Health consequences of illegal drug use

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There are no conflicts of interest.

Current Opinion in Psychiatry 2009, 22:287–292

Purpose of review

The aim of this article is to review recent research on the health consequences of illegal drug use and possible risk factors, with a particular focus on prospective evidence.

Recent findings

Mortality studies have revealed qualitative and quantitative changes in causes of death among heroin and injecting drug users (IDUs), probably due to increasing exposure to harm reduction programs, the introduction of highly active antiretroviral therapy (HAART), the aging of drug users, and rising concurrent use of illegal drugs and prescription drugs. For morbidity, nonfatal overdose is still one of the most important concerns; likewise the higher prevalence of hepatitis C among non-IDUs and hepatitis A, B, C coinfection. Cannabis use has been consistently reported to be associated with the emergence of psychotic symptoms, yet that seems not to be the case for anxiety and depressive disorders. Use of 3,4 methylenedioxymethamphetamine (MDMA) has been linked with short-term negative effects on cognitive performance (i.e. visual memory). A series of longitudinal studies have shown enduring unfavorable effects of prenatal cocaine and marijuana exposure on children's physical, cognitive, and language development.

Summary

Prospective evidence on illegal drug use in particular subpopulations may be needed to better understand health problems among users at different life stages and the possible long-term effects.

Keywords

amphetamine, cannabis, cocaine, consequences, ecstasy, health, heroin, illegal drugs, prospective

Curr Opin Psychiatry 22:287–292

0951-7367

Introduction

Over the past century, medicine and public health have made tremendous progress in reducing morbidity and lengthening life expectancy, but the pace of improvement seems not to be the same across all disease categories. Substance use and related problems have taken an increasingly heavy toll on health across different societies and populations, particularly in younger age populations and low-income and middle-income countries. In 2004, drug use disorders accounted for 0.2% of all deaths worldwide (approximately 91 millions deaths) and contributed to approximately 0.5% of disability adjusted life years (DALY) [1,2]. A recent review on the burden of 11 mental disorders by Eaton *et al.* [3] reported that the category of drug abuse/dependence in general has a median relative risk of 2 for all-cause mortality and leads to an estimated annual cost of over 200 billion US dollars.

Prior clinical and epidemiological studies have shown that a broad array of adverse health consequences may be attributed to illegal drug use. The severity of adverse health effects varies, depending on individual characteristics (e.g. age, gender), pharmacological attributes (e.g. dose, purity, route of administration), context or situation (e.g. party scene or driving), and concurrent use of other drugs or alcoholic beverages [4]. In this review, we seek to identify and summarize some of articles recently published on health problems associated with illegal drug use (mainly in 2007 and 2008). The literature review was performed by searching MEDLINE (via Pubmed). Search-term categories included illegal drugs, illicit drugs, substance, and drug names (such as marijuana, cannabis, hash, weed, and hashish for marijuana). It was limited to the English language and human samples.

The present paper begins by reviewing the impact of illegal drug exposure on mortality and causes of death. With consideration of the strength of evidence, particular attention will first be paid to the literature concerned with prospective study design. Next, we briefly summarize some recent findings on health problems associated with illegal drug use, with a primary focus on cannabis, amphetamine-type stimulants (including ecstasy), cocaine, and heroin and other opiates; these are the most commonly consumed four categories of illegal drugs worldwide.

Finally, we turn to the existing evidence of drug-associated negative health consequences in special populations and discuss some gaps that need to be addressed in future research.

Mortality

A number of studies have attempted to identify predictors for survival status and the leading causes of death among treatment recipients [5•,6–8]. Prospective evidence generally points to the beneficial effects of opioid maintenance treatment on reducing overall mortality rates, which still holds true in studies analyzed by the 'intention-to-treat' method [5•,6]. In a study conducted in Italy, Davoli *et al.* [7] evaluated possible treatment modality variation in reducing the risk of fatal overdose on the basis of data on 10 454 heroin users from multiple sites. The standardized mortality ratio (SMR) was estimated to be 3.9 for in-treatment and 21.4 for out-of-treatment; for out-of-treatment heroin users, the incidence of overdose death appears relatively lower in those receiving methadone maintenance programs and methadone detoxification than in therapeutic community, other pharmacological treatment, and psychological programs. Also, the hazard ratio of fatal overdose was surprisingly elevated within 30 days since last treatment, being almost 27-fold greater than that for the in-treatment group (95% confidence interval (CI) of adjusted hazard ratio (aHR) 11.6–61.1). Several individual factors were reported to account for these higher mortality rates among the illegal drug-using population, such as intravenous drug use, concurrent use of other drugs, prior history of chronic medical disease and psychiatric disorder, and treatment engagement. In a recent study conducted in Boston, the analyses found the age-adjusted mortality rate of urban drug addicts was roughly four to five times greater than that of the general population. After statistical adjustment for initial drug choice, suicide attempt, and chronic medical illness, persistent homelessness was related to a 2.4-fold increased hazard of death ($P = 0.03$) within 4 years of substance detoxification [8]. Using a competing risk approach to identify the primary causes of death among drug users, one study in Norway found the hazard ratio of fatal overdose was similar across the age strata; conversely, the hazard ratio for nonoverdose deaths appears considerably elevated after the age of 40 [9].

Studies on certain special populations may also provide insight into the links between illegal drug involvement and decreased survival. In a study of nearly 1700 HIV-positive women recruited since 1996, Cook *et al.* [10] found that persistent use of crack cocaine was not only associated with increased hazard of death (aHR 3.6, $P < 0.001$), but also with poor prognosis as shown by immunological and virological markers of HIV-disease progression and newly acquired AIDS-defining illnesses. Prior observation has suggested that injecting drug users (IDUs), generally under-represented in the HIV-infected treatment seekers, were more likely to experience a poor prognosis in this era of highly active antiretroviral therapy (HAART). Nonetheless, building upon a prospective population-based cohort study of HIV-infected patients enrolling in treatment programs in British Columbia, Canada, Wood *et al.* [11•] demonstrated that the history of injecting drug use had no relationship with either all-cause or nonaccidental mortality rate, in a period of 84 months of follow-up, indicating future efforts should be directed towards improving the utilization of HAART among IDUs.

Finally, with increasing availability of harm reduction programs, the introduction of highly active antiretroviral therapy (HAART), the aging of drug users, and rising concurrent use of illegal drugs and prescription drugs changes in drug-related mortality (both qualitative and quantitative) have been increasingly recognized [6,12]. As an example, Ferreros *et al.* [13••] followed up a cohort of IDUs in Spain to investigate long-term overall and cause-specific mortality rates from 1987 to 2004. Over a 17-year period, there was a gradual increase in mortality from hepatitis or liver-related causes, cardiovascular diseases, and non-AIDS-related malignancy among IDUs. Although HIV infection was associated with a four-fold risk of death in general, with adjustment for important confounders the excess death rates from hepatitis or liver-related causes was significant only in HIV-seronegative IDUs, indicating that the pattern in cause-specific mortality may shift heterogeneously across subgroups of drug users. Smit *et al.* [14] investigated the risk of mortality from hepatitis among IDUs in Amsterdam. With a focus on hepatitis C virus (HCV) infection and HIV infection status, the results indicated that the hazard ratio for liver-related death in HCV/HIV coinfected IDUs was nearly seven times greater than their HCV-infected only counterparts. This may well reflect the influence of HAART.

Morbidity

A number of adverse effects from illegal drugs occur within minutes of use. These include cardiac crises due to cocaine and respiratory depression with opioids. Chronic substance-induced physical problems generally emerge after a longer period of drug exposure, such as liver cirrhosis, nephropathy, and some forms of cardiac pathology [15]. Noteworthy is that chronic harm indirectly related to drug use can occur at any stage in the natural history of the drug use disorder. This includes infectious diseases (e.g. hepatitis, HIV, and tuberculosis) and injury-associated disability.

Within the domain of mental health problems, the spectrum of adverse health consequences extends from

relatively time-limited emotional, perceptual or cognitive disturbances [16], to full-blown episodes of psychiatric disorder. Examples of the latter include methamphetamine psychosis and cannabis psychosis [17].

The spectrum of drug-associated adverse health effects occurs at different stages of the lifespan. In the first years of life, the adverse effects may begin with obstetric complications, fetal distress, stillbirth, and low birth weight, as a result of maternal drug taking during pregnancy [18,19]. In the adolescent and young adult years, self-inflicted injuries and homicides become more prominent [20,21]. Among the young adult population, the excess morbidity may be manifested by non-age-appropriate and unexpected physical conditions. Even in middle age and late life, the health harms associated with illegal drug use and drug dependence still exist.

To take one of the most common illegal drug-associated health problems – nonfatal overdose – as an example, two recent studies investigated this issue prospectively. One study was carried out by Wines *et al.* [22•], utilizing the data collected from 470 individuals participating in a randomized trial for detoxification from heroin, cocaine, and alcohol. They found that having a prior history of overdose (aHR 6.2; 95% CI 3.2–11.9), Caucasian race/ethnicity (aHR 3.9) and higher levels of depressive symptoms (aHR 1.1) strongly predicted subsequent experiences of nonfatal overdose within 2 years of discharge. Longitudinal evidence also indicates that nearly one in six or seven have a first episode of nonfatal overdose. Among opioid users, it was more than one in four (27%), and one in three in polydrug injecting drug users in Vancouver [23]. The last research indeed reported that, in terms of predicting the incidence of nonfatal overdose, the effects of drug-using behaviors (e.g. heroin or cocaine injection, benzodiazepine use, binge drug use, street injection, crystal methamphetamine use) seem more salient than individual characteristics and psychological well being [23,24]. The observed discrepancies across studies may be, in part, due to the variation in the length of observation period and the source of case ascertainment.

Recently, increasing attention has been paid to the higher prevalence of HCV in noninjecting drug users (NIDUs) who administer drugs primarily by smoking or inhalation [25••]. The rate of anti-HCV seropositivity ranged from 2.3 to 35.3%, with the median value being 14%. Some risk factors have been proposed, including tattooing, having unsafe sex, or sharing noninjecting drug equipment; however, to date available evidence seems less convincing given that noninjecting drug use was not a principal focus in prior investigations on the links between drug use and blood-borne hepatitis. Issues such as the definition of NIDUs, the assessment of NIDU-specific risky behaviors, and a larger sample size should be taken into account in future epidemiological research. This would enable evidence-based programs to be devised to reduce HCV-related harms among NIDUs. Similar concerns have been raised regarding the higher prevalence of coinfection of hepatitis A, B, C among treatment seekers [26]. Indeed, once infected with HCV, noninjecting drug experience appears to affect prognosis. Evidence from 204 patients with chronic HCV infection suggests that daily cannabis consumption may serve as a strong predictor in the pathogenesis process transitioning from none-to-mild as well as from mild-to-moderate/severe liver fibrosis [27]. With adjustment for heavy alcohol drinking and number of portal tracts, daily cannabis use alone was associated with approximately six to seven-fold increased odds of moderate/severe liver fibrosis (95% CI 1.9–24.3, $P = 0.003$). Cannabis use has also been implicated in one of the most common chronic diseases, periodontitis. As noted by Thomson *et al.* [28], the incidence of periodontitis in young adulthood exhibit a dose–response relationship with cannabis exposure in early life, and this association still holds regardless of cumulative tobacco smoking.

Several psychiatric disorders are associated with illegal drug use. The link between cannabis use and psychotic outcome is well documented [29–31]. A recent meta-analysis of 35 longitudinal population-based studies concluded that excess risk of psychotic outcome associated with any lifetime use of cannabis was moderate (adjusted odds ration (aOR) 1.4, 95% CI 1.2–1.7); there was evidence of a dose–response relationship [17]. In a clinical follow-up study, Rais *et al.* [29] considered that, in addition to triggering an episode of psychosis, the consumption of cannabis probably exerts other detrimental effects. Specifically, they examined the brain volume of patients with first episode schizophrenia and matched healthy controls using MRI scans. Over a period of 5 years of intensive observation, cannabis-exposed schizophrenic patients were found to have more pronounced gray matter volume loss and significant lateral ventricle enlargement compared with their cannabis-naïve schizophrenic peers.

Several researchers have examined whether cannabis use may be associated with other psychological disturbance, such as anxiety disorders and depression. The results are rather inconclusive [30–35]. For example, analyses built upon the Netherlands Mental Health Survey and Incidence Study (NEMESIS) show that a baseline history of cannabis use was significantly associated with the first episode of depression (aOR 1.6, 95% CI 1.1–2.5), bipolar disorders (aOR 5.0, 95% CI 1.8–13.8), but not with anxiety disorders, including panic disorder, phobia, general anxiety disorder (GAD), and obsessive compulsive disorder (OCD) [33]. In contrast, utilizing the Young Adult Self-Report (YASR) to measure symptoms of anxiety/depression among nearly 3000 individuals in

Australia, Hayatbakhsh *et al.* [32] found that frequent cannabis use was independently associated with higher levels of anxiety and depression in later life (aOR = 2∼3), and the increased risk was even more salient for early-onset cannabis use. These observed differences might be explained by variation in measurement instrument for psychological problems, heterogeneity in study population (i.e. age range or prior history of mental disorder), length of follow-up, or even the tetrahydrocannabinol (THC) content of cannabis. Clearly, more work is needed to disentangle the complex connection linking cannabis (or THC) to different clinical manifestations of psychiatric disorders.

There is also another example demonstrating the possibility that drugs may affect cognitive performance even with low cumulative exposure. Following up a group of ecstasy-naïve volunteers who had the intention to initiate ecstasy use in the near future, comparison of cognitive performance between incident ecstasy users and age, sex, and verbal intelligence quotient (IQ)-matched controls found no differences in attention and working memory, visual memory, and visuospatial function. However, a significant decline was noted in verbal memory, as indexed by immediate and delayed verbal recall and verbal recognition [16,36]. The same series of studies also indicated that ecstasy may exert specific negative effects on associative memory performance with heavy consumption, but seemingly less impact on cognitive function such as working memory, selective attention and associative memory at low-dose use [37,38].

Special populations

With regard to drug-associated health consequences, particular attention should be paid to certain subpopulations given their minority or vulnerability status, including pregnant women and children. Substantial empirical evidence supports that prenatal drug exposure has unfavorable and enduring effects on subsequent development [39]. Cocaine, marijuana, methamphetamine, and polydrugs have all been implicated. Recently, a series of studies on children with prenatal cocaine exposure found that they were at greater risk of suboptimal growth between infancy and mid-childhood (as indexed by weight and head circumference) [40], to have poor development of language skills and cognitive ability [41,42], and even to experience higher levels of internalizing and externalizing behavioral problems [43]. Similarly, a longitudinal study analyzing data from the Maternal Health Practices and Child Development (MHPCD) project suggested that prenatal exposure to marijuana may be associated with a significant reduction in the Stanford–Binet Intelligence Scale composite score and three subsets (i.e. verbal reasoning, quantitative reasoning, and short-term memory). Generally, the reduction in cognitive performance at age 6 seems more sizeable in relation to heavy marijuana exposure in the second trimester, suggesting developmental vulnerability may vary by timing of brain development.

Methodological considerations

To date, studies of illegal drug-related mortality and causes of death have mostly relied on cohorts of treatment seekers and IDUs [44]. Information on mortality is generally gathered from two sources: the first is vital statistics (e.g. death registrations) and the other is information from medical examiners and coroners. Possible drug-related excess mortality is then evaluated by several approaches, including the comparison with other groups (e.g. general population) and direct estimation of cohort mortality rates. It is important to note that both vital statistics and coronial data are affected by the definition of drug-related death and comprehension of assessment; nevertheless, vital statistics is considered more vulnerable to underestimation. Given the circumstances, the results from cross-system or cross-regional comparison and intrasystem long-term trend analyses should always be interpreted with caution. Similarly, although the use of illegal drugs has been long implicated in diverse health problems (both acute and chronic conditions), the accuracy of information in the history of substance use still poses a major concern for such research. To illustrate, a study comparing information validity of clinical assessment and toxicological assays in patients admitted for intentional drug overdose to the emergency department showed that information specificity in medical charts was by and large better than sensitivity, and the sensitivity estimate for opiates was even as low as 4% (95% CI 1.7–6.3) [45]. For that reason, it is generally recommended that a history of substance use is elicited using multiple approaches, such as self-report, clinical assessment, and biological techniques, which is particularly true for recent drug exposure.

Conclusion

The connection between illegal drug use and negative health consequences has been investigated in numerous longitudinal studies. Nevertheless, previous literature was commonly derived from treatment seekers (e.g. either detoxification or substitute maintenance programs). Such a body of knowledge barely exists for the drug-involved population with limited access to medical interventions for addiction treatment. Also, prospective evidence concerning mortality and morbidity derived from Australia, Europe and North American countries was mostly on marijuana, cocaine, and heroin. Although technologies such as neuroimaging have been introduced to evaluate possible short-term effects and related pathological mechanisms for 3,4 methylenedioxymethamphetamine

(MDMA) [46•], longitudinal studies with a focus on emerging illegal drugs (i.e. methamphetamine and ecstasy) or polydrug use are still needed in order to better understand their negative impacts on users at different life stages and their possible long-term health effects [47–49].

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 334–335).

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