

Organ Toxicity Associated with Illicit Drug Use

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Introduction

There is growing concern about illicit drug use, their complications and health hazards in many countries. Approximately 16 million people between 15-64 years old inject illicit drugs regularly all over the world [1]. Non-medical use of multiple classes of prescription drugs (opioid analgesics, benzodiazepines, and anxiolytic and sedative hypnotics) should be considered because of serious health related harms [2]. Steep rise in the use of licit and illicit drugs for non-medical purposes had led to demand for medical care and also intoxication and death [3,4]. Use of prescription opioids with illicit drugs and alcohol as it is seen in the pattern of polydrug uses have contributed to death in many countries [2]. Injection of illicit drugs and unsterile prepared crushed tablets result in the entrance of many pathogens and other contaminants to the body. Moreover many adulterants and impurities within the street drugs are introduced to the blood stream via injection [1,5]. In addition to the risk of overdose, toxicity and death, there is a high incidence of acute and chronic diseases and organ failure in illicit drug consumers. There are many classes of drugs that are abused in the globe, but their use has different extent, pattern and trend in different countries and societies. Each class of drugs, their adulterants and impurities has their own side effect in the body and almost no organ in the body remains unscathed by illicit drugs [6].

The aim of the present article is to focus on the wide spectrum of illicit drug-related vital organs complications.

Histopathologic features of illicit drugs in pulmonary system

The route of illicit drugs administration is one of the most important factors in the occurrence of pulmonary complications. Systematic and inhalational exposure to illicit drugs causes damage to pulmonary system [7]. Toxicity occurs after illicit drugs use as a result of acute lung injury or hypersensitivity reaction or delayed response representing as reactive airway dysfunction syndrome or cancer. Direct chemical reactivity, activity of alveolar macrophages and neutrophils to produce inflammatory cascade and free radicals production are suggested mechanisms that produce lung injury after illicit drug use. The level of lung injury and the location of inhaled substances deposition are affected by the water solubility of entered particles to the respiratory system and also their particle size. Ultrafine particles (<0.1 µm) deposit in all over the lungs. Small particles (<2.5 µm) may reach the alveoli, whereas larger particles (<2.5-6 µm) impact the bronchial tree [8]. Some drugs act as systemic toxicants and alter gas exchange by destroying or thickening alveolar septa [8]. Aspiration pneumonia serves as the most common pulmonary complications related to illicit drugs especially opioids [9].

Non-cardiogenic pulmonary edema is a major complication in almost all fatal opioid, cocaine and amphetamine type stimulants

overdose cases [10,11]. Crack cocaine induces pulmonary syndrome when inhaled. The chief complaint of the patient is shortness of breath, melanoptysis and fever. In histologic investigation diffuse alveolar damage and hyaline membrane can be seen [12-14]. Also alkaloidal cocaine smoking is accompanied by haemoptysis and alveolar haemorrhage [11]. Some other rare complications of cocaine abuse are septic embolism that result pulmonary nodules [15]. There are some reports that combustion products of cannabis may be carcinogen and produce interstitial lung disease too. Immunohistochemical markers confirmed carcinogenic effects of marijuana and cocaine in the bronchial mucosa [11].

Illicit drugs are manufactured in clandestine laboratories using low-cost, easily obtained precursors, acids, bases and other organic and volatile solvents including acetic anhydride, acetic acid, hydrochloric acid, sodium bicarbonate, iodine, red phosphorous, lead acetate, gasoline, ether, paint tinner and etc. [6,7,16,17]. Inhalations of laced illicit drugs that contain corrosive and noxious impurities promote airway injury. Throat mucus membrane irritation, pneumonitis, dyspnoea, pulmonary edema, fibrosis, bronchospasm and aggravation of asthma, acute respiratory failure, stimulation of nonspecific inflammation processes are major health consequences induced by impurities in street drugs [18].

Many adulterants and diluents are added to abuse substances for many purposes such as bulking, enhancing the pharmacologic effect of illicit drug or facilitating the use of illicit drug [3]. Talk (hydrated magnesium silicate), corn starch, sand, glass beads, microcrystalline cellulose, mannitol, sugar and flour are common adulterants added to street drugs especially heroin to increase the weight and volume of final product [3,7]. In addition to bulking agents, other impurities of origin that are produced during manufacturing process of illicit drugs and other active pharmaceutical ingredients that are deliberately added to abused substances are among the most important factors to make organ defects. Talc is one of the general fillers and lubricants for producing tablets in pharmaceutical industries [3,19]. Repeated intravenous injection or insufflation of crushed tablets or laced drugs result in the deposition of particles in the lungs. Foreign body granulomas, arterial obstruction, vasculitis leading to interstitial lung disease and talcosis or pneumoconiosis are pulmonary complications reported in drug abusers [3,19-23]. There are some reports that intravenous administration of some crushed oral medications such as methylphenidate, methadone, cocaine, diazepam, oxymorphone and heroin can produce pulmonary talcosis [24]. In a case report of intravenous drug abuser computed tomography of lungs showed bilateral areas of micro nodules and in pulmonary biopsy granulomatous reaction, giant cell and foreign bodies indicating talcosis was observed [8].

Cardio toxicity associated with illicit substance abuse

Cardiac manifestations are frequently observed complications in individuals using illicit and designer drugs [25]. Amphetamine type stimulants (ATS) exert their pharmacologic effect via catecholamine release. Myocyte degeneration, hypertrophy, necrosis and fibrosis are cardiac manifestations of methamphetamine abuse-related deaths. Potentially, fatal cardiac pathology in methamphetamine abusers is accompanied by aortic dissection, myocardial infarction, cardiomyopathy, atherosclerosis and sudden cardiac death [26]. In a case-control retrospective study on cardiac tissue of chronic heroin abuse related deaths, it was concluded that there was a significant correlation between opioid abuse and myocardium fibrotic alterations [27]. Alghamdi et al. in a study conducted on 42 patients who were hospitalized due to methamphetamine abuse showed that bradycardia, tachycardia, arrhythmia, atrial fibrillation, myocarditis and cardiomyopathy were considered as methamphetamine abuse effects [28]. Sadegi et al. reported cardiomyopathy and congestive heart failure in methamphetamine abusers [29]. Jouanjus et al. stated that serious cardiovascular complications such as acute artery syndrome, spasm of cerebral artery and lower limb arteriopathies were associated with cannabis use [30]. Atrial fibrillation associated to marijuana smoking was reported in previous studies [31]. Myocardial infarction, cardiomyopathy, transient ischemic attack, stroke, arteritis and sudden cardiac death were reported as adverse cerebrovascular and cardiovascular effects of marijuana inhalation [32].

In some studies it was reported that marijuana smoking develops bolus and subsequent pneumothorax due to deep inhalation to hold the smoke in the lungs [33]. Also smoking of fungi contaminated marijuana without filters is associated with pulmonary infections. In some instances bronchial biopsy of marijuana smokers showed histological and molecular changes indicative of precancerous changes [33].

Renal toxicity associated with illicit substance abuse

Acute or prolonged exposure to illicit drugs leads to drug-induced renal complications [34]. Renal hemodynamic changes, glomerular matrix degeneration and synthesis, renal atherogenesis and also oxidative stress and reactive oxygen species production are the main causes of cocaine induced renal complications. Renal biopsy of a case that abused cocaine for ten years showed mild interstitial fibrosis in kidneys [35]. Carrara et al. reported a case involving necrotizing and glomerulonephritis in a patient who abused levamisole-adulterated cocaine [34]. Some factors are believed to play a key role in the pathogenesis of heroin-associated nephropathy; these include: heroin and its impurities potential as an antigen in the body, chronic hepatitis B and C infections and acute glomerulonephritis induced by acute infections [36].

Previous studies confirmed renal complications associated with heroin abuse and others suggested that drug adulterants and vehicles are responsible to produce kidney injuries such as focal segmental glomerulonephritis and membrane proliferative glomerulonephritis in opioid abusers [35,37-39]. However some researches scrutinized that renal histopathologic changes are dependent to viral infections in intravenous drug abusers rather than the drug itself [40-41]. In a post-mortem case-series analysis on 129 suspected illicit drug abuse cases, evaluation of kidneys demonstrated interstitial fibrosis, tubular atrophy, renal parenchymal calcification and hypertensive ischemic

nephropathy. Some lesions such as renal calcification and interstitial inflammation are associated with severe intravenous drug use [42].

Synthetic cannabinoids are among abused drugs responsible to produce renal complications. Synthetic cannabinoids known as "Spice" or "K2" are solubilized and sprayed onto herbal preparations. They are sold as bath relaxing additives or air fresheners. Renal ultrasonography in 21 synthetic cannabinoid users demonstrated increased cortical echogenicity and bilateral symmetrical enlargement. In renal biopsy acute tubular necrosis and acute interstitial nephritis were detected [43]. In most cases of ecstasy (methylenedioxymethamphetamine=MDMA) users non-traumatic rhabdomyolysis as a result of hyperthermia was seen [43].

Hepatotoxicity of illicit drugs

Liver is one of the important organs in the body. Liver complications and liver related deaths due to substance abuse are frequent. Liver and especially hepatocytes enable the biotransformation of many lipophilic drugs through the action of metabolizing enzymes in the body and then removal from the organ system. During the metabolism process of many drugs, ultra structural hepatocyte changes and liver damage may occur [44]. Drugs induced hepatotoxicity is a major cause of liver damage. Liver is responsible for the detoxifying of drugs entered to the body, to do so liver have to work harder, leading to significant damage and also hepatic failure [45]. Drug-induced hepatotoxicity is dependent on various mechanisms through which liver is affected. Reactive oxygen species, mechanistic metabolite generation as the product of drug biotransformation and interaction of hepatocytes with drugs and their metabolites are among the most important causes of drug-induced liver injury [45]. ATS act on liver as hepatotoxic agents and liver is one of the most important vulnerable targets for ATS toxicity [46]. In an *in vitro* study methamphetamine liver toxicity was investigated in freshly rat hepatocytes. Results showed rapid increase in hepatocyte mitochondrial membrane damage as a consequence of reactive oxygen species formation [47]. In another study on human HepG2 cells exposed to ATS at 37°C and 24 h, HepG2 death by apoptosis was observed [46]. Hepatic fibrosis and acute liver failure was reported in young ATS abusers in previous studies [45]. In a study on autopsy cases of heroin abusers, liver samples were investigated from pathologic point of view with classical haematoxylin and eosin and also biochemical methods. Vacuolar degeneration, presence of small and large vacuoles within hepatocytes, hepatocytes fatty changes, cirrhosis, chronic active hepatitis, chronic persistent hepatitis and viral B hepatitis were observed in the liver of heroin addicts [48]. Bile duct dilation, microscopic bile duct injury, significant liver fibrosis and sclerosing cholangitis-like hepatobiliary disease were reported in recreational ketamine abusers [49].

Conclusion

The increase in the use of street drugs means that health practitioners must be aware of clinical manifestations and organ toxicity of these drugs. Further research is warranted to investigate the pathogenesis of different types of drug-organ reaction in the body.

References

1. Canales M, Gerhard J, Younce E (2015) Lower extremity manifestations of "skin-popping" an illicit drug use technique: A report of two cases. Foot (Edinb) 25: 114-119.

2. Rönkä S, Katainen A (2016) Non-medical use of prescription drugs among illicit drug users: A case study on an online drug forum. *Int J Drug Policy* 39: 62-68.
3. Akhgari M, Etemadi-Aleagha A, Jokar F (2016) Street Level Heroin, an Overview on Its Components and Adulterants. In: *Neuropathology of Drug Addictions and Substance Misuse Volume 1: Foundations of Understanding, Tobacco, Alcohol, Cannabinoids and Opioids*, Preedy VR editor. UK: Academic Press; p. 867-77.
4. Iravani FS, Akhgari M, Jokar F, Bahmanabadi L (2010) Current trends in tramadol-related fatalities, Tehran, Iran 2005-2008. *Subst Use Misuse* 45: 2162-2171.
5. Farquhar S, Fawcett P, Fountain J (2002) Illicit intravenous use of methylphenidate (ritalin) tablets: A review of four cases. *Australian Emerg Nurs J* 5: 25-29.
6. Amini N, Etemadi-Aleagha A, Akhgari M (2015) Impurity Profiling of Street Methamphetamine Samples Seized in Kermanshah, Iran with Special Focus on Methamphetamine Impurities Health Hazards. *J Clin Toxicol* 5: 258.
7. Mégarbane B, Chevillard L (2013) The large spectrum of pulmonary complications following illicit drug use: features and mechanisms. *Chem Biol Interact*. 206: 444-451.
8. Pritchard JN (2001) The influence of lung deposition on clinical response. *J Aerosol Med* 14 Suppl 1: S19-S26.
9. Marik PE (2001) Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med* 344: 665-671.
10. Dinis-Oliveira RJ, Carvalho F, Moreira R, Duarte JA, Proenca JB, et al. (2012) Clinical and forensic signs related to opioids abuse. *Curr Drug Abuse Rev* 5: 273-290.
11. Tomaszefski Jr JF, Felo JA (2004) The pulmonary pathology of illicit drug and substance abuse. *Diagn Histopathol* 10: 413-426.
12. Forrester JM, Steele AW, Waldron JA, Parsons PE (1990) Crack lung: an acute pulmonary syndrome with a spectrum of clinical and histopathologic findings. *Am Rev Respir Dis* 142: 462-467.
13. Leece P, Rajaram N, Woolhouse S, Millson M (2013) Acute and chronic respiratory symptoms among primary care patients who smoke crack cocaine. *J Urban Health* 90: 542-551.
14. Hui P, Walker B, Levy RD (2012) Patient with fever, hypoxemia, and pulmonary consolidations. *Chest* 142: 1348-1351.
15. Nguyen ET, Silva CI, Souza CA, Müller NL (2007) Pulmonary complications of illicit drug use: differential diagnosis based on CT findings. *J Thorac Imaging* 22: 199-206.
16. Shekari A, Akhgari M, Jokar F, Mousavi Z (2016) Impurity characteristics of street methamphetamine crystals seized in Tehran, Iran. *J Subst Use* 21: 501-505.
17. Haskin A, Kim N, Aguh C (2016) A new drug with a nasty bite: A case of krokodil-induced skin necrosis in an intravenous drug user. *JAAD Case Rep* 2: 174-176.
18. Roberts WC (2002) Pulmonary talc granulomas, pulmonary fibrosis, and pulmonary hypertension resulting from intravenous injection of talc-containing drugs intended for oral use. *Proc (Bayl Univ Med Cent)* 15: 260-261.
19. Scheel AH, Krause D, Haars H, Schmitz I, Junker K (2012) Talcum induced pneumoconiosis following inhalation of adulterated marijuana, a case report. *Diagn Pathol* 7: 26.
20. Gotway MB, Marder SR, Hanks DK, Leung JW, Dawn SK (2002) Thoracic complications of illicit drug use: an organ system approach. *Radiographics Spec No*: S119-S135.
21. Restrepo CS, Carrillo JA, Martínez S, Ojeda P, Rivera AL, et al. (2007) Pulmonary complications from cocaine and cocaine-based substances: imaging manifestations. *Radiographics* 27: 941-956.
22. Lemoine R, Dusmet M (2000) Images in clinical medicine. Pulmonary granulomas in an intravenous drug user. *N Engl J Med* 343: 1312.
23. Griffith CC, Raval JS, Nichols L (2012) Intravascular talcosis due to intravenous drug use is an underrecognized cause of pulmonary hypertension. *Pulm Med* 2012: 617531.
24. Siddiqui MF, Saleem S, Badireddi S (2013) Pulmonary talcosis with intravenous drug abuse. *Respir Care* 58: e126-e128.
25. Luciano RL, Perazella MA (2014) Nephrotoxic effects of designer drugs: synthetic is not better!. *Nat Rev Nephrol* 10: 314.
26. Kaye S, McKetin R (2005) Cardiotoxicity associated with methamphetamine use and signs of cardiovascular pathology among methamphetamine users, Sydney: National Drug and Alcohol Research Centre. Technical Report No 238.
27. Seltenhammer MH, Marchart K, Paula P, Kordina N, Klupp N, et al. (2013) Micromorphological changes in cardiac tissue of drug-related deaths with emphasis on chronic illicit opioid abuse. *Addiction* 108: 1287-1295.
28. Alghamdi M, Alqahtani B, Alhowti S (2016) Cardiovascular complications among individuals with amphetamine-positive urine drug screening admitted to a tertiary care hospital in Riyadh. *J Saudi Heart Assoc* 28: 129-135.
29. Sadeghi R, Agin K, Taherkhani M, Najm-Afshar L, Nelson LS, et al. (2012) Report of methamphetamine use and cardiomyopathy in three patients. *Daru* 20: 20.
30. Jouanjus E, Lapeyre-Mestre M, Micallef J (2014) French Association of the Regional Abuse and Dependence Monitoring Centres (CEIP-A) Working Group on Cannabis Complications*. *J Am Heart Assoc* 3: e000638.
31. Korantzopoulos P (2014) Marijuana smoking is associated with atrial fibrillation. *Am J Cardiol* 113: 1085-1086.
32. Thomas G, Kloner RA, Rezkalla S (2014) Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. *Am J Cardiol* 113: 187-190.
33. Lutchmansingh D, Pawar L, Savici D (2014) Legalizing Cannabis: A physician's primer on the pulmonary effects of marijuana. *Curr Respir Care Rep* 3: 200-205.
34. Carrara C, Emili S, Lin M, Alpers CE (2016) Necrotizing and crescentic glomerulonephritis with membranous nephropathy in a patient exposed to levamisole-adulterated cocaine. *Clin Kidney J* 9: 234-238.
35. Jaffe JA, Kimmel PL (2006) Chronic nephropathies of cocaine and heroin abuse: a critical review. *Clin J Am Soc Nephrol* 1: 655-667.
36. Alexandrov A, Kiryakova T, Landzhov B, Hristov S, Hinova-Palova D, et al. (2015) Morphological changes in kidneys after prolonged use of illicit drugs via intravenous administration. *Int J Tech Res Appl* 3: 157-159.
37. Cunningham EE, Brentjens JR, Zielezny MA, Andres GA, Venuto RC (1980) Heroin nephropathy. A clinicopathologic and epidemiologic study. *Am J Med* 68: 47-53.
38. Cunningham EE, Venuto RC, Zielezny MA (1984) Adulterants in heroin/cocaine: implications concerning heroin-associated nephropathy. *Drug Alcohol Depend* 14: 19-22.
39. Friedman EA, Tao TK (1995) Disappearance of uremia due to heroin-associated nephropathy. *Am J Kidney Dis* 25: 689-693.
40. Garfein RS, Vlahov D, Galai N, Doherty MC, Nelson KE (1996) Viral infections in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. *Am J Public Health* 86: 655-661.
41. Vlahov D, Anthony JC, Munoz A, Margolick J, Nelson KE, et al. (1991) The ALIVE study, a longitudinal study of HIV-1 infection in intravenous drug users: description of methods and characteristics of participants. *NIDA Res Monogr* 109: 75-100.
42. Buettner M, Toennes SW, Buettner S, Bickel M, Allwinn R, et al. (2014) Nephropathy in illicit drug abusers: a postmortem analysis. *Am J Kidney Dis* 63: 945-953.
43. Pendergraft WF, Herlitz LC, Thornley-Brown D, Rosner M, Niles JL (2014) Nephrotoxic effects of common and emerging drugs of abuse. *Clin J Am Soc Nephrol* 7: 9.
44. Ilić G, Karadžić R, Kostić-Banović L, Stojanović J (2005) Chronic intravenous heroin abuse: impact on the liver. *Med Biol* 12: 150-153.
45. Roy DN, Goswami R (2016) Drugs of abuse and addiction: A slippery slope toward liver injury. *Chem Biol Interact* 255: 92-105.
46. Dias da Silva D, Carmo H, Lynch A, Silva E (2013) An insight into the hepatocellular death induced by amphetamines, individually and in

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- combination: the involvement of necrosis and apoptosis. *Arch Toxicol* 87: 2165-2185.
47. Eskandari MR, Rahmati M, Khajeamiri AR, Kobarfard F, Nobarani M, et al. (2014) A new approach on methamphetamine-induced hepatotoxicity: involvement of mitochondrial dysfunction. *Xenobiotica* 44: 70-76.
48. Winklhofer S, Surer E, Ampanozi G, Ruder T, Stolzmann P (2014) Post-mortem whole body computed tomography of opioid (heroin and methadone) fatalities: frequent findings and comparison to autopsy. *Eur Radiol* 24: 1276-1282.
49. Wong GL, Tam YH, Ng CF, Chan AW, Choi PC, et al. (2014) Liver injury is common among chronic abusers of ketamine. *Clin Gastroenterol Hepatol* 12: 1759-1762.