Heroin is a Schedule I drug, with no currently accepted medical use in the USA (GPO, 1970).

Despite efforts to control opioid production and trafficking, use and dependence remain global problems. In 2007, the UN Office on Drugs and Crime (UNODC) estimated the total number of global opioid users to be between 15.2 and 21.1 million, with 11 million heroin users. More than half of all users live in Asia, with the highest proportion along trafficking routes out of Afghanistan. Opiates are the major illicit drug problem for the populations of Central and Southwest Asia and continue to be a prominent issue in Europe (particularly the UK, France, Germany, Spain, Russia, and Ukraine). In the USA, heroin use has remained stable over the years, with approximately 1.2 million users. However, a new trend has emerged, with 5.2 million people reporting inappropriate use of prescription opioids (particularly oxycodone) in 2007. Though globally, opium production has been reported to be in decline, opioids remain one of the world's largest drug problems, and recent reports document a resurgence of opium production in Afghanistan (UNODC, 2007).

Approximately 60% (3.2 million) of injection drug users (IDUs) use opioids (most frequently heroin; Needle & Zhao, 2010). IDU is strongly associated with HIV and Hepatitis C throughout the world. IDU accounts for 30% of HIV infections outside Sub-Saharan Africa and up to 80% in some eastern European and central Asian countries (UNAIDS, 2006). Unsafe injection practices account for approximately 90% of new Hepatitis C infections. However, measures that arrest the spread of these infections among IDUs, including opioid agonist maintenance treatment, have limited application globally (U.S. Census Bureau, 2004), though this situation has been changing with the more recent increase in methadone treatment in China (WHO, 2008), and increasing use of methadone and buprenorphine in Vietnam (WHO, 2009a), Indonesia (WHO, 2005a), and Malaysia (WHO, 2005b).

Substance use disorders (SUDs) are increasingly seen as chronic health conditions with alternating periods of full-blown use, lessened use/abstinence, exacerbations (i.e., relapses), and treatment re-entry. They are similar in course to other chronic diseases, such as diabetes, hypertension, and asthma (Dennis & Scott, 2007; Hser, Anglin, Grella, Longshore, & Prendergast, 1997; Hser, Longshore, & Anglin, 2007; McLellan, Lewis, O'Brien, & Kleber, 2000; NIDA, 2009). Opiate dependence is associated with neurological changes (e.g., Kieffer & Evans, 2002; Volkow & Li, 2004; Williams, Christie, & Manzoni, 2001) and is viewed as a chronic, brain-based disorder with a high potential for relapse (WHO, 2004).

**EVOLUTION OF OPIOID ADDICTION TREATMENT: FROM HUMANITARIAN TO EVIDENCE-BASED**

Long before modern treatment programs existed, medical professionals recognized the need to address addiction. Addiction treatment services have evolved from...
humanitarian, moral, legalistic, and criminal to scientific and evidence-based. A major turning point in attitudes regarding addictions came in 1810 when Benjamin Rush, the father of American psychiatry, proposed that excessive alcohol use was a disease, rather than a moral defect (Jaffe, 2000). This has been viewed as the beginning of the medical model of addictions. Nevertheless, efforts to treat SUDs in 19th-century America reflected the views of the Temperance Movement: that addiction was a result of moral weakness and lack of self-control (Bacon, 2008).

Early U.S. Temperance societies promoted humane treatment and healthful moral reform for addicts. Organizations such as the Women’s Christian Temperance Union and the Sons of Temperance held meetings in which addicts pledged abstinence and provided mutual assistance. These meetings promoted sobriety through communal encouragement and surveillance. Several temperance societies established “inebriate homes,” including the Washingtonian Homes in Boston and Chicago, in which patients were committed for voluntary stays to achieve abstinence and moral reform (White, 1998). Patients in these received room and board with minimal formal treatment; attending mutual assistance meetings was paramount. Inebriate asylums and private sanitaria provided residential treatment programs.

During the early 20th century, withdrawal alone, often “cold turkey” or accomplished with substances considered ineffective or even harmful today (e.g., strychnine, alcohol, Cannabis indica, belladona, quinine, placebos, etc.), was considered adequate treatment for opiate addiction. Not surprisingly, relapse rates were high (Kleber, 1998). The large number of addicts and the Temperance Movement led to a public outcry against the easy availability of alcohol and drugs. The Harrison Narcotics Act of 1914 banned the purchase of heroin without a prescription and was interpreted as banning the treatment of addictions by physicians in private offices. Between 1919 and 1935, nearly 25,000 physicians were indicted, and 2,500 were imprisoned (Kleber, 2008).

High relapse rates after treatment and the public health crisis created by the ban on the prescription of morphine by the Harrison Narcotics Act led to the creation of between 44 and 60 narcotic clinics that legally provided morphine or heroin to dependent individuals between 1912 and 1925 (Federal Bureau of Narcotics, 1955; Musto, 1987a). Many clinics were run by law enforcement. Because these clinics did not lead to abstinence, the primary goal of the Temperance Movement popular at that time, they were considered failures, and all of the US clinics were closed by 1925, due to threats of federal indictment of medical staff (White, 1998).

During and immediately following Prohibition in the USA, addiction treatment became more punitive. Addicts who could not afford to undergo detoxification in private hospitals were sent to jails, work farms, and psychiatric hospitals. In 1935, the U.S. Public Health Service established two federal “narcotic farms” in Lexington, Kentucky, and Fort Worth, Texas, to confine and treat addicts (Government Services, 1935; JAMA, 1935). These were

self-contained prison hospitals specializing in the treatment of individuals dependent on drugs considered illegal under federal law, mostly narcotics. The goals of the “farms” were to segregate addicts from society and provide them with medical treatment (Hawkins, 1937; Lowry, 1956). Although most patients were addicted prisoners or probationers, voluntary admission was available. Treatment included a 4–10-day detoxification followed by periods of convalescence and rehabilitation. Length of stay varied; most offenders were sentenced to a year or longer, but voluntary patients were able to sign themselves out without staff permission. Life was regimented, and there was an emphasis on work assignments (Acker, 1997). The Lexington and Fort Worth facilities provided most of the treatment for addicts between 1935 and the early 1950s, and outside of them, formal treatment was still difficult to obtain (White, 1998).

In the wake of Prohibition, few addictions treatment resources became available in the USA until the founding of Alcoholics Anonymous (AA), the first 12-step program in 1935. An abstinence-based fellowship, AA makes use of mutual support and the 12 steps of character reform (Baumohl & White, 2003). This method was adopted by other 12-step programs, including Narcotics Anonymous (NA), a similar group founded in 1953. Though NA membership declined throughout the 1950s, the group experienced resurgence during the 1960s, as heroin gradually replaced morphine as the primary drug used by opioid addicts (White, 2002). NA has become global, with over 53,000 weekly meetings held in North, Central, and South America, Europe, Africa, and Asia (Narcotics Anonymous World Services, 2009).

By the 1960s, the political atmosphere surrounding addictions treatment in the USA had changed markedly. In 1962, the Supreme Court ruling in Robinson v. California (370 U.S. 660) stated that narcotic addiction is a “disease,” and that an individual may not be punished solely for being addicted. Addictions research flourished, with healthcare providers testing new treatment models and several states opening specialized institutions (White, 2002). Such efforts have brought about an enhanced understanding of SUDs, as well as new pharmacotherapeutic and psychosocial interventions. In addition to mutual assistance groups such as NA, today’s patients can choose treatments with goals ranging from total abstinence to

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2 Initially assisted with hot baths during the day and chloral hydrate for sleep; assisted with methadone after 1948.

3 Robinson v. California was a decision regarding the constitutionality of a California statute making the state of being addicted a crime. The decision reads, “... a law which made a criminal offense of such a disease would doubtless be universally thought to be an infliction of cruel and unusual punishment in violation of the Eight and Fourteenth Amendments.”

4 The reader is asked to consider that treatment can be briefly and usefully defined as a planned, goal directed, temporally structured change process, of necessary quality, appropriateness, and conditions (endogenous and exogenous), which is bounded (culture, place, time, etc.) and can be categorized into professional-based, tradition-based, mutual-help based (AA, NA, etc.) and self-help (“natural recovery”) models. There are no unique models or techniques used with substance users.
harm reduction (e.g., Marlatt, 1998) and improvement in quality of life.

INNOVATIONS IN OPIOID DEPENDENCE TREATMENT

Methadone
In the 1960s, US physicians Vincent Dole and Marie Nyswander postulated that heroin addiction was a disease that caused enduring metabolic changes in the central nervous system; thus addicts needed an on-going pharmacological treatment for metabolic stabilization (Dole & Nyswander, 1967). They reasoned that previous attempts at maintenance were unsuccessful because the correct drug had not been employed. Dole and Nyswander tested morphine, heroin, and several synthetic opioids but were unable to find an appropriate dose to create a stable plateau between withdrawal and sedation (White, 1998). However, in 1964, Dole and Nyswander had great success with methadone, a long-acting opioid agonist analgesic developed by I.G. Farben in 1943 (Dole & Nyswander, 1965; Kleber, 2008; White, 1998). Methadone acts as a replacement therapy, mitigating withdrawal, reducing craving, and inducing tolerance to block the average dose of heroin for 24 to 36 hours. Methadone is used both to assist in withdrawal (e.g., Amato, Davoli, Minozzi, Ali, & Ferri, 2005) and for maintenance (i.e., methadone maintenance therapy; MMT).

Although Dole and Nyswander’s initial trials took place on inpatient units (White, 1998), methadone is now dispensed in specialized outpatient Methadone Maintenance clinics. MMT is the standard opioid agonist therapy for opioid dependence. Systematic reviews (e.g., Mattick, Breen, Kimber, & Davoli, 2009) have demonstrated MMT’s overall efficacy in reducing heroin use and retaining patients in treatment. Research studies have consistently demonstrated MMT’s efficacy in reducing morbidity and mortality (Zanis & Woody, 1998), HIV infection (Metzger et al., 1993), and criminal activities (Ball & Ross, 1991). In all types of MMT, dosing is contingent upon participation in psychosocial interventions. Most patients require daily doses, and any “take-home” doses are strictly regulated to prevent diversion (Kleber, 2008).

Two models of MMT have developed, Blockade Treatment (Dole, Nyswander, & Kreek, 1966) and the Low-Dose approach. In Blockade Treatment, addicts are maintained on doses sufficient (80–120 mg/day or more) to forestall withdrawal and block the euphoric effects of any potential heroin use. The Low-Dose approach maintains addicts on low doses (usually ≤30 mg/day). Although the optimal maintenance dose must be decided on a case-by-case basis (ASAM, 2006; Payte & Khuri, 1993), a systematic review (Faggiano, Vigna-Taglianti, Versino, & Lemma, 2003) found that outcomes are best with doses between 60 and 100 mg per day, and multiple studies have demonstrated that patients on doses ≥60 mg per day fare better than those on lower doses (e.g., Ball & Ross, 1991; Caplehorn & Bell, 1991; Caplehorn, Bell, Klein, & Gebski, 1993; Hartel, 1990; Hartel, Schoenbaum et al., 1989; Hartel, Selwyn et al., 1988). The American Society of Addiction Medicine (ASAM, 2006) warns against “inadequate dosing, sometimes deriving from arbitrary low-dose policies” (p. 2).

Despite MMT’s empirically demonstrated benefits, it continues to be controversial. Where MMT is legally available, it is highly regulated by federal and state agencies. In some geographic areas, access remains a major problem, with less than 10% of the global population in need of this treatment actually receiving it (WHO, 2008). Most of the unmet need can be found in Russia, China, and Southeast Asia, though this situation is changing in China. Although Russia has one of the highest rates of opiate use in the world, federal laws have banned agonist therapy there, and all addiction treatment programs there are abstinence-oriented. China opened its first MMT clinic in 2004, with 503 in 23 provinces by 2007 (WHO, 2008).

Naltrexone
Naltrexone, a long-acting opioid antagonist synthesized in 1965 (Blumberg & Dayton, 1973), was regarded with high hopes in the 1970s as the future of opioid addiction treatment. Approved by the U.S. Food and Drug Administration (U.S. FDA) in 1983, Naltrexone completely blocks the effects of opioids and produces no euphoric effects; it operates on the principle of behavioral extinction (Sullivan, Vosburg, & Comer, 2006). While naltrexone’s pharmacologic properties make it an ideal candidate for opioid addiction treatment, research demonstrates that daily oral dosing is associated with poor compliance and inadequate retention in treatment among all but the most motivated patients (Resnick, 1998; Sevarino & Kosten, 2009). However, despite poor compliance, the research literature indicates that oral naltrexone alone or with psychosocial treatment is more efficacious than placebo alone or placebo with psychosocial treatment in reducing heroin use during treatment; naltrexone combined with psychosocial treatment was more effective than psychosocial treatment alone in preventing re-incarceration during treatment (Amato et al., 2008a). Naltrexone may also have short-term benefits, as seen in the case of a suicide attempt by heroin overdose made ineffective by...
naltrexone (Krupitsky et al., 2001). Russian studies (e.g., Krupitsky et al., 2004, 2006) are the sole exception to the poor compliance seen in the US and other Western settings. Better compliance in Russia has been attributed to the unavailability of agonist treatments there and the role of cohesive families in monitoring and encouraging patients’ daily compliance (Krupitsky & Blokhina, 2010).

A promising development for opioid addiction treatment is sustained-release naltrexone in the form of injections (Vivitrol, Depotrex) and implants (Prodetoxon). Vivitrol was approved by the U.S. FDA in 2006 to treat alcoholism and in 2001 to treat opiate dependence (Krupitsky et al., 2011). Naltrexone implants are also being used in clinical trials in Russia, Australia, China, Germany, Egypt, and England. None are currently approved for opiate addiction except Prodetoxon in Russia (Lobmaier, Kornør, Kunøe, & Bjørndal, 2008). Although it may be premature to draw conclusions about the efficacy of sustained-release naltrexone due to a paucity of published randomized controlled trials (RCTs; Lobmaier et al., 2008), data from the sole published RCT and from other types of studies are promising. In the US RCT of Depotrex (Biotek, Inc.), Comer et al. (2006) compared varying doses with placebo to treat heroin dependence. They found a dose-dependent effect on treatment retention and substance-negative urines. A UK report on patients receiving naltrexone implants to treat heroin addiction (Foster, Brewer, & Steele, 2003) demonstrated substantial protection from early relapse and increased abstinence after opioid withdrawal. A Spanish study (Carreño et al., 2003) of maintenance with depot naltrexone after rapid antagonization found higher rates of treatment retention and opioid abstinence relative to patients from the same clinic taking oral naltrexone.

Buprenorphine

Buprenorphine, a partial opioid agonist, was synthesized and developed by British chemist Dr. John Lewis of Reckitt Coleman. Initially, buprenorphine was developed as an analgesic; it is also used in opioid detoxification and maintenance treatment (Lewis, 1998). Buprenorphine is available both as a monotherapy (Subutex; Reckitt Coleman) and in combination with naltrexone (Suboxone, Reckitt Benckiser). France was the first country to approve buprenorphine for the treatment of opioid dependence in 1996; the USA followed in 2002. As of 2005, buprenorphine had been approved in 44 countries (Carriere et al., 2006). It is available in the USA and many other countries as a prescription medication. Buprenorphine has several important advantages: Because it is a partial agonist, associated physical dependence and withdrawal are less severe than with full agonists, and it has a substantially greater margin of safety (Eissenberg et al., 1996, 1997; Walsh, Preston, Sitzer, Cone, & Bigelow, 1994). Buprenorphine is available as a prescription medication outside of the highly regulated methadone clinic system, and while methadone usually requires daily dosing, buprenorphine can be taken once every two days, which makes it more appealing to many patients (Mattick, Kimber, Breen, & Davoli, 2008). Buprenorphine has greatly expanded the availability of opioid agonist treatment globally and engaged patients who did not want methadone maintenance or were unable to access it. Buprenorphine has become a frontline treatment option in many countries, especially those where MMT is limited or unavailable. Increasing injection heroin use has permitted several eastern European countries, Russia not included, to implement MMT and buprenorphine maintenance therapy (BMT; Carriere et al., 2006).

The research literature demonstrates that buprenorphine at medium (8–15 mg) and higher (16–32 mg) doses is more effective than placebo at reducing heroin use, but it is somewhat less effective than methadone, particularly when methadone is prescribed at adequate doses (e.g., 60–120 mg; Mattick et al., 2008). A recent trial in which patients were randomized to methadone or Suboxone has shown better retention with methadone than with Suboxone (Teruya et al., 2010). Buprenorphine has been used successfully with adolescents and young adults (e.g., Subramaniam, Fishman, & Woody, 2009; Woody et al., 2008). In France, which has had the longest experience with buprenorphine treatment for opioid dependence, its use has been associated with significant reductions in deaths from drug overdose, from 465 in 1996 to 89 in 2004 (Emmanuelli & Desenclos, 2005; Guye et al., 2002). In conjunction with buprenorphine, methadone, and needle exchange programs, there has been a reduction in HIV prevalence among IDUs from 40% in 1996 to 20% in 2003 (Emmanuelli & Desenclos, 2005).

Heroin

Although any use of heroin in the USA has been illegal since 1924, heroin is currently used for general medical purposes in the UK, Belgium, the Netherlands, Iceland, Malta, Canada, and Switzerland (Gossop, Keaney, Sharma, & Jackson, 2005; Stimson & Metrebian, 2003), most often to relieve severe pain. In some countries, heroin maintenance therapy (HMT) is used in the treatment of very severely addicted, treatment resistant heroin addicts. The UK has had legal HMT since at least 1968. During HMT’s years of popularity, approximately from 1968 to 1972, oral heroin was given as a take-home prescription with instructions. HMT’s method of administration was subsequently switched to injection (Strang & Gossop, 2005). Interest in HMT has declined over the years, and only a very small number of UK patients receive take-home injectable HMT today. For example, only 448 patients received it in 2002 (Metrebian, Carnwath, & Stimson, 2002).

HMT with completely supervised injectable dosing was legalized for very severely addicted, treatment resistant addicts in Holland in 2006, in Switzerland in 2008, in

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4 In France, buprenorphine is prescribed by family physicians.
5 In the USA, buprenorphine is prescribed by specially trained physicians with a “waiver” to prescribe it. They are limited to treating 30 patients during the first year and up to 100 in subsequent years, after obtaining an additional waiver (CSAT Buprenorphine Information Center, 2010).
Much progress has been made in psychopharmacological research has not adequately demonstrated the efficacy of psychotherapy, psychoeducation, behavioral contingency psychosocial treatments used substance use over medication-only paradigms (Amato et al., 2009). The North American Opiate Medication Initiative (NAOMI) trial (Oviedo-Joekes et al., 2009) demonstrated that maintenance on injectable heroin was actually more effective than oral methadone among very highly treatment resistant addicts in increasing treatment retention and reducing illicit drug use and illegal activities. Not surprisingly, heroin maintenance remains highly controversial. Some policy-makers believe that heroin maintenance is an effective option for very severely addicted patients for whom methadone has not worked, while others condemn any use of it outright. Heroin maintenance is an issue on the forefront of the debate between advocates and opponents of harm reduction. Advocates argue that for the most severely addicted, providing regular access to a minimal quantity of the drug in a safe and controlled manner is preferable to the alternative of continued high-risk and illegal activities associated with the use of illegally obtained drugs, and emphasize the good done by reducing disease transmission and crime (Rehm & Fischer, 2008). Opponents argue that HMT is not a form of treatment and reduces motivation to discontinue heroin use; they interpret reductions in risk behaviors seen in clinical trials as possibly due not to the prescription of heroin but to other therapeutic elements of HMT programs (McKeganey, 2008).

**Adjunct Psychosocial Treatments**

Much progress has been made in psychopharmacological treatments for opioid addiction, and adjunctive psychosocial treatments play an important role in improving their efficacy, helping to prevent relapse, and reducing risky behaviors. Psychosocial treatments include, but are not limited to: individual, group, and family counseling, psychotherapy, psychoeducation, behavioral contingency interventions, and expressive arts therapies. Although research has not adequately demonstrated the efficacy of psychosocial treatments used without medication-assisted treatment for opioid dependence (Mayet, Farrell, Ferri, Amato, & Davoli, 2005), multiple studies demonstrate that psychosocial treatments added to agonist maintenance treatments result in improved decreased illicit substance use over medication-only paradigms (Amato et al., 2008b). Multiple studies also support combined agonist and psychosocial treatment for dual opioid and cocaine addiction (Castells et al., 2009).

One important adjunctive psychosocial intervention is contingency management (CM), which uses a system of incentives and disincentives to encourage abstinence and discourage illicit drug use (Higgins, Silverman, & Heil, 2008). CM gained recognition in the 1990s with the development of Voucher-Based Reinforcement Therapy (VBRT), in which patients receive vouchers to reinforce abstinence and compliance (Higgins et al., 2008). CM used in conjunction with methadone maintenance has been demonstrated to reduce illicit drug use (Prendergast, Podus, Finney, Greenwell, & Roll, 2006; Griffith, Rowan, Szal, Roark, & Simpson, 2000; Preston, Umbricht, & Epstein, 2000; Silverman et al., 1996) and increase duration of sustained abstinence (Preston et al., 2000). Bickel, Amass, Higgins, Badger, and Esch (1997) found that patients who received CM with buprenorphine had increased treatment retention and achieved longer continuous abstinence. CM is also associated with improved retention in naltrexone therapy (Carroll et al., 2001; Preston et al., 1999), increased adherence to naltrexone (Preston et al., 1999), and reduced illicit drug use (Carroll et al., 2001). Another important psychosocial intervention is Community Reinforcement and Family Therapy (RAFT), developed by psychologists Robert Meyers and Jane Smith (Meyers & Smith, 1995). RAFT aims to engage users in treatment by changing their social environment (Meyers, Miller, Hill, & Toniga, 1998; Meyers & Smith, 1995). RAFT uses family members and/or partners to provide motivational support (Smith, Meyers, & Miller, 2010). Patients who participated in RAFT have also been found to have more consecutive opiate-negative urine drug screens (Abbott, Weller, Delaney, & Moore, 1998). Psychosocial therapies addressing HIV risk behaviors during the methadone maintenance have also demonstrated efficacy in reducing those behaviors (e.g., Avants, Margolin, Usubila, & Doebriek, 2004). In addition, there is evidence that receiving additional psychosocial and health services outside of medication-assisted treatment clinics is associated with reduced illicit substance use (Wu, El-Bassel, Gilber, Chang, & Sanders, 2010).

**Peer Health Change Agents**

The increasing role of trained former and even active substance users as peer health educators and change agents is a burgeoning extension of the harm reduction approach. The literature demonstrates that peer health change agents have been successful in promoting safer injection practices and reversing overdoses. User-run organizations, such as the Vancouver Area Network of Drug Users (VANDU), have made significant contributions through advocacy, activism, public education, and community care and support activities: the Alley Patrol (provision of sterile needles and education on safe injection practices by peers on the streets), office-based needle exchange and recovery, peer visits to hospitalized users, and peer support and advocacy (Kerr et al., 2006). VANDU has accessed and intervened with IDUs at great risk of adverse health consequences, who probably could not have been reached by traditional agencies without peer health change agents (Hyashi, Wood, Wiebe, Qi, & Kerr, 2010). Current and former opioid abusers have been successfully trained to recognize opioid overdose symptoms and to determine when naloxone is necessary (Green, Heimer, & Grau, 2008); these trained peers have successfully reversed opioid overdoses with naloxone (Galea et al., 2006; Strang et al., 2008). There have been calls to extend these overdose prevention programs...
(e.g., Kim, Irwin, & Khoshnood, 2009; Lenton, Dietze, Degenhardt, Darke, & Butler, 2009).

**CHALLENGES FACED BY TREATMENT PROVIDERS**

Clinicians treating patients with opioid dependence frequently face multiple challenges, including attitudes towards addiction and its treatment that are reflected in varying laws, policies, politics, and funding and may ultimately affect the diffusion and adoption of evidence-based treatments. The gap between research to develop and validate empirically based treatments and the widespread implementation of those treatments is well known (e.g., IOM, 2006) and is currently being addressed on both national and international levels (e.g., NIDA/SAMHSA Blending Initiative, NIDA, 2010; UNODC TreatNet, UNODC, 2010).

**Attitudes and Their Implications**

As history suggests, addiction and its treatment are controversial issues associated with strongly held attitudes and opinions by a range of individuals and systemic stakeholders. Public opinions, and their makers and sustainer, vary throughout the world and have been reflected in differing laws, policies, and treatment trends historically (Durrant & Thanker, 2003). Although a detailed presentation of the interactions between global attitudes and treatment trends is beyond the scope of this paper, the literature on attitudes of general clinicians and addiction specialists towards addicted patients and medication-assisted treatments will be briefly reviewed. In general, it appears that non-addictions healthcare professionals’ attitudes towards addicted patients tend to be more negative than their attitudes towards patients with other problems (e.g., Abouyanni et al., 2000; Chappell, Veach, & Krug, 1985). Addictions clinicians’ attitudes vary, and these variations are reflected in program philosophies and goals, as well as specific techniques. A study of physicians prescribing methadone to opioid-dependent patients in the Westfalen-Lippe region of Germany demonstrated an association between decreased knowledge of the risks and benefits of methadone maintenance and increased support for abstinence-oriented policies (Gerlach & Caplehorn, 1999). Findings from American studies demonstrate that clinicians with more formal training are less supportive of confrontative techniques and more supportive of medication-assisted treatments (Caplehorn, Hartel, & Irwig, 1997; Forman, Bovasso, & Woody, 2001).

Differing attitudes regarding addiction and treatment are reflected in politics, as well as the overall approaches of opioid addiction treatment programs and dosing strategies; these philosophies directly impact whether and how medications are used. For example, despite MMT’s well-documented efficacy, it has seen vigorous political opposition in some areas. Agonist maintenance therapies are illegal in Russia, and although they are legal in the USA, they continue to elicit controversy.

Opposition to MMT has resulted in decreased public funding over the past three decades; between 1979 and 1986, funding for methadone increased by only 9%, while per-slot costs increased by 35%-40% (Browne-Miller, 2009). This has facilitated the development of for-profit methadone clinics. These facilities are often short-staffed, with patients receiving dosages with little counseling or other services (Browne-Miller, 2009). In 1991, reports of methadone-related deaths in Texas prompted officials to investigate claims that methadone was being diverted from poorly monitored for-profit clinics (Rettig & Yarmolinsky, 1995). Following six months of investigations, the Drug Enforcement Administration shut down a for-profit methadone clinic in Houston on multiple charges including illegally administering take-home doses and administering methadone to patients who failed required urine tests (Hunt, 1992).

Attitudes and opinions may also influence program philosophies that dictate whether and how medications will be used, regardless of empirical evidence. Maintenance approaches support long-term or indefinite maintenance, concurrent with social rehabilitation (e.g., Dole et al., 1966). Abstinence-oriented approaches allow stabilization with medications for a brief time with a taper; the goal is complete abstinence from all substances, including opiate agonists (e.g., Brown, Jansen, & Bass, 1974). Abstinence-oriented program philosophies and staff attitudes have been demonstrated to negatively impact treatment outcomes in methadone programs. Bell, Chan, and Kuk (1995) compared a maintenance philosophy methadone program with an abstinence-oriented program and found higher rates of heroin use in the abstinence-oriented program attributable to lower doses and time-limited treatment. High physician and staff endorsement of abstinence-only beliefs was associated with premature patient discharge in Australian methadone clinics (Caplehorn, Irwig, & Saunders, 1996; Caplehorn, Lumley, & Irwig, 1998). An Italian longitudinal study of treatments for heroin dependence demonstrated that treatment modality was the most significant predictor of patient dropout, with abstinence-oriented programs showing the lowest retention rates (Salamina et al., 2010). The persistence of low methadone dosing contrary to empirical evidence on the efficacy of higher doses, discussed above, is another example.

Studies on research implementation demonstrate that physicians’ beliefs about addictions and treatment efficacy play a vital role in determining whether they engage in desired behaviors (Giannetti, Steppert, & Holosko, 2002; Rush, Powell,Crowe, & Ellis, 1995). Positive physician attitudes regarding substance user interventions are associated with increased use of them (Bendtsen & Akerlind, 1999; Kahan et al., 2004). Therefore, it is not surprising that educational campaigns and training about medication-assisted treatments impact staff attitudes and philosophies. Caplehorn, Lumley, Irwig, and Saunders (1998) demonstrated a reduction in support of abstinence-oriented policies among methadone program staff in New South Wales, Australia, subsequent to an official attempt and educational programs by the government to change from abstinence-oriented to harm-reduction...
strategies. In an American study comparing addictions counselors affiliated with the NIDA Clinical Trials Network (CTN) to unaffiliated counselors, CTN-affiliated counselors reported significantly higher acceptance of buprenorphine. The difference could not be explained in terms of counselor characteristics, but only in terms of specific training. CTN-affiliated counselors had experienced significantly more buprenorphine-specific training and implementation because of their involvement with CTN (Knudson, Ducharme, & Roman, 2007). A study of American Therapeutic Communities (TCs) permitting methadone demonstrated an association between methadone sensitivity training and increased knowledge about methadone and decreased abstinence-only orientation (Andrews, Sorensen, Guydish, Delucchi, & Greenberg, 2006). Thus, it would seem that educational campaigns and training are effective in changing attitudes and affecting implementation.

Financial Challenges
Financial issues also impact service provision and the implementation of evidence-based treatments. In some geographic areas, lack of financial resources and shifts and declines in provider reimbursements have left many patients with limited treatment options and providers and programs with challenges to overcome. Though the majority (58% as of 2007) of US facilities are non-profit, an increasing proportion of treatment centers are for-profit (Substance Abuse and Mental Health Services Administration, 2008); this trend has also been documented in methadone clinics (Sloan, 2005; Solomon, 2002). The shift from non-profit to for-profit programs has brought up concerns about potential implications for the quality and accessibility of care (e.g., Friedman, Lemon, Stein, & D’Aunno, 2003; Nahra, Alexander, & Pollack, 2009).

Treatment programs are influenced by their clientele and funding sources. Highly exclusive private treatment programs serving only the very wealthy can charge much more than other programs and are minimally influenced by managed care and declining reimbursements. Thus, they are free to invest large amounts to provide luxurious and hopefully efficacious care while making a profit. Unfortunately, relatively few people have sufficient financial resources to access those programs. Programs catering to middle-class patients are more subject to managed care and declining reimbursement rates. Publicly funded programs serve economically disadvantaged patients and are highly influenced by declining public reimbursement rates. Programs facing declining reimbursement rates are left with several options for their survival: they could invest considerable time, effort, and funds to provide strong services and profit less. Or they could provide lower quality services with less qualified clinicians, investing fewer resources, treating more patients, and cutting costs to create a greater profit. Nahra et al. (2009) empirically evaluated the relationship between ownership and profit status and treatment access and duration in US outpatient addiction treatment programs. They found associations between private ownership and for-profit status and restricted access to treatment and shorter treatment durations due to financial reasons. They also demonstrated that the methadone clinics in the study provided initial access to fewer patients who were unable to pay for services and were more likely to discharge patients who became unable to pay during treatment than drug-free programs. Additionally, while for-profit facilities are known for shorter wait times, they also turn away significantly more patients.
than private non-profit and public programs, likely due to inability to pay (Friedmann et al., 2003). In 2008, the National Survey on Drug Use and Health reported that the most common reason why individuals did not seek treatment was inability to pay, due to lack of funds or insurance (Substance Abuse and Mental Health Services Administration, 2010). Some facilities, the vast majority of which are non-profit, offer treatment at no charge or on a sliding fee scale based on income. According to the 2008 National Survey of Substance Abuse Treatment Services (Substance Abuse and Mental Health Services Administration, 2008), 73.8% of clinics that provided free treatment to all patients, and 68.1% of clinics that provided free treatment to patients who could not afford to pay, were run by private non-profit organizations. Most (76.4%) for-profit programs did not offer free treatment, whereas only 38.3% of private non-profit organizations did not (Substance Abuse and Mental Health Services Administration, 2008).

Furthermore, decreases in funding and other conditions have made it difficult for many addictions treatment programs to attract and retain clinicians. It has been estimated that just half of US substance user treatment programs have a part time physician, and few programs outside of methadone clinics have "registered" nurses (McLellan, Carise, & Kleber, 2003). Thus, it is hardly surprising to see treatment centers staffed by overloaded counselors and a single physician who does little more than sign prescriptions. As a result, compassion fatigue is quick to set in, and clinicians quickly burn out. Rates of staff turnover in US addiction treatment programs are estimated to be between 18.5% and 49%, with a dearth of professionals at the Masters level or higher (Carise, McLellan, & Gifford, 2000; Carise, McLellan, Gifford, & Kleber, 1999; Johnson, Knudsen, & Roman, 2002; McLellan et al., 2003; McLellan & Meyers, 2004). Staff turnover is an even greater problem in for-profit facilities (McNulty, Oser, Johnson, Knudsen, & Roman, 2007). The for-profit motive provides a strong incentive for hiring fewer healthcare workers while retaining more professionals. This is costly, as time and money are spent rehiring staff, and detrimental to patient care, as patients slip through the cracks between counselors. Thus, it seems that non-profit facilities may be better at addressing the treatment gap that exists between high- and low-income patients. For-profit centers are becoming increasingly prevalent in the USA, and addiction treatment demand continues to exceed the available resources. However, this situation may change in the future due to the passage of the Mental Health Parity and Addiction Equity Act in 2008, which requires health insurance to cover mental health—including SUDs—and physical health equally (Dave & Mukerjee, 2011).

Increasing Patient Complexity
Another major challenge for healthcare providers is the increasing complexity of patients seeking addictions treatment. High rates of substance users suffer from non-substance use psychiatric disorders (Regier et al., 1990) and serious physical illnesses, such as HIV (Chander, Himelhoch, & Moore, 2006) and Hepatitis C (Loftis, Matthews, & Hauser, 2006). Modified treatments are often necessary for these complex patients (McIntosh & Ritzer, 2001), and many programs are ill-equipped to meet all of their needs. In fact, programs often attempt to decrease costs by cutting ancillary services in ways that may compromise patient care. In comparison to non-profit addiction treatment programs, for-profit organizations offer fewer tailored services for specific groups such as persons with HIV/AIDS, individuals with diverse sexual orientations, pregnant women, and persons with co-occurring substance abuse and mental health disorders (Substance Abuse and Mental Health Services Administration, 2008).

CONCLUDING REMARKS
Opioid dependence treatments have evolved from solely humanitarian to scientific and evidence-based and include agonist and antagonist medication assisted treatments with adjunctive psychosocial interventions. The full range of treatment options, including agonist treatment, is available in many geographic areas. However, public opinions, stigma, restrictive legislation, and funding difficulties have led to the current situation, in which agonist treatments are unavailable or have limited availability in some areas, such as the Russian Federation.

Although there is already extensive empirical support for medication-assisted treatment for Opioid Dependence, it is essential to: 1) continue to broaden and deepen the evidence base, especially with randomized controlled trials, and; 2) to address attitudes towards opioid addiction and medication-assisted treatments at multiple levels. Reducing resistance to medication-assisted treatments would assist in making them more broadly available worldwide, thereby addressing some of the global problems associated with opioid misuse. Training and education for the range of professional clinicians and non-professional treatment agents, dissemination of research results to clinicians, policy makers, and stakeholders, and national and international policies to facilitate access to evidence-based treatments are needed.

Declaration of interest
Alkermes, Inc, is providing Vivitrol for a study of amphetamine dependence treatment in Iceland; Dr. Woody is a co-investigator. Fidelity Capital has provided Prodetoxon at reduced cost for two studies in the Russian Federation; Dr. Woody is the principal investigator. The other authors report no conflicts.
MEDICATION-ASSISTED TREATMENTS FOR OPIOID DEPENDENCE

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GLOSSARY

Abstinence-only/drug-free approach: A treatment in which medications with effects similar to the drug(s) of abuse are used only during acute withdrawal and detoxification; primarily psychosocial in nature.

Abstinence-oriented approach: A treatment approach in which medications with effects similar to the drug(s) of abuse are used during acute withdrawal and detoxification and for a brief time afterward with a taper; the goal is complete abstinence from all substances of abuse, including opioid agonists.

Agonist treatment: A treatment in which medications with effects similar to the drug(s) of abuse are used over an extended period of time; examples are methadone or buprenorphine maintenance.

Antagonist treatment: A treatment in which a medication that blocks the effects of the abused drug is used over an extended period of time; an example is naltrexone for treatment of opioid dependence.

Adjunctive psychosocial treatment: An intervention that is used in conjunction with medication-assisted therapy but that relies on interpersonal, milieu or other non-medication approaches; examples are psychotherapy, counseling, education, and behavioral techniques such as contingency management.

Maintenance approach: A treatment in which patients continue a medication with effects that are similar to the drug of abuse or that block the effects of the drug of abuse; examples are long-term treatment with methadone, buprenorphine, or naltrexone.

Substance use disorders: Patterns of problematic substance use that result in significant psychiatric, medical, or psychosocial problems such that they meet criteria for Abuse or Dependence as defined in DSM-IV, or Harmful Use or Dependence as defined in ICD-10.

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