

Substance Use Disorder, Intravenous Injection, and HIV Infection: A Review

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Shao-Cheng Wang^{1,2}  and Brion Maher²

Abstract

DSM-V-defined substance use disorder comprises four groups of symptoms: impaired control, social impairment, risky use, and pharmacological reactions. Behavioral patterns of impaired control, including impulsivity and risk taking, are associated with HIV risk behaviors. Substance users with stronger craving symptoms are more likely to use drugs via intravenous injection than other routes because of the faster drug effect and the higher bioavailability; thus, they are at high risk of HIV infection. HIV risk behaviors such as unprotected sex and intravenous injection facilitate HIV disease spread. Public health policies such as Needle and Syringe Exchange Programs and medication-assisted treatment are proven to reduce HIV risk behaviors such as the frequency of intravenous injection and even the incidence of HIV infection, but both of them have limitations. While intravenous injection is a frequently discussed issue in public policies and the HIV-related literature, it is a much less frequent topic in the addiction literature. We believed that understanding the mental substrate behind impulsivity/risk taking and the possible biological mechanism of intravenous injection may help in creating more effective strategies to slow down HIV infection.

Keywords

substance use disorder, HIV risk behavior, intravenous drug injection

Introduction

Substance use disorder is a complex phenotype, and is the result of a series of causal influences such as genetic factors, diverse environmental factors, and predicted drug-induced effects^{1–4}. Several behavior patterns such as impulsivity, risk taking, and stress response resulting from specific personality and physiological traits are considered to contribute to the vulnerability or liability to addictive disease, partially accounting for the influence of genetic variation, indexed as heritability, on addiction. Moreover, different personality and physiological traits may affect different stages of addiction, chronologically defined as initiation of drug use, continued regular drug use, and subsequent abuse/dependence and relapse⁵.

Substance use disorder is complicated in its symptoms and signs, which involve several domains such as cognition, behavior, and physiology. Persistent substance use changes brain reward circuits and causes specific behavior patterns such as craving. According to DSM-V, the criteria of substance use disorder can be grouped into four groups: impaired control, risky use, biological reactions, and social impairment caused by substances. Impaired control includes taking larger amounts than originally intended, multiple unsuccessful efforts to decrease or discontinue use, spending a great deal of time on substance use, and craving. Using

substances in a physically hazardous situation and/or using substances despite the knowledge of its physical or psychological consequences belong to the risky use category. The development of substance tolerance and withdrawal comprise the biological reactions⁶.

DSM-V defines symptoms such as tolerance, withdrawal, and uncontrolled increasing intake as the basic elements of substance use disorders, and these symptoms are associated with intravenous drug use. As a result of tolerance development, the longer these symptoms persist, the greater the amount of drug the user needs to consume to have the same effect. Among the most frequent (and tolerant) drug users, injection is more common, because injection causes an

¹ Jianan Psychiatric Center Ministry of Health and Welfare, Tainan, Taiwan

² Mental Health Department, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

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Corresponding Author:

Shao-Cheng Wang, Jianan Psychiatric Center Ministry of Health and Welfare, 71742 No.539, Yuzhong Rd., Rende Dist., Tainan City 717, Taiwan.

Email: WShaocheng@gmail.com



immediate and strong drug effect, leading to frequent reuse of contaminated needles and needle sharing. DSM-V also defines impaired control and risky use as the other two basic elements of substance use disorders, which are also associated with intravenous drug use. When severe substance abusers exhibit strong craving and impaired self-control, there is a desire to experience the drug effect immediately, ignoring the hazard of blood-borne diseases, such as HIV, hepatitis B, and hepatitis C. Impulsivity is an internal mental urge and impaired self-control is associated with poor judgment. Impulsivity and impaired self-control are the tendency to act without forethought, leading to increased external risky behaviors such as unsafe intravenous drug use. In brief, several symptoms of substance use disorders such as the increasing drug use with tolerance and impulsivity/poor self-control are obviously associated with intravenous drug use. Though intravenous drug use is highly associated with severe forms of substance use disorder and persons who inject drugs (PWID) are at high risk of blood-borne disease such as HIV/AIDS and hepatitis, the biological, psychological, and molecular mechanisms underlying the liability to intravenous drug use are less frequently discussed. In this article, we reviewed the literature related to the symptoms of substance use disorder, the mechanisms of intravenous drug use, and the public approaches to HIV/AIDS infection prevention. We hope this review may provide insight into all possible avenues that can be explored in current and future public health approaches to reducing the spread of HIV infection by reducing injection rates.

Symptoms and Signs of Substance Use Disorder: DSM-IV and DSM-V Diagnosis

According to DSM-IV, the criteria of substance use disorder include tolerance, withdrawal, uncontrolled increasing intake, spending more time and money on substances, and impaired social, occupational, or recreational function, and use that continues in spite of knowledge of the impact of substance on physical and psychological health⁷. In 2013, DSM-V was published and revealed the criteria change of substance-related disorders. DSM-V removed the criterion of recurrent substance use resulting in legal problems and added the criterion of craving to use substance, and kept all other criteria from DSM-IV. Furthermore, the criteria of DSM-V substance use disorder can be used to specify current severity, with mild, moderate, and severe⁶.

This change between DSM-IV and DSM-V in substance-related disorders means the movement from a categorical view to dimensional approach. A categorical view is used by clinicians to meet the needs of reporting for health care planners; on the other hand, a dimensional approach conceptualizes a quantitative disorder that is more useful for the purpose of research⁸.

Intravenous Injection

Injection and Other Routes of Drug Administration

Several routes of drug administration are commonly used by substance abusers: oral, sniffing or intranasal using, and injection. Injection is the act of putting a drug into a person's body using a needle and a syringe, delivering drugs by parenteral administration, including subcutaneous, intramuscular, intraperitoneal, intracardiac, intraarticular, and intravenous injection. Injection can cause several side effects, including high fever, pain over the injection site, swelling or hardness under the injection site, and anaphylaxis. In addition, injection can cause skin and soft tissue infections (SSTIs) such as abscesses and cellulitis; PWID are at high risk of SSTIs, especially those with high injecting frequency⁹. Compared with the other administration routes, intravenous injection results in the fastest drug effect because the drug reaches the brain through the circulatory system almost immediately. Bioavailability is the fraction of an administered dose of unchanged drug reaching the systemic circulation, and the bioavailability of intravenous administration was defined as 100%; the bioavailability of other administration routes such as oral, sniffing or intranasal use, subcutaneous, intramuscular, intraperitoneal, intracardiac, and intraarticular injection generally decreases due to incomplete absorption and/or first-pass metabolism¹⁰. In brief, compared with other drug administration routes, substances have the strongest and fastest effect via intravenous injection.

Intravenous injection and needle sharing are a consequence of severe forms of drug addiction. For example, it is common for PWID to inject heroin multiple times per day, thereby reusing or sharing needles due to limited resources. Because of the fast drug effect on the brain, the highest bioavailability, and cost, intravenous injection and sharing of needles are more among the PWID with the most severe craving symptoms. With more severe craving symptoms, substance abusers are at higher risk of risky behaviors and are more likely to use drugs impulsively, regardless of the hazard of blood-borne diseases⁶.

Impact of Injection and Drug Addiction

Injection behavior is very common among severe substance abusers. Drug addiction is associated with several psychiatric conditions including psychosis, mood disorders, depression, suicide, violence, and aggression; consequently, many PWID suffer from multiple morbidities and lose family support and occupational functioning. As a result, drug addiction causes serious social problems, with a substantial human and financial cost. In 2009, worldwide, an estimate showed that 271 million people have used at least one illicit drug, 39 million opioid, amphetamine, or cocaine users, and 21 million people who inject drugs¹¹. This estimate excluded several kinds of illicit drug—3,4-methylenedioxy-N-methylamphetamine (MDMA or ecstasy), hallucinogens,

and inhalants—so the true numbers of illicit drug users may be higher. Opioid overdose and opioid dependence are potentially lethal; injection of opioids, cocaine, or amphetamine is a substantial risk factor for transmission of HIV, hepatitis C, and hepatitis B¹². According to the results from the National Epidemiologic Survey on Alcohol and Related Condition (NESARC) in 2004, the 12-month prevalence in the United States of substance use disorder and any drug use disorders were 9.35% and 2.00%, respectively. The prevalence of opioid use disorder, amphetamine use disorder and cocaine use disorder were 0.35, 0.16, and 0.27, respectively¹³. Based on the result of the Monitoring the Future study, the number of injecting heroin users has fluctuated in recent years, with the annual prevalence rising from 0.3% in 2009 to 0.7% in 2010, and then went back to 0.5% or less in 2015^{14,15}. In Western countries, almost 3.5% of gross domestic product was consumed by both alcohol abuse and drug addictions¹⁶. In 2007, in the United States, \$55.7 billion (USD in 2009) were lost due to prescription opioid abuse. Workplace, health care, and criminal justice costs accounted for \$25.6 billion, \$25.0 billion, and \$5.1 billion, respectively.

Over the past decades, the high prevalence of HIV/AIDS among substance abusers drew the attention of many infectious disease physicians and epidemiologists, so several evidence-based approaches have been developed to reduce the frequency of risky injection behavior among those substance abusers who are at high risk of HIV infection. In the next paragraph, we review the previous studies which link HIV infection and PWID, and the related approaches to reduce the frequency of injection behavior.

Impact of HIV

AIDS was first reported within a small group of homosexual men with opportunistic infections and Kaposi's sarcoma^{17,18}. Two years later, HIV was identified as the cause of AIDS. The transmission pathway was identified as spreading through certain body fluids such as blood, semen, vaginal secretions, and breast milk. Several preventive measures were implemented such as risk reduction programs, condom distribution, and needle exchange programs. Since the last decade, the number of HIV infections has increased rapidly, and the public's concern has been aroused. According to a UNAIDS estimate, in 2011, 34.2 million persons were infected by HIV, as compared with 29.1 million in 2001, and 2.5 million persons were newly infected and 1.7 million persons died¹⁹. In 2015, the number of people living with HIV/AIDS reached 38.8 million²⁰. The infection trend decreased from 1990 but then steadily increased from 2002 to 2015. Based on the CDC fact sheet, in the United States there are 1.2 million people with HIV infection and 20% of them are unaware of their infection²¹. Currently, highly active antiretroviral therapy (HAART), which combines at least three drugs from two classes of antiretroviral agents, is used to treat HIV²². However, this virus is highly mutable so

drug resistance may develop. Prevention is a good alternative to reduce HIV transmission.

Ten years after HIV was first described, three main transmission routes were identified: blood-to-blood, sexual, and perinatal. Transmission by blood included transfusion of blood and blood products, needle sharing among intravenous drug users, and injection with unsterilized needles. Though sexual transmission plays an important role in PWID, in this article, we focus on needle sharing and unsterilized needles among PWID²³. A host of behavioral risk patterns, now defined as HIV risk behaviors, are observed in those at highest risk of HIV infection, including injection drug use and sexual behaviors including multiple partners, sex trade, and sex without using condom^{24,25}. Injection drug use, which is becoming increasingly associated with severe substance dependence, is also a well-known transmission pathway for HIV infection^{26–28}. Rosenberg et al. showed that substance use disorder and sexual orientation is directly associated with HIV risk behaviors such as needle sharing and intravenous injection²⁹.

Psychosocial Interventions and Public Policies Related to Drug Injection Behavior and HIV Infection

Psychosocial Interventions and Public Policies

Dutra et al. reviewed psychosocial interventions for substance use disorders and concluded that psychosocial interventions have low-moderate to high-moderate treatment effect for illicit drugs³⁰. Carroll and Onken reviewed the literature and found support for behavioral and pharmacological treatment effects on drug abuse, and that combinations of behavioral and pharmacological treatments have better potency than either one alone³¹. Two randomized clinical trials found that the Holistic Harm Reduction Program with behavioral therapy reduced HIV risk behaviors and improved adherence to medical treatment among intravenous drug users^{32,33}.

A systematic review by Mathers et al. finds PWID have increased in several countries over the last decade and are reported with a high prevalence of HIV³⁴. The high HIV incidence among PWID in many developing countries can be controlled by key harm reduction and treatment interventions such as needle and syringe programs, medication-assisted therapy (MAT), HIV counseling and testing, and antiretroviral therapy³⁵. In addition, opioid substitution is being used to reduce the prevalence of HIV infection, thereby causing modest reduction in HIV transmission rates³⁶.

Needle and Syringe Exchange Program (NSEP)

NSEP is a public health innovation which provides clean needles and syringes to reduce the time that contaminated needles are in circulation. NSEP also offers legal, social and

health counseling, sex education, and referrals to medical services as part of comprehensive approaches^{37,38}. While the range of NSEP practices varies broadly by country, needles and syringes are available for free from vending machines and pharmacies in some countries in Europe and Australia³⁹. The theory behind NSEP is that the less time the contaminated needles and syringes are in use; the less likely they are to be used by uninfected drug users. There is strong evidence that NSEP reduces the frequency of injection behavior with contaminated devices. Separate reviews by Drucker et al. and Palmateer et al. showed a positive association between NSEP and the reduction of injection risk behavior^{39,40}. The relationship between NSEP and the incidence of HIV is controversial. Two reviews support the idea that NSEP reduces HIV^{41,42}; however, a review by Degenhardt et al. also claimed that NSEP is negatively associated with HIV³⁶. MacArthur et al. found that NSEP can reduce the injection risk behavior, but the effectiveness in preventing blood-borne disease is insufficient⁴³. A review by Sawangjit et al. also showed that pharmacy-based NSEPs are effective for injection risk behaviors, although the effectiveness on blood-borne disease is still unclear⁴⁴. Noroozi et al. conducted a multilevel analysis in Iran and found that NSEPs might reduce HIV risk behavior, as well as injection-related risk behaviors, among PWID^{45,46}. Fernandes et al. conducted a systematic review and found that NSEP was effective in reducing HIV and injection risk behaviors among PWID⁴³.

Medication-Assisted Therapy

Heroin, cocaine, and amphetamine are the three most commonly injected drugs, but only heroin agonist pharmacotherapy is available for treating heroin addiction. Hence, this review only focuses on heroin agonist pharmacotherapy, also called substitution or maintenance pharmacotherapy. The best-known heroin substitution treatment, methadone maintenance therapy, is the standard protocol for treating heroin addiction⁴⁷. Methadone is a long-acting synthetic opiate agonist. It is initially administered in low doses to prevent respiratory depression and the dose is gradually raised to a maximum and maintain at that level in order to minimize withdrawal symptoms. Methadone doses at a high level can block the superimposed effects of heroin, so the PWID does not experience euphoria when they inject heroin under this treatment^{48,49}. In addition, methadone can be taken orally, thus reducing cues associated with injection behaviors in PWID⁵⁰. Methadone maintenance treatment has proven effective in reducing heroin use after 24 months of treatment, and the longer patients remain in the treatment program the better the results⁵¹. Remaining in a treatment program longer can bring about a range of positive outcomes, for example, improved family relationships, more stable employment, and fewer legal problems⁴⁰. The Three Cities Study by Ball and Ross and The Treatment Outcome Evaluation Study (TOPS) both showed a reduction in injection behaviors among the

PWID with methadone treatment^{52,53}. There is strong evidence that methadone maintenance treatment decreases HIV seroconversion rates among PWID because fewer people engage in HIV risk behaviors such as drug injection and/or needle sharing⁴⁰. Dutta et al. found consistently lower rates of AIDS among PWID in methadone treatment programs. HIV seroconversion is associated with the length of time in methadone maintenance treatment³⁵. In addition to methadone, buprenorphine and naltrexone are currently two other medications for opioid addiction⁵⁴. Buprenorphine is a partial agonist for the μ opioid receptor; thus, buprenorphine has a ceiling effect when it binds to and activates the μ opioid receptor, providing less euphoric feelings, as well as respiratory depression, making it a safer alternative to methadone⁵⁵. Long-acting injectable naltrexone can block opioid receptors and decrease the feeling of craving, as well as the risk of overdose⁵⁶. Naltrexone implants also had a lower mortality rate than buprenorphine⁵⁷, and a randomized clinical trial supported that long-acting injectable naltrexone was as safe and effective as buprenorphine with naloxone⁵⁸.

Discussion

The Possible Mechanism behind Intravenous Drug Use

Intravenous injection is strongly associated with HIV infection. PWID become infected with HIV when they share needles with other infected PWID; consequently, they become HIV carriers and transmitters through HIV risk behaviors such as needle sharing and having unprotected sex. This global spread of HIV infection ultimately results in dramatic loss of health and financial productivity. Intravenous injection is very common among PWID with severe craving symptoms as it has the fastest drug effect on brain and the highest bioavailability. Thus, PWID with more severe craving symptoms are more likely to use intravenous injection, regardless of the legal problems and the hazard of blood-borne diseases; in other words, they are more likely to take risks and are more impulsive, which are also associated with other HIV risk behaviors.

As mentioned above, intravenous injection can cause local pain, swelling, or hardness over injection sites, and possible anaphylaxis. Intravenous injection, with the fastest drug effect on brain and the highest bioavailability, can relieve craving symptoms. While intravenous injection is a frequently discussed risk factor in the HIV-related literature, it is a much less frequent topic in the addiction literature. In particular, the causal relationship between impulsivity/risk taking and intravenous injection is still unclear, as is the biological mechanism behind the liability to intravenous injection.

The Alternative Approach to Reduce HIV/AIDS Distribution

In the past decade, NSEP and MAT have succeeded in reducing the rate of HIV infection; meanwhile, there is strong

evidence that HAART is effective in reducing HIV transmission rates and prolonging life⁵⁹. However, as there is no proven cure for HIV, the best way to reduce infection rates is to prevent its spread. More effectively identifying those at a high risk of HIV infection is the key. NSEP is a widely used public health innovation which is significantly reducing contaminated needle distribution, but the relationship between NSEP and the incidence of HIV is controversial. Only heroin agonist pharmacotherapy is available for treating heroin addiction in MAT, despite other substance such as cocaine and amphetamine being injectable.

While intravenous injection is a frequently discussed target in the public policies, it is a much less frequent topic in the addiction literature. We believed that understanding the mental malfunction behind impulsivity/risk taking and the possible biological mechanism of intravenous injection will provide new information about more effective preventives. Several key findings are suggested. First, PWID use drugs intravenously because their effects kick in immediately; however, intravenous drug users and those who share needles are at risk of blood-borne diseases. This suggests that PWID will more likely take risks when they become severe substance abusers with stronger craving, needing more drugs to reach the same effect and having impaired self-control. Second, individual personal traits such as impulsivity/risk taking are symptoms of severe substance use disorder. This review supports that impulsivity/risk taking are associated with HIV risk behavior, especially using intravenous drugs and sharing needles. Finally, there is evidence that substance use disorders are associated with HIV risk behaviors directly and indirectly through impulsivity/risk taking, and psychosocial interventions are beneficial to substance abusers. In two small randomized controlled trials, psychosocial interventions also had an effect on reducing the frequency of HIV risk behaviors such as intravenous injection. NSEP and the MAT both showed a reduction in HIV risk behaviors, but they have their own limitations. In this review, we suggest that interventions to reduce the severity of substance use disorder and the frequency of intravenous injection could be beneficial to reducing HIV infection. However, more research is needed to illuminate the biological mechanisms behind intravenous injection and the casual relationship between drug addiction and intravenous injection, so that we can provide more effective strategies for prevention.

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ORCID iD

Shao-Cheng Wang  <https://orcid.org/0000-0002-7009-5338>

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