Medication Assisted Treatment of Drug Abuse and Dependence: Global Availability and Utilization

Thomas F. Kresina*

Division of Pharmacological Therapies, Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, Rockville, MD 20857, USA

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Abstract: Clinical trials and clinical studies, using patented drugs and drugs off patent, provide data that impact the best treatment practices for substance abuse and dependence. In the United States, medications have been approved for use in the treatment of both alcohol and opioid dependence. Medications are used in the detoxification from drug abuse and dependence in the symptomatic relief of withdrawal. For long term treatment or medical maintenance treatment, medications eliminate the physiological effects of drug use by blocking drug-receptor binding in the brain. Therefore, patented drugs showing interactions with neurotransmitters in the brain, are attractive candidates for treatment efficacy trials. An effective long term treatment paradigm for reducing drug dependence is the combinatorial use of medications that block the effects of drug use with behavior change counseling and psychotherapy. Medications used for the long term treatment of opioid dependence are methadone, buprenorphine, and naltrexone. Pharmacotherapies used in the treatment of alcohol dependence include acamprosate, antabuse and naltrexone. A reliable indicator for successful treatment of drug dependence is time in treatment. Patients remain in long term treatment when they perceive that their health care environment is supportive and non-stigmatizing and with a good patient-provider relationship where their needs are identified and met. Additional medications are needed for individual comprehensive substance abuse treatment plans, particularly for individuals who abuse stimulants. Patented drugs remain an important source of candidate pharmacotherapies comprising medication assistant treatment, part of a comprehensive treatment plan for drug dependence that addresses the medical, social, and psychological needs of the patient. Adapting this drug treatment paradigm globally requires identifying and testing new drug candidates while building and changing programs to patient centered treatment programs that promote access to care and treatment and integrate medical, psychological, and social services.

Keywords: Pharmacotherapy, addiction, methadone, buprenorphine, naltrexone, opioid dependence, alcoholism.

GLOBAL ALCOHOL AND ILLEGAL DRUG ABUSE AND DEPENDENCE

Illicit drug/ alcohol abuse and dependence are global problems of major medical importance. In understanding the global burden of disease, the World Health Organization (WHO) has noted that the three leading causes of disability are behavioral diseases: mental illness, alcohol and drug use disorders and Alzheimer's disease/dementias [1]. Alcohol consumption causes 4% of the total of Disability-Adjusted Life Years and 3.2% of deaths, globally. The WHO estimates that about 2 billion individuals worldwide consume alcoholic beverages [2], (see Table **1**). Approximately 76.3 million individuals have a diagnosable alcohol use disorder. Alcohol and drug use disorders are defined clinically as alcohol/drug abuse or dependence [3]. Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV) definitions of abuse and dependence are maladaptive patterns of alcohol or drug use that result in clinically significant impairment or distress as well as significant behavior modifications as presented in Table **2**.

*Address correspondence to this author at the Division of Pharmacological Therapies, Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, 1 Choke Cherry Road, Rockville, MD 20857; Tel: 240-276-2713; Fax: 240-276-2710; E-mail: tkresina@samhsa.gov

Efforts to legally control the use of psychoactive drug began in the early 1900's with The International Opium Commission that was convened in Shanghai, China, and was fundamental in the development of the Hague Opium Convention of 1912, the first instrument of international law to deal with psychoactive substances. A multilateral drug control system has originated from this convention and spread to address cocaine, cannabis and other psychotropic substances. Current international drug control regulates the production, classification, and trade of medical drugs leading to the goal of international cooperation against the multi-faceted problems associated with illicit drugs.

Significant medical problems are associated with alcohol and drug use, abuse and dependence. These include a high prevalence of co-occurring psychiatric illness diagnosed in individuals who abuse or are dependent on illicit drugs and/or alcohol as well as hepatitis virus infection and HIV infection. These medical co-occurring conditions are specifically prevalent in injection drug users (IDU). Estimates for IDU's are available for at least 130 countries with approximately 78% of the 13.2 million IDU's living in developing or transitional countries [4]. Forty-one countries have reported a high prevalence (>5%) of HIV infection in the high-risk population. Globally IDU's now account for at least 10% of all new HIV infections which are estimated at 5 million per year. Recent epidemiological data on HIV have

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Table 1. Per Capita Adult Consumption in Liters of Alcohol by Region and Top Ten Countries With the Highest Beverage Specific Consumption

Per Capita Consumption		Top Ten Ranking: Country Specific Consumption of			Rank
Region	**Total**	**Beer**	**Wine**	**Spirits**	
Global	5.1	Czech Republic	Luxembourg	Republic of Moldova	#1
Americas	6.2	Ireland	France	Reunion	#2
Europe	10.1	Swaziland	Portugal	Russian Federation	#3
Africa	3.9	Germany	Italy	Saint Lucia	#4
South East Asian	1.8	Austria	Croatia	Dominica	#5
Western Pacific	5.0	Luxembourg	Switzerland	Thailand	#6
Eastern Mediterranean	0.2	Uganda	Argentina	Bahamas	#7
		Denmark	Spain	Latvia	#8
		United Kingdom	Bermuda	Haiti	#9
		Belgium	Greece	Belarus	#10

Adult consumption- individuals 15 years or older for the year 2000.

Table 2. Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV) Definitions of Substance Use Disorders

A maladaptive pattern of drug or alcohol use with clinically significant impairment or distress with:

ABUSE

More than 1 of the following in the same 12-month period:

1. failure to fulfill major role obligations
2. use in physically hazardous situations
3. recurrent legal problems
4. continued use despite social and interpersonal problems

DEPENCENCE

More than 3 of the following in the same12 month period:

1. tolerance
2. withdrawal
3. used for longer periods than intended
4. can't cut down or quit
5. time spent getting using or recovering from drug/alcohol use
6. give up social, work or fun activities
7. continued use despite knowledge of negative consequences

The presence of item 1 or 2 defines physiological dependence

shown that generalized HIV epidemics have resulted due to diffusion transmission of HIV from high risk groups, such as IDUs. Thus, it becomes important for countries and regions to undertake surveillance studies to identify current alcohol and drug use patterns and develop best practices for the treatment of individuals who use and abuse alcohol and illicit drugs.

Surveillance of Drug Use

Based on the 2006 World Drug Report [5] from the United Nations Office on Drug and Crime (UNODC) approximately 200 million people from almost every country, or 5 percent of the global population age 15-64, have used illicit drugs at least once in the last 12 months. Cannabis is by far the most widely used drug, followed by stimulants, such as amphetamines and ecstasy, then cocaine use and finally opioids. However, it is estimated that only half of these individuals (2.7%) use drug regularly, defined as at least one a month. The estimated number of individuals who fulfill the criteria for a diagnosis of drug abuse or dependence is 25 million or (0.6% of the population between the ages of 15-64). Thus, understanding the burden of illness due to drug abuse and dependence provides a window into the need for medical interventions and treatment paradigms to reduce drug use and dependence. Table **3** provides the global statistics by region of primary problem drug use based on the need for drug treatment.

Treatment

Drug dependence is a chronic, relapsing neurophysiological disease resulting from the prolonged effects of drugs on the brain. The neurochemical abnormalities resulting from chronic use are the underlying cause of many of the observed physical and behavioral aspects of addiction. The brain abnormalities associated with addiction are wide ranging, complex, and long lasting [6,7]. They can involve abnormal brain signaling pathways, psychological conditioning or stress, coupled to social factors that result in cravings leading to a predisposition to relapse even months or years after drug use cessation. Thus, substance abuse/dependence can be most effectively addressed in a multifaceted medical-based

Table 3. Illegal Drugs of Abuse and Dependence Based on Treatment Need

Region	Percentage of Individuals in Treatment with Primary Drug of Abuse				
	Opiods	Cannabis	Cocaine	Stimulants	Other
North America	7	32	31	9	21
South America	0.4	24	54	5	21
Europe	59	16	7	9	9
Africa	12	63	10	6	9
Asia	65	12	--	17	6
Oceania	34	35	0.2	14	--

North America-average treatment demand for Canada, United States and Mexico, 2001-2004
South America-average treatment demand in 26 countries comprising South America, Central America, and the Caribbean 1998-2004
Europe- average treatment demand in 38 countries for 2000-2004
Africa-average treatment demand in 26 countries 1995-2004
Asia- average for treatment demand for 39 countries for 1997-2004
Oceania- 2003-2004 average treatment demand for Australia and New Zealand, opioids includes heroin and morphine

paradigm that comprises a comprehensive treatment program of interventions that are delivered through the course of treatment. Such treatment includes behavioral, social rehabilitative components, and biological (pharmacological), Table **4**. Behavioral therapy interventions have been extensively researched and are critical components of the treatment of all drug addictions. Social rehabilitative components are also important and may prove suited to certain treatment environments.

In the United States, opioid dependence can be treated in two differing medical paradigms. In a highly regulated and structured environment, methadone is dispensed daily at Opioid Treatment Programs (OTPs) that are increasing providing "wrap-around" services to address important patient needs, enhance time in treatment, and promote recovery. Alternatively, buprenorphine can be prescribed in a primary care health care setting similar to other illnesses to reduce the stigma of drug dependence. Both paradigms need to address the reduced quality of life, physical and mental functioning, compared to the general population, that is associated with drug dependence [8]. In addition multiple comorbidities are associated with substance abuse and dependence that also contribute to the lower quality of life experienced and documented by opiate users. Life priorities of opioid users have been reported as concern about and treatment of infection with HIV, housing, money, and protection from violence [9].

Patients dependent on heroin are also highly likely to abuse alcohol and/or cocaine, comprising a group of 'hard core" substance abusers [10]. For these individuals, the combination of pharmacotherapy and behavioral intervention may be most useful to reduce risk behavior. Addressing alcohol addiction is an important issue for individuals addicted to opioids for multiple reasons. Alcohol stimulates the release of dopamine in the brain. The alcohol-dopamine activation, induces drug craving, involves the endogenous opioid system, and is blocked by opiate receptor antagonists [11]. Thus, opioid addicted individuals may use or view

Table 4. Components of United States Treatment Paradigms Comprising a Comprehensive Substance Abuse Treatment Plan for Alcohol and Opioid Abuse and Dependence

Pharmacotherapy

Opioid Dependence

Methadone- federally regulated, opioid receptor antagonist for substitution therapy

Buprenorphine- office based, partial opioid receptor antagonist for substitution therapy – federally regulated

Naltrexone- office based, opioid receptor antagonist for relapse prevention

Alcohol Dependence

Naltrexone- opioid receptor antagonist, reduced reward effect with daily use, new forms are long acting

Acamprosate-normalizes glutamatergic neurotransmission, slow acting, attenuates relapse

Disulfiram- aversion medication supporting complete abstinence, blocks the oxidation of alcohol with acetaldehyde build-up

Behavioral Therapy

- Brief interventions
  - for 1 to 3 visits (low intensity)
  - for early drug use
  - in many different outpatient settings
- Long term comprehensive psychotherapy to restructure belief and cognitive systems, enhance coping strategies, and change behavior
  - Individual interpersonal one-on-one therapy
  - Group therapy
- Family based
- Therapeutic communities
- Self-help groups

alcohol as part of their "stepping down" process away from opioid drug dependence. The emerging issue of liver disease in HIV populations, particularly HIV/hepatitis C virus (HCV) coinfected populations, is important because all patients with HCV infection should be counseled to refrain from alcohol consumption. HCV viral loads have been shown to be elevated in patients with HCV infection, who consume alcohol. Elevated HCV viral loads and alcohol use are associated with a decreased therapeutic response rate to interferon-based treatment regimens.

PHARMACOTHERAPY IN THE TREATMENT OF OPIOIDS AND ALCOHOL ABUSE AND DEPENDENCE

Substance abuse is a complex medical disorder composed of multiple physiologic, social and behavioral problems often interrelated with psychological illness. Health care providers need to screen substance misusing patients for psychological illness [12]. Although it can be difficult to ascertain whether substance abuse, psychological illness, or infectious comorbidities should be addressed first, an initial focus on the medical treatment of substance misuse is often necessary to create sufficient patient stability from which other treatments can begin. Stability is further increased with both mental health services and substance abuse treatment, subsequently enhancing the medical outcomes of treatment for comorbidities.

In the United States pharmacological treatments, both agonists and antagonists have been developed and approved by the Food and Drug Administration for specific drug dependence. Currently, medications are available for the treatment of nicotine, alcohol, and opioid dependence. Although none are available for stimulants, like cocaine and methamphetamine, many potential medications are now being developed for these drugs of abuse and are expected to be available over the next few years. An effective treatment strategy for drug abuse and dependence is to match a comprehensive treatment plan to the individual's particular substance abuse problems and needs. Desired treatment outcomes are: a) reduce dependence on drugs of abuse, b) reduce morbidity and mortality of and associated with drugs of abuse, and c) maximize the patients' abilities to access services and achieve social integration.

Methadone- Methadone, a full opiate agonist, is the mainstay of pharmacotherapy treatment for opioid addiction and helps addicted individuals abstain from illicit drug use and achieve recovery. In the United States, OTPs or methadone maintenance treatment programs, MMTP, under the certification of the Substance Abuse and Mental Health Services Administration (SAMHSA), dispense methadone and can provide a comprehensive therapeutic milieu comprised of primary medical care, psychosocial counseling, vocational rehabilitation, HIV testing and counseling, hepatitis C education and testing and other vital medical and social services. Methadone treatment has been proven to be effective for both primary and secondary HIV prevention [13] and cost-effective to society [14,15]. In addition to improving health outcomes, methadone treatment also substantially improves the quality of life of patients over the course of methadone treatment [16].

Methadone is a synthetic μ-opioid receptor agonist with pharmacological properties qualitatively similar to morphine and was originally used to treat the painful symptoms of withdrawal from heroin and other opioids [17,18]. Administered daily as an oral dose for the treatment of opioid dependence, an individual therapeutic dosage needs to be determined to maintain an asymptomatic state and stabilize a patient, without episodes of opioid overmedication or withdrawal. The therapeutic dosage for a patient is a function of many factors including: absorption, metabolism, drug-drug interactions, physiology, diet and the use of alternative medications. When appropriately dosed and utilized, methadone is safe and effective and does not modify a patient's ability to function in any capacity for which the person is qualified, including intellectual activities, driving motor vehicles, or performing work tasks.

Minimum retention time in treatment varies for residential and outpatient methadone treatment programs. The National Institutes of Health consensus panel on opioid-addiction treatment [19] concluded that individuals treated for fewer than three months with methadone do not show substantial medical gain. As time in treatment progresses, study outcomes have reported varying from partial reductions of illicit opioid use progressing to abstinence. Relapse to drug use is common if methadone is discontinued without further support or behavioral treatment.

Barriers to retention in methadone treatment include problem severity at program intake, as well as patient readiness for treatment and motivation. Components of the drug treatment program are key to successful treatment outcomes. Treatment programs that offer a broader array of "wrap-around" services and a greater frequency of services have reported improved retention in treatment and treatment outcomes [20]. Programs responsive to the severity of drug abuse during initial stages of drug treatment have been shown to produce high positive treatment outcomes based on greater retention time in treatment and patient satisfaction with treatment services. Maximum retention time in methadone treatment is associated with comprehensive treatment, provision of frequent health service, as well as appropriate methadone dosing [21].

Buprenorphine- Primary care physicians can expand the accessibility of substance abuse treatment while mitigating the stigma associated with drug use and treatment through the use of buprenorphine. Buprenorphine, a partial mu-receptor opiate agonist [22], differs significantly from full agonists (Table **4**). Buprenorphine has a plateau of its agonist properties at higher doses. This limitation on agonist properties results in an improved safety profile compared with a full agonist, such as methadone. Specifically, buprenorphine has a favorable 'ceiling effect' on respiratory depression [23]. However, the abuse of other substances which may cause respiratory depression (e.g., benzodiazepines) remains a contraindication with buprenorphine as with methadone. In addition to improved safety, flexible dosing (e.g., thrice weekly) is feasible since buprenorphine has a high binding affinity for the opiate receptor and slowly dissociates. Importantly, buprenorphine has two features that decrease street diversion. Firstly, buprenorphine has a higher binding affinity for the mu-opiate receptor than heroin and

can precipitate opiate withdrawal when buprenorphine is taken by an opiate dependent patient [24]. It is for this reason that buprenorphine inductions must occur in patients already in mild to moderate opiate withdrawal. Secondly, in the United States buprenorphine is marketed both alone (Subutex) and in combination with naloxone (Suboxone). In the latter formulation, naloxone is minimally bioavailable via sublingual ingestion. If the tablet is crushed and injected, an increase in the availability of naloxone will precipitate acute opiate withdrawal, a potent disincentive for this behavior.

Pharmacotherapy for Alcohol Dependence- Pharmacotherapy for alcohol dependence is an important adjunct to behavioral therapies to reduce the risk of relapse to drinking after an initial period of abstinence. Pharmacotherapy for alcohol consumption is also important for patients with co-occurring conditions such as patients with HIV or HCV infection where alcohol consumption can augment disease progression. For these patients treatment has been reported with either acamprosate, naltrexone, or disulfiram [25]. Acamprosate and naltrexone have different mechanisms of action and modify different behavioral aspects of addiction. Acamprosate, a long acting compound, prolongs periods of abstinence by normalizing glutamateric neurotransmission that is dysregulated during chronic alcohol consumption and withdrawal. Naltrexone is a fast acting opioid receptor antagonist that reduces heavy drinking through decreasing the rewarding effects of ethanol. An evidence-based risk - benefits assessment can be used to inform health care providers on medication choice [26]. However, the safety and efficacy of treatment using both drugs for alcohol dependence has been shown in double blind studies [27]. Disulfiram blocks the oxidation of alcohol at the acetaldehyde stage in its metabolism increasing the levels of acetaldehyde resulting in a series of unpleasant symptoms (e.g., flushing, headache, and vomiting). Although disulfiram is widely used, data are more supportive of naltrexone and acamprosate as pharmacologic treatments of alcoholism [28]. For developing countries, a series of factors acting synergistically may be creating the "perfect storm" promoting alcohol availability, alcohol consumption, and reducing alcohol control policies, thereby increasing the need for the use of medication-assisted treatment for alcohol abuse and dependence [29].

GLOBAL AVAILABILITY AND UTILIZATION OF MEDICATION-ASSISTED TREATMENT

Medication assisted treatment for opioid abuse and dependence in the form of buprenorphine and methadone is available in specific regions and countries as depicted in Fig. **1**. In 2005, as noted in a presentation by Dr. Wodak at the most recent international AIDS conference [30], methadone is available in 48 countries, buprenorphine in 34 countries. Both medications are available only in the United States, countries of Western Europe, Israel, Iran, Indonesia, Taiwan and Australia. The Ukraine has recently piloted the use of both methadone and buprenorphine, while Vietnam will legalize the use of methadone in January 2007. More importantly, each medication is not uniformly available in each country. For buprenorphine, two formulations have been developed for use in a primary care setting, Subutex (buprenorphine) and suboxone (buprenorphine/naloxone). Suboxone, which is widely used in the United States, combines buprenorphine with naloxone to reduce diversion of the drug. A four year study of diversion in the United States has shown this formulation to be very successful in limiting diversion [31]; while in the Republic of Georgia street use and diversion of subutex from Europe has resulted in epidemic of abuse of buprenorphine [32]. For methadone, there is considerable variation in the dispensing of methadone in drug treatment programs both in-country as well as among countries [33]. Variations also occur in policies detailing dosage and time limitations for treatment, program entry criteria, staffing of programs, as well as urine testing. Thus, availability of medication assisted treatment does not indicate continuity of care and treatment across programs or countries.

Treatment demand, as shown in Table **3**, provides some insight into the global drug problem and somewhat correlated to the availability of medication-assisted treatment for opioid dependence [34,35]. The region with highest treatment demand is Asia, and the recent implementation of methadone treatment in China, as a component of their nationwide HIV prevention program, has greatly augmented the treatment capacity of the region. This coupled with the use of methadone in Thailand, buprenorphine and methadone in Indonesia, and a growing use of naltrexone in Vietnam indicates an acceptance of medication-assisted treatment as a tool to address drug abuse and regional HIV transmission. Europe also addresses opioid abuse and dependence with medication assisted treatment using methadone and buprenorphine, as well as, a strong harm reduction program for those not treatment ready. The United States, India, Australia and South Africa utilize medication assisted treatment to address their growing epidemics of opioid abuse and dependence. Australia has a growing abuse problem with morphine [36], as reflected in Table **3**. The use of medication-assisted treatment in South Africa highlights the growing problem of injection drug use in Eastern African countries in connection with their ongoing HIV epidemic. In the United States there is an epidemic of prescription opioid drug abuse and dependence that is treated with both methadone and buprenorphine.

There has been limited global availability and use of medication-assisted treatment for alcohol abuse and dependence. However, as captured in Table **1**, every region of the world is touched by the problems associated with alcohol consumption. Naltrexone has been predominately used in the United States and acamprosate predominately used in Europe to as medications in the treatment of alcohol abuse and dependence.

TREATMENTS FOR ALCOHOL/ STIMULANT ABUSE AND DEPENDENCE IN DEVELOPMENT

Numerous medications are in development and have application to correct aberrant brain physiology due to continued drug use and abuse. Current behavior therapies for psycho-stimulant abuse have limited efficacy and the addition of medications is predicted to enhance the success rate of current behavioral treatments [37]. One approach is to develop compounds that indirectly target γ-aminobutyric acid systems to manage stimulant dependence [38]. An alternative approach is to develop compounds that share

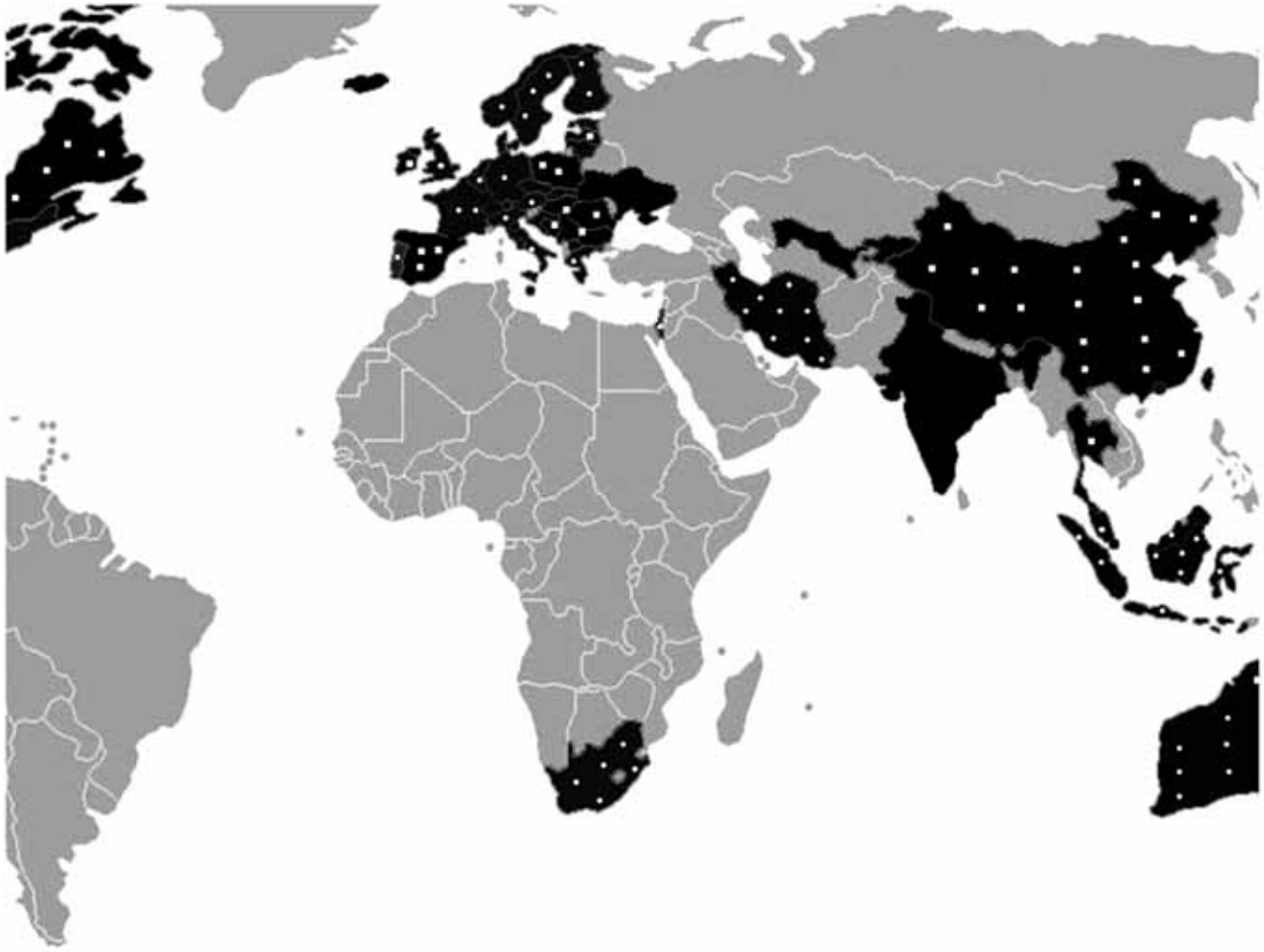

Fig. (1). Pictorial representation of the availability of medication assisted treatment in the form of buprenorphine or methadone for opioid abuse and dependence. Larger dots signify the availability of methadone while smaller dots indicate the availability of both methadone and buprenorphine. Adapted from [30] plenary presentation at the XVI International AIDS conference August 13-18, 2006 by Dr. Alex Wodak.

pharmacological properties of the drug of abuse, such as monoamine transporter ligands or agonist substitution therapies to manage psycho-stimulant dependence. Both cocaine and methylphenidate analogs have been developed targeting dopamine transporters and serotonin transporters. Clinical trials have substituted these analogues in cocaine dependent primates and shown the importance of psycho-stimulant receptor blockage to inhibit self administration of stimulants of abuse [39].

Other clinical trails have shown efficacy at reducing cocaine use with the administration of disulfiram, an inhibitor of sulfhydryl-containing enzymes [40]. Maximum efficacy was noted in cocaine and alcohol using patients when patients received both disulfiram and behavioral therapy. Naltrexone has been shown to be efficacious in preventing relapse to cocaine use in abstinent patients undergoing behavioral therapy [41]. Baclofen, a γ-amino-butyric acid agonist, has been reported to reduce the craving for cocaine and has been shown to reduce cocaine use in placebo -controlled clinical trials [38]. Tiagabine has recently been shown to significantly reduce cocaine taking behavior in a double blind placebo controlled-trial [42]. Other clinical trials have shown that modafinil treatment can result in reduced craving for amphetamines, as well as cocaine, and improve performance in neuropsychological tests. Thus, modafinil may act to reduce the symptoms of cocaine withdrawal, inhibit craving for cocaine, and enhance cognitive processes [40]. Thus, numerous medications remain in the development pipeline and show significant promise in enhancing treatment paradigms for stimulant abuse and dependence.

RECENT AND IMPORTANT PATENTS FOR SUBSTANCE USE DISORDERS

A review of recent patents in the field of treatment of substance use disorders shows that patents can be divided into two groups: (1) those addressing preventing overdose of a broad range of drugs and (2) those addressing the reduction of alcohol consumption. In the first group, an important patent is [43] relating to the use of heterocyclic carboxamide

compounds in preventing or reducing self administration of benzodiazepines, narcotics and hallucinogens most notably as a 50mg caplet or tablet. Other enhance the efficacy of opioid agonists [44] or target the Cannabinoid receptor [45]. For alcohol use and abuse, patents have been issued for new screening methods for compound development [46] as well as for compounds that could be used in the treatment of alcohol abuse and dependence [47-50]. Theses compounds target alcohol dehydrogenase [47,50], dopamine receptors [48,51,52], voltage sensitive sodium channels [53] in the form of long acting combination depot formulations [49] to reduce alcohol consumption.

CURRENT & FUTURE DEVELOPMENTS

The structural fabric and elements of society are harmed by substance abuse and dependence. Alcohol and drug abuse and dependence results in a breakdown of family structure, homelessness, increased school drop-outs, and crime as well as multiple forms of violence [54,55]. There are community and personal risk factors for drug and alcohol use as well as protective factors against drug use [56]. Important risk factors for drug and alcohol use are a supportive school environment as well as family and peer drug and alcohol use. Communities that undergo rapid social change, such as Westernization or urbanization, have been shown to have large increases in drug use and abuse with a resultant breakdown in the societal fabric requiring communities, state, and federal authorities to address the drug abuse and institute prevention and treatment programs [57,58]. Additional medications are needed as components of a drug addiction treatment and prevention toolbox that can be used by society in addressing the societal ills brought on by alcohol and drug abuse and dependence.

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