Science Publications

Open Access
Author Manuscript

American Journal of Infectious Diseases 3 (4): 184-190, 2007
ISSN 1553-6203

Medical Consequences of Drug Abuse and Co-occurring Infections: A Brief Review

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Abstract: Today substance abuse remains one of the major problems in the world with millions of people abusing legal and illegal drugs. In addition, almost one-third of the world population of 6.7 billion people may also be infected with one or more infections. Both drugs of abuse and infections are associated with enormous burden of social, economic and health consequences. This paper briefly discusses a few medical consequences of drugs of abuse and infections such as human immunodeficiency virus and hepatitis C virus. Research is encouraged to study interactions between infections, drugs of abuse, and underlying pathophysiologic and molecular/genetic mechanisms of these interactions.

Key words: Medical Consequences, Drug Abuse, HIV/AIDS

INTRODUCTION

Today substance abuse and infections are two of the major problems in the world with an estimated 200 million people abusing illegal drugs regularly[1] and an estimated one-third of the world's population of 6.7 billion people living with one or more infections[2]. In the US alone, according to the 2005 National Survey on Drug Use and Health[3], about 112 million Americans 12 years and older (46%) used at least one illicit drug (e.g., amphetamines, cocaine, heroin, or marijuana) in their lifetime. An estimated 20 million people are current users of an illicit drug. Unfortunately no data are available on the nature and extent of drug abuse in India. There are an estimated 40 million people in the world living with human immunodeficiency virus (HIV) infection, about 200 million infected with hepatitis C virus (HCV), 2 billion people infected with tuberculosis (TB) and many more millions with various other bacterial and viral infections[4]. An estimated 1 million people infected with HIV, and 4 million people infected with HCV live in the US. Both infections are prevalent among substance abusers. Injection drug use (IDU) directly and indirectly accounts for more than one-third (36%) of AIDS cases; of the 42,156 new cases of AIDS reported in the US in 2000, 11,635 (28%) were associated with injection drug use [5]. About 80% to 90% of HIV positive IDUs may also infected with HCV (5). In addition to HIV and HCV, other viral and bacterial infections such as mycobacterial leading to tuberculosis (TB), sexually-transmitted infections, streptococcal and staphylococcal infections (leading to endocarditis) and others have all been reported in drug abusers[6].

Sociopolitical, economic, and health costs to the society from substance abuse and infections are enormous. Legal and illegal substance abuse alone costs the American society an estimated one-half a trillion dollars annually[8], while diabetes and cancer cost an estimated $132 billion[9] and $263 billion[10], respectively. Both drugs of abuse and infections such as HIV and HCV affect almost every physiological/biochemical system in the body. Thus, health effects may range between neuropsychiatric complications, anxiety and depressive disorders, cardiovascular complications, impairment of immune system, metabolic/endocrine disorders (lipodystrophy), and hepatic failure, to name a few. Because the subject of health consequences of drugs of abuse and infections is very wide and could not be covered in a mini-symposium at the Drug Abuse and HIV/AIDS conference, held for the first time in Kerala, India, a brief review of the current status of research on medical consequences of drug abuse and infections supported by the US National Institute on Drug Abuse, a part of the National Institutes of Health, is being presented herein.

Medical Consequences: In general, stimulants such as cocaine and methamphetamine ('met', 'speed', or 'ice') increase the heart rate while constricting the blood vessels; in susceptible individuals, these two actions together set the stage for cardiac arrhythmias and strokes[11]. Methamphetamine also causes serious hyperthermia, increases wakefulness and physical activity, creating the potential for a combination of activity and overheating that leads to convulsions and dangerous, sometimes lethal elevation of body temperature[11]. Cocaine use decreases the blood flow to

the brain, increases the heart rate, and elevates the blood components that promote clotting—effects that can lead to stroke or heart attack even in those not otherwise at risk for these serious cardiovascular events[11]. NIDA-funded research also shows that chronic cocaine use is associated with left ventricular dysfunction[12] and increased calcium deposits in the coronaries[13] of HIV infected African-Americans, and that its use may also facilitate the entry of HIV into brain cells[14], possibly leading to HIV encephalopathy. The club drug methylene-dioxy-methamphetamine (MDMA), also known as 'ecstasy', which many users mistakenly believe to be safe, may cause malignant hyperthermia, permanent kidney damage, and death. In non-human primate studies, MDMA also damages serotonin nerve fibers in the brain. Heroin can cause a life-threatening kidney renal condition called focal glomerulosclerosis[15]. Opiate (heroin) use is associated with consequences ranging from nausea and constipation to renal, dental, and orofacial complications. PCP (phencyclidine, or 'angel dust') decreases heart rate and blood pressure, triggers violent aggression, and may trigger muscle contractions strong enough to break a bone[11]. Marijuana, the most abused illicit drug in the world and often perceived by many as an innocuous drug, is associated with consequences ranging from memory, cognitive and motor problems in young and adult individuals to possible lung cancer in chronic marijuana smokers, although the latter have not been confirmed. The NIDA-published special supplement reviewed the most up-to-date research on clinical consequences of marijuana[16]. Injecting drug use and drug use associated impulsive sexual activity further promotes acquisition and transmission of sexually-transmitted and blood-borne infections including life-threatening endocarditis, viral hepatitis, HIV/AIDS and STDs.

Human Immunodeficiency Virus (HIV): HIV, a blood-borne retrovirus that infects CD4 T-cell lymphocytes and macrophages, causes profound immunosuppression that eventually develops into full-blown AIDS. HIV infection results into flu-like syndrome consisting of fever, fatigue, pharyngitis, decreased CD4 T-cell lymphocytes, increased viral load, and finally progression to AIDS, the latter depending on factors such as the use of illicit drugs, opportunistic infections (OI) prophylaxis, and antiretroviral therapy. It may be noted that in about 5% of the individuals, the disease does not progress to AIDS. These individuals are known as long-term non-progressors and have a low viral load burden, strong virus-specific immune responses, and moderate viral attenuation[17]. Since the virus may infect almost every organ, the effects of HIV infection may also range from immunosuppression to wasting and other metabolic/endocrine disorders, cardiomyopathy, nephropathy, neuroAIDS, and many other health consequences. The course of HIV infection and the development of AIDS are further complicated by metabolic and endocrine abnormalities secondary to the direct toxic effects of HIV, other OIs such as HCV, TB, STIs, neoplasms, and complications of drugs used during treatment.

Hepatitis C Virus: Hepatitis C virus is another blood-borne pathogen that is easily transmitted through contaminated drug injection paraphernalia. Approximately 40% of chronic liver disease is related to HCV infection, making it the most common cause of chronic liver disease and the major reason for liver transplantation performed in the US. An estimated 8,000 to 10,000 persons with HCV-related liver cancer may die each year[18]. Because HIV and HCV have common transmission pathways, coinfection is quite frequent, with prevalence as high as 90% of HIV-infected IDUs also infected with HCV in some countries in Central, South, and Southeast Asia and Eastern Europe[19, 20, 21], 50 to 75% in countries in Southeast Asia[22]; 33% in St. Petersburg, Russia[23]; and 50 to 55% in Australia[24]. Recent reports from India show that there are an estimated 5.6 million people living with HIV infection[25]; no numbers are available on co-infections with HIV/HCV.

During the acute phase of HCV infection, which is difficult to diagnose and which may last about six weeks, symptoms may include malaise, nausea, right upper quadrant pain, and jaundice. About 75 to 85% of these patients may become chronically infected. During the chronic phase of HCV infection, which may last several decades, symptoms may include nausea, anorexia, myalgia, and arthralgia, with fatigue being the most common complaint[26]. Alcohol use and advanced age accelerate the disease progression of HCV infection, especially among men. Approximately 20% of these chronic patients will develop liver cirrhosis within 20 years, and 1 to 5% of them will die from HCV-related liver cancer. HCV infection is also associated with the development of diabetes mellitus among IDUs[27]. Dual infections with HIV and HCV also occur from common routes of transmission and these individuals are at risk of developing chronic liver inflammation and hepatic cancer or liver failure requiring transplantation. Hepatic injury seems to occur in dual infections through the induction of a novel signaling pathway, that is cooperatively activated by specialized protein molecules, known as HCV E2 and HIV gp120, thereby providing a rationale for therapeutic interventions[28] . NIDA supports a wide spectrum of research on epidemiology, natural history,

underlying pathogenesis, prevention and treatment of HIV/HCV co-infections among drug abusers.

Tuberculosis: Among all the infectious diseases that affect humans, TB remains the deadliest contagious disease caused by *Mycobacterium tuberculosis,* a pathogenic bacterium that establishes its infection mainly in the lungs. An estimated 2 billion people in the world are living with TB and an estimated 2 million die each year. India has the largest number of TB cases with an estimated 1000 people dying each day[29]. In the United States, a total of 13,767 tuberculosis (TB) cases (4.6 per 100,000 population) were reported in 2006 with rates of TB incidence declining from 7.3% per year during 1993--2000 to 3.8% during 2000--2006. Progression of TB is accelerated by a number of factors such as co-occurring infections, e.g., HIV, drugs of abuse, poor nutrition, and many others. HIV contributes to the TB pandemic because HIV-induced immune suppression increases the likelihood of rapid progression from primary TB infection to active TB disease. But from 2005 to 2006, the percentage of TB cases with HIV infection has also decreased from 13.0% to 12.4% [30]. Drug users are at particularly high risk of TB infection with reported high rates of active TB among drug users[31, 32]. TB infection can be effectively treated with currently available drugs including isoniazid, rifampin, streptomycin, ethambutol, pyrazinamide, ciprofloxacin, and ofloxacin. On the other hand, although the rates of TB incidence have declined in the US and elsewhere, the emergence of multi-drug resistant strain of mycobacterium (MDR) and extremely drug resistant (XDR) strain of the bacterium is of major concern. A total of 124 cases of multidrug-resistant TB (MDR TB) were reported in 2005, mostly in foreign-born individuals. Thus, vigorous efforts are underway to find better diagnostic tests/tools and to design/develop effective intervention, prevention and treatment modalities.

Nutrition also might play an important role in HIV disease progression. Research suggests that drug abusers with inadequate nutrition, particularly with sub-optimal levels of anti-oxidant micronutrients such as selenium and zinc, may be at high risk of mortality if they are also co-infected with HIV[33]. NIDA-supported clinical trials are in progress to determine if supplementation with selenium, zinc, and other anti-oxidant micronutrients would slow the progression of HIV/AIDS disease. Daily supplementation with 200 ug of selenium increases the CD4 T cell lymphocyte counts and decreases the viral load in HIV-infected patients[34]. This type of research would have worldwide implications, such that, in underdeveloped countries where poor people cannot afford expensive antiretroviral therapy, they could benefit from inexpensive treatment modality to slow disease progression and improve the quality of life.

Both viral infections of Hepatitis C and HIV continue to spread in an epidemic fashion among vulnerable populations, including those with mental illness and drug addiction. Drug abuse remains the major vector in the acquisition and transmission of both infections with serious consequences[35] including psychiatric disorders that in turn may further maintain Hepatitis C epidemic. Major depression, severe mental illness, and personality disorders lead to high risk behaviors for Hepatitis C, and yet these disorders may be made worse by Hepatitis C and the medications used to treat it[36]. Major depression is a common co-morbidity in patients with Hepatitis C infection[37].

Hepatitis C patients also have poorer outcomes if they are ongoing drug users[26]. Alcohol is risk factor for Hepatitis C infection, probably through the indirect mechanisms, but it is also associated with more rapid progression of HCV and more frequent development of liver cancer[38]. Despite these ominous problems, patients with substance use disorders can be successfully treated for HIV and Hepatitis C if the clinical resources needed for treatment are provided[39-41].

Mental illness including anxiety disorders, major depression and bipolar disorder are associated with substance use, increased high risk sexual behavior, and with other self destructive behaviors[42]. Depression may also increase the risk of acquiring HIV and HCV infections and may interfere with treatment. On the other hand, depression may also be caused by antiretroviral medications such as efavirenz[43] and interferon used in the treatment of HCV infection. Although ribavirin, also used in the treatment of HCV infection, may worsen depression, interferon is associated with severe CNS side effects such as frank psychosis, which may persist after discontinuation. Other common symptoms are: apathy, fatigue, irritability, sleep disturbance (both hypersomnia and insomnia), confusion, inattention, anorexia, sexual dysfunction, and suicidal feelings[44]. Treatment with antidepressants is effective but does not favor any one class of medications. Thus, treatment agents need to be developed that are safe (devoid of severe side effects) and effective against single or dual infections of HIV and/or HCV in drug abusing populations.

Drug Interactions: Pharmacokinetic and pharmacodynamic interactions between medications used in the treatment of infections and addiction should be considered when designing treatment protocols for drug addicts. Despite the large number of drug abusers with HIV disease, HAART is frequently underutilized in this population because of the difficulties

experienced in obtaining adherence adequate to maintain viral suppression[45-48]. Provision of drug abuse treatment is often a key component to successful treatment of HIV disease in this population. Multiple studies have shown that drug interactions between antiretrovirals and other medications having effects on cytochrome p450 enzymes can lead to altered therapeutic profiles, toxicities and side effects with drugs used for the treatment of HIV[49]. This, in turn, may decrease adherence to medical treatment for HIV/AIDS[50] leading to lack of efficacy of HIV treatment, development of viral resistance to currently available therapies, and increased illicit drug abuse. Because opioid pharmacotherapies are the treatment of choice for opioid-addicted individuals with HIV/AIDS, it is essential that clinicians have a thorough understanding of possible drug interactions between opioids, specifically methadone and buprenorphine, and antiretroviral therapies in order to enhance the clinical care of drug users with HIV/AIDS.

The earlier studies showed interactions between methadone and antiretrovirals. For example, the plasma levels of zidovudine increased by 41% when used in the treatment of AIDS in methadone maintained patients[51] but not in buprenorphine maintained patients[52]. On the other hand, patients treated with protease inhibitors like lopinavir/ritonavir or non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz, the plasma levels of methadone decreased resulting in opiate withdrawal[53-55]. By contrast, no clinically significant interactions occurred between ARVs and buprenorphine[53,54]. Data show that now buprenorphine may offer an alternative opioid therapy that could help to improve adherence to antiretroviral medications prescribed for the treatment of HIV disease in opioid-dependent patients.

New Pharmacotherapeutics on the Horizon: Since the discovery of the first case of HIV, many effective medications including highly active antiretroviral therapy (HAART) and the newest drug, Fusion, have been developed for the treatment of HIV/AIDS. On the other hand, only pegylated interferon alfa and ribavirin are available for the treatment of hepatitis C infection. However, new drug therapies to treat hepatitis C (HCV) and HIV infection are being developed with improved understanding of the molecular structures of the viruses themselves, the pathogenesis of infection and the specific immune responses needed to eradicate or control these infections. Interferon and ribavirin based therapies will continue to be a component of HCV therapy for the near future combined with other novel compounds directed at targets of viral replication, immunomodulation or cell entry. The goals of anti-HCV therapy are viral eradication for various genotypes, prevention of hepatic morbidity such as hepatocellular carcinoma and cirrhosis. Future antiretroviral therapies for HIV will include agents that focus on new classes of inhibitors of viral replication and cell binding. The new treatment choices in HIV will need to ensure effective and durable viral suppression especially against highly resistant virus strains, regimen tolerability and improved toxicity

Targets for Hepatitis C Infection: A number of new agents are in development for the treatment of HCV infection since the goals of ARV therapy are to limit viral replication, prevent new infection, and enhance clearance of infected cells. Currently, drug candidates in various stages of development are: (i) A derivative of interferon, such as albuferon[56, 57], and derivatives of ribavirin such as viramadine or taibivirin); (ii) Drugs directed against components of HCV genome (e.g., protease inhibitors such as telaprevir or VX-950; SCH 503034; nucleoside HCV RNA polymerase inhibitors such as valopicitabine (NM283), R1626 and HCV-796); and (iii) Immune modulators including vaccines (such as isatoribine, a Toll-like receptor agonist that stimulates the natural immune response to a pathogen such as hepatitis C; and CPG 10101, a TLR9 receptor agonist that acts as an antiviral and Th1 immune enhancer[58, 59].

Targets for HIV Infection: Currently there are at least 26 FDA approved drugs for the treatment of HIV/AIDS and these belong to four classes of drugs and include: nucleoside reverse transcriptase inhibitors (NRTI's), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and one fusion inhibitor (FI). New formulations of drugs are available to reduce pill burden such as a single pill daily (emcitritabine/tenofovir/efavirenz) or newer agents in a class that may suppress resistant virus strains e.g. darunavir, a PI with excellent virologic activity against HIV with multiple resistance mutations[60].

Newer therapeutic agents in development include the following: (1) Entry inhibitors such as CXCR4 (AMD 070) or the CCR5 receptor blockers (maraviroc and vicriviroc); (2) integrase inhibitors such as MK-0518 and GS-9137 and (3) maturation inhibitor such as PA-457[61] are in various stages of development. These new agents, singly or in combination to overcome acquired resistance development, may provide options for both naïve and treatment experienced HIV infected patients. In the absence of preventive or therapeutic vaccines for hepatitis C or HIV, the intersections of human behavior, genetics and pharmacology will provide ongoing challenges to the management of infected persons.

CONCLUSION

In summary, both drug abuse and single or dual infections of HIV and HCV are associated with a wide variety of serious medical and health consequences. Although treatment of drug addiction and infections of HIV and/or HCV is complex, it is achievable with integrated programs of health care for dually infected drug addicts. The problem of drug interactions that appeared between HIV antiretrovirals and methadone seems to be less with the newly approved buprenorphine. Future research will show whether similar interactions would occur between buprenorphine or methadone and newer drugs that are being developed for the treatment of HIV and HCV. It is also anticipated that the newer antiretroviral medications would have lesser neuropsychiatric complications or pharmacokinetic interactions.

ACKNOWLEDGMENTS

Author is grateful to Dr. Glenn Triesmann of Johns Hopkins, Dr. Elinore McCance-Katz of Virginia Commonwealth University, and Dr. Ellen Tedaldi of Temple University for valuable information neuropsychiatric complications of drug abuse and infections, drug interactions, and new drugs in development.

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