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REVIEW

Effects of drug abuse, smoking and alcohol on donor hearts and lungs

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SUMMARY

Potential heart and lung donors with a history of illicit drugs and/or smoking and alcohol are frequently offered, though there is no clear guidance on when it is safe to use these organs. A review of the literature on effects of drugs, alcohol and smoking on donor outcomes, and the effects of these on the intact heart and lung was undertaken. There has been a marked increase in deaths from opioid abuse in many developed countries, though recent evidence suggests that outcomes after cardiothoracic transplantation are equivalent to nonopioid donor causes of death. For donor smoking, there is an increased risk with lung transplantation; however, that risk is less when compared to further waiting on the transplant list for a nonsmoking alternative. Heavy alcohol consumption does not adversely affect heart transplantation, and there is no clear evidence of adverse outcomes after lung transplantation. There are no overall effects of cannabis or cocaine on survival after heart or lung transplantation. In all these cases, careful donor assessment can establish if a particular organ can be used. In most cases, use of drugs requires careful assessment, but is not in of itself a contraindication to cardiothoracic transplantation.

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A global perspective of drug overdose deaths

For the purposes of cardiothoracic transplantation, a frequently developing problem is donor offers from patients who have died as a result of drug overdose, have a history of drug abuse, or significant smoking or alcohol abuse history. In some countries, there is great concern about the recent increases in drug overdose-related deaths. For instance, in the United States in 2017, there were over 70 000 drug overdose deaths, comparing to 36 000 in 2007. Of these deaths in 2017, the most common type of drug is synthetic narcotics (other than methadone), with prescription opioids and heroin the second and third most common categories [1]. Deaths from psychostimulants, antidepressants and benzodiazepines also involved opioids in the majority of cases. There are significant variations across developed countries in the rates of drug overdose deaths. Not only the United States, but British Columbia in Canada [2], Scotland [3], Australia [4] and Estonia [5] have very high rates, and in most countries, there have been recent increases, most obvious in the United States and United Kingdom [5] (Fig. 1).

Published guidelines are scanty; there are none from the UK's Advisory Committee on Safety of Blood, Tissues and Organs (SaBTO). The most recent edition (2018) of the Guide to the Quality and Safety of Organs for Transplant (7th edition) [6], published by the European Directorate for the Quality of Medicines & HealthCare (EDQM), has a

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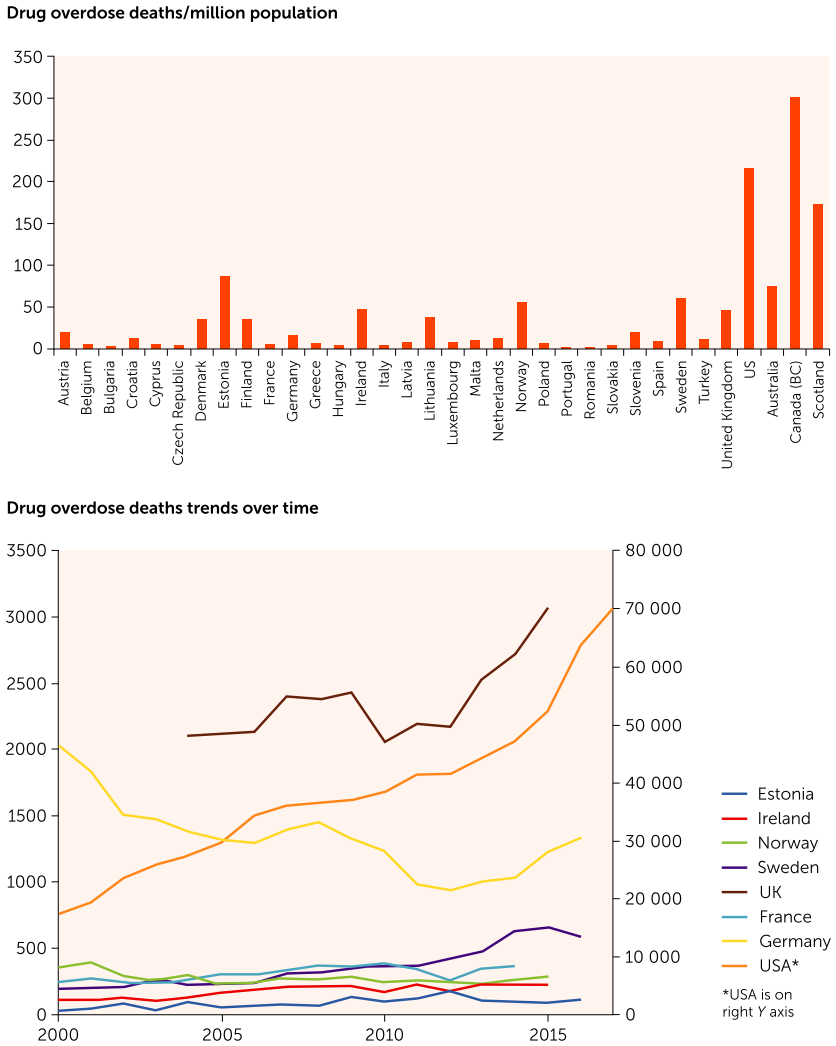

Figure 1 (Top) International rates of deaths from drug overdoses obtained from national resources [1–5] normalized to per million head of population. Most recently available data from each resource are used (2016–2017; British Columbia: BC). (Bottom) Changes in drug overdose rates over time in selected countries.

quite extensive section on poisoning in the donor. Some limited data on the effects of drugs are included, along with commentary on the legal and ethical framework for the removal of organs from victims of poisoning (Table 1).

In this review, we examine the effects of commonly used drugs including smoking and alcohol, looking at direct effects on heart and lung transplantation outcomes and on the intact heart and lung. Priority is given to outcomes in cardiothoracic transplantation, and where appropriate, direct effects on the native heart and lung are also considered.

Cardiothoracic transplantation outcomes with opioids

The increase in drug overdose deaths has had important implications for donor assessment for transplantation. Mehra *et al.* [7] have recently demonstrated the increase in heart and lung transplant donors from donors who died from drug intoxication in the United States, compared to transplants in the Eurotransplant area (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia). Between 2000 and 2016, they noted an approximate 11-fold increase in the proportion of transplants from drug intoxicated donors, though no such increase in the Eurotransplant zone (though as noted in Fig. 1, other European countries do have significant drug overdose death rates). However, outcomes after heart and lung transplant from these donors were not significantly different compared to other categories of donor death. These good outcomes are important to document as they refute reports suggesting the hypotension and hypoxia that may develop after drug intoxication could adversely affect ischaemic

Table 1. List of most commonly used drugs according to FRANK (https://www.talktofrank.com/ [92]), which is a national drug education service jointly established by the UK Department of Health and Home Office, and a synopsis of effects on the donor heart and lung with recommendations

	Donor lung	Donor heart
Alcohol	Possible increased risk of primary graft dysfunction	Potential for cardiomyopathy with long-term chronic use
Amphetamine	No available evidence of harm. ECG and echocardiogram to assess for the presence of pulmonary hypertension	Donors can be used for transplantation provided cardiac function is normal and left ventricular hypertrophy is absent. Echocardiogram recommended
Cannabis	No effects on overall transplant survival	No effects on overall transplant survival
Cigarettes	Adverse effect of smoking history on outcomes outweighed by risk of waiting on transplant list for a nonsmoking donor	Predispose to coronary artery disease. Coronary angiogram is recommended when smoking and other risk factors present
Cocaine	No available evidence of harm. ECG and echocardiogram to assess for the presence of pulmonary hypertension	Donors can be used for transplantation provided cardiac function is normal and left ventricular hypertrophy is absent. Echocardiogram recommended
Crystal meth	No available evidence of harm. ECG and echocardiogram to assess for the presence of pulmonary hypertension	Donors can be used for transplantation provided cardiac function is normal and left ventricular hypertrophy is absent. Echocardiogram recommended
Diazepam	No available evidence of harm	No available evidence of harm
Ecstasy	No available evidence of harm. ECG and echocardiogram to assess for the presence of pulmonary hypertension	Donors can be used for transplantation provided cardiac function is normal and left ventricular hypertrophy is absent. Echocardiogram recommended
GHB	No available evidence of harm	Donors can be used for transplantation provided cardiac function is normal and left ventricular hypertrophy is absent. Echocardiogram recommended
Heroin	Should not preclude donor acceptance	Haemodynamic and ECG assessment with overdose recommended (as for other narcotics)
Ketamine	No available evidence of harm	Potential for cardiomyopathy. Echocardiogram recommended
LSD	No available evidence of harm	Cardiovascular complications rare
Magic mushrooms (psilocybin)	No available evidence of harm	Cardiovascular complications rare
Methadone	No available evidence of harm	ECG to check for QT prolongation
Steroids	No available evidence of harm	Risk of cardiomyopathy with anabolic steroids
Temazepam	No available evidence of harm	No available evidence of harm

injury occurring after organ retrieval [8]. These findings have been further substantiated by a study of all solid organ transplants in the United States between 2000 and 2017 showing no adverse effects of drug overdose deaths on survival [9]. Neither of these studies was able to differentiate from opioid and nonopioid causes of death, though based on the US national statistics above, the majority of cases will involve opioids alone (prescription or illicit) or often in combination with other drugs. Other reports dealing separately with hearts and lungs have also recently shown no adverse effects on survival [10,11]. Thus, heart and lung donors from drug overdose patients should be considered for transplantation.

Despite the reassuring data on outcomes, several specific issues related to drug abuse can affect potential heart and lung donors. It should also be recognized that as well as potential heart and lung-specific complications, drug abusers have higher risks of hepatitis, TB and HIV [12,13].

Specific issues related to opioid use on the intact lung relevant to transplantation:

1. Pulmonary infection in intravenous drug abusers: there is a 10-fold increased risk of community-acquired pneumonia [14]. Smoking cigarettes and/or illicit drugs results in impaired local lung defences, macrophage activity and mucociliary clearance. There is an increased risk of human immunodeficiency virus (HIV). Smoking illicit drugs increases the risk of bacterial pneumonia in HIV subjects [15]. Resulting stupor can lead to aspiration pneumonia or lung abscess [16]. There is an increased risk of tuberculosis from donors from intravenous drug abuse [17–20].
2. Heroin: heroin can induce severe bronchoconstriction in patients with already recognized asthma.

Possible mechanisms are as follows: local airway irritation from the heroin fumes and impurities, and opiate stimulated histamine release. Smoking rates are four times higher in substance abusers [21], and the average number of cigarette per day among heroin inhalers is higher than that among heroin injectors [22]. There is a significant association between heroin-smoking, forced expiratory volume in one second (FEV_1) and prevalence of dyspnoea, which is in part confounded by tobacco smoking [23]. Heroin can lead to a diminished level of consciousness and depressed cough reflex, resulting in aspiration pneumonitis (because of infection or aspirated gastric contents) and lung abscess. Lower lobe bronchiectasis has been reported following prior episodes of aspiration or pulmonary infection [24]. Heroin smoking or injecting alone should not preclude use of donor lungs if other criteria met.

Specific issues related to opioid use on the intact heart relevant to transplantation:

1. Heroin and other narcotic analgesics. Narcotic analgesics increase parasympathetic activity, reduce sympathetic activity and release histamine from mast cells which can produce bradycardia and hypotension [25]. The bradycardia in combination with enhanced automaticity can precipitate an increase in ectopic activity, atrial fibrillation, idioventricular rhythm or potentially lethal ventricular arrhythmias. Overdose may result in noncardiogenic pulmonary oedema. Profound cardiovascular collapse and arrhythmias may also develop with overdose. Haemodynamic assessment of the potential donor with opiate use particularly overdose is essential.
2. Methadone: can be associated with QT prolongation (also buprenorphine) [26]. Those with recent cocaine use, uncontrolled blood glucose and heart failure are particularly at risk [27]. Electrocardiogram (ECG) essential and review by cardiologist.

Cardiothoracic transplantation outcomes with cigarette smoking

Lungs

There have been numerous studies looking at the influence of donor smoking on outcomes following lung transplantation. None satisfactorily address the issue of total 'dose' though there has been an attempt to estimate and quantify qualitatively into heavy, moderate and light. In general, these show that both short-term and long-term outcomes are adversely affected by a donor smoking history [28–30], and when using older age donors [31]. One single-centre study suggested worse outcomes with heavy smoking (>40 pack-years smoking history) versus less heavy smoking [32].

In this regard, data from a large UK multicentre study showed (1295 transplants, 39% smoking history) that there was an adverse effect on early and late mortality (unadjusted hazard ratio at 3 years = 1.46); however, this effect was outweighed by the survival advantage of accepting an offer of a donor with a smoking history rather than waiting on the lung transplant list [28]. In addition, there is supporting evidence from the United Network for Organ Sharing database of more than 5900 transplants with 13% heavy smoking donors that show comparable post-transplant safety outcomes from heavy smoking donors when compared to non-heavy smoking donors [33].

Heart

Whereas smoking is a well-established risk factor for coronary artery disease, it, in of itself, is not a reason to reject a heart donor offer, despite a higher risk in the transplant recipient. In a study of transplanted healthy hearts using intravascular ultrasound ($N = 198$) 4 weeks after transplantation [34], there was an age-dependent increase in the presence of atherosclerotic coronary arteries (defined as intimal thickness >0.5 mm at any site) from 5.9% at 10–19 years of age to 78.4% at 40–49 years. In those with atherosclerosis, there was a 41% incidence of donor smoking, compared to a 17% incidence of smoking in those without atherosclerosis. The dose-related effects of smoking were not quantified. There is a statistically significant (hazard ratio 1.123, $P < 0.01$) effect of donor smoking on 5-year mortality and development of cardiac transplant vasculopathy (hazard ratio 1.141, $P < 0.05$) post-heart transplantation [35]. Coronary angiogram of the donor is the definitive method of diagnosis. Alternatives when coronary angiography is not available at the donor site are coronary artery bypass grafting of palpable lesions [36], stress echocardiography [37], early coronary angiogram after transplant or an *ex vivo* coronary angiogram [38] when the explanted donor heart is supported on a perfusion apparatus and brought to the implanting centre.

Cardiothoracic transplantation outcomes with alcohol

Lungs

Heavy alcohol use is independently associated with a twofold to fourfold increased risk of adult respiratory

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distress syndrome (ARDS) in critically ill patients raising potential concerns of increased primary graft dysfunction in donors. This stems from alcohol abuse lowering the thresholds to develop acute lung injury and airway inflammatory response [39]. The real-life data in terms of increasing risk of primary graft dysfunction from heavy alcohol use donors are variable. Lowery *et al.* [40] reported an eightfold increased risk of primary graft dysfunction in recipients who received allografts from heavy alcohol use donors from a large single centre which utilized donor history as the basis of classification of abuse. Pelaez *et al.* [41] used a validated alcohol abuse questionnaire to stratify alcohol abuse in 74 donors and studied the effects on primary graft dysfunction. Their conclusions were more measured in terms of a higher likelihood of multiple and consecutive days of primary graft dysfunction grade 3 noticeable within 48 h of transplant. There was, however, very minimal difference in overall intensive care and hospital stay between the heavy and light alcohol use cohort. The evidence for a true association between heavy alcohol use and primary graft dysfunction is far from being conclusive and merits multicentre studies.

Heart

Chronic alcohol abuse increases the risk of atrial fibrillation, myocardial infarction and heart failure [42]. Acute toxicity with alcohol (often in the setting of drug overdose) can lead to arrhythmias especially atrial fibrillation [43]. Studies of human donors and alcohol consumption show conflicting outcomes – some suggest benefit, others detrimental, all are small studies [12,44–46]. A study in 2015 using the United Network for Organ Sharing database was examined for all primary, adult heart transplants carried out from 2005 to 2012 incorporating 2274 heavy drinking donors (defined as 2+ drinks/day) – there was no adverse effect on mortality [47], and that has been confirmed even more recently [48]. These studies do not adequately address the issue of dose and duration-related effects of alcohol.

Cardiothoracic transplantation outcomes with cannabis, cocaine, crack cocaine

Lungs

There is little evidence with which to base a firm conclusion but several studies did not find any evidence of increased adverse outcomes following use of lungs from cocaine or cannabis abusers whose lungs met other criteria for donation [49–52]. With respect to intravenous substances cut with talc, there is little evidence with which to base a firm conclusion but one small study did not find any evidence of increased adverse outcomes following the use of donors whose lungs had evidence of talc granulomas but met other criteria for donation [53].

Specific issues of inhalational and intravenous drugs including cocaine, methamphetamine (crystal meth) and cannabis use on the intact lung relevant to transplantation:

1. Wide range of pulmonary complications but all generally overt and give rise to symptoms and signs in life. There is a risk of pulmonary hypertension with cocaine and amphetamines which requires screening with an ECG and echocardiogram in potential donors [54–61]. In a cohort of 106 patients with methamphetamine use admitted to hospital in Melbourne, Australia, who had transthoracic echocardiograms ($n = 24$) because of abnormal ECGs (thus a preselected group), 13% had pulmonary hypertension [57].
2. Cannabis: there is convincing evidence that cannabis causes large airway inflammation, symptoms of bronchitis and increased airway resistance and lung hyperinflation [62–64]. However, there is no convincing evidence that long-term pure cannabis use leads to chronic obstructive pulmonary disease (COPD) and emphysema [65]. Nevertheless, there are several case reports of giant lung bullae particularly in the upper lobes among (very heavy) cannabis smokers [66]. The primary confounding factor that makes disentanglement of individual pulmonary effects difficult is the coexistence of tobacco smoking in most cannabis users. Cannabis smokers should not be excluded as potential donors and it is highly likely that in many recreational cannabis smokers lungs are currently being used given widespread use.

Heart

There is no evidence of adverse effects on survival with cannabis [49]. Studies of human donors and cocaine show no detrimental outcomes [13,67,68]. International Society for Heart and Lung Transplantation (ISHLT) Monograph 'ISHLT Guidelines for the Care of Heart Transplant Recipients' [69] suggests hearts from donors with a history of past or current non-i.v. cocaine abuse can be used for transplantation provided cardiac function is normal and left ventricular hypertrophy is absent. The guidelines state that i.v. cocaine is more toxic to the heart than non-iv though no specific

evidence is cited for this. As for alcohol, a normal echocardiogram is reassuring. In a recent large study, the United Network for Organ Sharing (UNOS) database was examined for primary adult heart transplants from 2000 to 2010 with 2274 cocaine users [70]. There was no effect on recipient outcomes with past or present cocaine use. Two other studies have looked at donor substance abuse for various compounds – in one tobacco, inhaled and iv. drug abuse and alcohol in 150 transplants [12]. They concluded that a history of donor substance abuse does not have a negative impact on overall survival, cardiac function, risk of transplant-associated coronary artery disease. In patients who receive organs from virus-positive donors, the risk of viral conversion is high, but survival seems not to be influenced. In the second study in 143 transplants [13], cocaine use ($n = 60$), heroin smoking ($n = 6$), marijuana use ($n = 79$), oral narcotic abuse ($n = 20$) and intravenous drug use ($n = 21$) were documented. These had no significant effects on outcomes. There was, however, a considerable risk for transmission of hepatitis B and C viruses when these were detected by pretransplant screens. There is a case report of two instances of using ecstasy-induced brain dead donors for multiorgan transplantation (includes one heart) without obvious adverse effects [71].

Specific issues of inhalational and intravenous drugs including cocaine and methamphetamine (crystal meth) use on the intact heart relevant to transplantation.

1. Cannabis: cannabis has a biphasic effect on the autonomic nervous system [25]. At low or moderate doses, the drug leads to an increase in sympathetic activity and a reduction in parasympathetic activity, producing a tachycardia and an increase in cardiac output. At high doses, sympathetic activity is inhibited and parasympathetic activity increased, leading to bradycardia and hypotension. In the absence of major underlying structural heart disease, the autonomically mediated changes in heart rate and blood pressure are usually well tolerated. There is an increased risk of myocardial infarction because of coronary vasospasm [72]. Recommendation is for haemodynamic monitoring if recent use.
2. Cocaine and related drugs (amphetamine, and ecstasy): these have sympathomimetic acute effects which can cause tachycardia, hypertension, vasoconstriction and myocardial ischaemia because of coronary vasoconstriction and prothrombotic effects [25] (see below also for drug-induced valvular heart disease and ecstasy).
3. Methamphetamine (crystal meth): as for cocaine and amphetamines above, there are reports of cardiomyopathy [73], hypertension, aortic dissection, acute coronary syndromes, pulmonary arterial hypertension and methamphetamine-associated cardiomyopathy [74] and in rat models cardiac pathology [75]. Recommendations as for Cocaine and Ecstasy above.
4. GHB (gamma-hydroxybutyrate): GHB is generally thought to be a central nervous system depressant; however, GHB also has sympathomimetic cardiovascular actions. Hicks *et al.* [76] have shown in rats that i.v. GHB causes increases in heart rate, blood pressure and renal sympathetic activation. Recommendations as per Cocaine and Ecstasy above.

Other drugs, effects on the intact lung

Benzodiazepines: no direct effect.

Ecstasy: three reports of acute lung injury associated with liquid ecstasy ingestion [77–79].

GHB (gamma-hydroxybutyrate): no direct effect.

Ketamine: may protect against lung injury [80].

LSD (Lysergic acid diethylamide): no direct effect.

Magic Mushrooms (Psilocybin): no direct effect.

Methadone: pulmonary oedema after overdose reported [81,82].

Steroids: oral and injected slight increase in pneumonia reported [83].

Other drugs, effects on the intact heart

Ketamine: can be associated with cardiomyopathy. Animal experiments suggest considerable myocardial toxicity, including susceptibility to arrhythmias [84]. Echocardiogram recommended.

Steroids: concern is with anabolic steroids used for bodybuilding which can cause cardiomyopathy [85,86]. No data on corticosteroids causing ventricular dysfunction in humans, indeed growing interest in using corticosteroids to treat muscular dystrophy cardiomyopathy [87]. Echocardiogram recommended in those who take anabolic steroids.

Lysergic acid diethylamide (LSD) and psilocybin ('magic mushrooms'). These drugs are structurally related and have similar physiological, pharmacological and clinical effects. Both drugs are usually ingested orally, with LSD being 100 times more potent than psilocybin. Both drugs are indole derivatives and chemically resemble serotonin. Cardiovascular complications are rarely serious, although occasional instances of supraventricular tachyarrhythmias and myocardial infarction have been reported [25].

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Drug-induced valvular heart disease: ergot derivative drugs used for the treatment of migraine and drugs used for Parkinson's disease (pergolide and cabergoline) are known to cause valvular heart disease – a mechanism thought to be similar to that seen with carcinoid syndrome – the difference being that carcinoid is associated with right heart valve problems and drugs affect the left [88]. Ecstasy may be associated with left heart valve problems according to one report [89]. Interference with serotonin metabolism and its associated receptors and transporter gene seems a likely mechanism for the development of the drug-induced valvular heart disease. Echocardiogram recommended and reviewed by experienced sonographer in those on pergolide or cabergoline or have used ecstasy.

Benzodiazepines: generally safe. Can cause hypotension and respiratory depression.

Conclusions and summary

Donor acceptance decisions in cases of drug overdose are often complex and involve more than one potential drug and comorbid conditions. Nevertheless, there is a clear and expanding literature that supports the use of many of these organs, with careful donor assessment. Donor deaths related to opioids, and in those with smoking, alcohol, cannabis and cocaine and its related compounds should not be rejected without careful assessment. By the nature of illicit drug use, this is constantly changing and newer formulations (such as 'legal highs') are becoming available with potential adverse respiratory and cardiac effects [90,91]. There is even less information about newer drugs, though again a thorough assessment is recommended.

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Conflict of interest

GMG is a paid speaker for Medtronic and receives research grant funding from European Union. JD receives research funding from XVIVO Perfusion. AN has none to declare. PAC receives research grant support from Actelion and Bayer, and served as a member of advisory boards of and is a speaker for Bayer, Actelion and MSD.

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