Transplant International

Transplant International ISSN 0934-0874

REVIEW

Illicit drug use and liver transplantation: is there a problem and what is the solution?

Kerry Webb,[1] Liz Shepherd[2] and James Neuberger[1]

1 Liver Unit, Queen Elizabeth Hospital, Birmingham, UK
2 Liver Unit, Royal Free Hospital, London, UK

Keywords
guidelines, illicit drug use, Liver Advisory Group, liver transplantation, organ allocation.

Correspondence
Kerry Webb, Liver Unit, Queen Elizabeth Hospital, Birmingham B15 2TH, UK. Tel.: +44 121 627 2414; fax: +44 121 627 2449; e-mail: kerry.webb@uhb.nhs.uk

Received: 17 March 2008
Revision requested: 30 March 2008
Accepted: 28 May 2008

doi:10.1111/j.1432-2277.2008.00724.x

Summary

Liver transplantation is indicated in carefully selected patients with alcohol-induced liver disease. There has been less debate to date on the issues surrounding assessment of patients with an illicit drug history and outcome post-transplantation. UK guidelines on assessment and selection have been agreed. Careful assessment and access to treatment should be considered.

Background

Liver transplantation is accepted as an appropriate treatment for selected patients with end-stage alcohol-related liver disease (ALD) where there is a small likelihood of graft damage either from further alcohol use or from poor compliance with treatment and follow-up [1–4]. Nevertheless, the use of scarce grafts for patients with ALD continues to provoke debate and controversy both within the transplant community and among the general public [5,6].

The two key ethical issues in transplantation for ALD surround the moral argument of a 'self-induced disease' and the ongoing shortage of donor organs [7]. Mortality on the waiting list (including removal) is as much as 19% (http://www.uktransplant.org.uk; accessed 9th May 2008), although it can be argued that many potential transplant candidates are not being referred to specialist centres and therefore the overall mortality may be higher [8].

Specialists in addiction and psychosocial assessment have increasingly been introduced into the assessment process to evaluate and develop plans to minimize alcohol-related risks [9,10]. It is acknowledged that a proportion of ALD patients will resort to some alcohol use post-transplant and there remains debate on which factors are associated with reduced relapse; however, with careful selection, graft loss from recurrence or poor treatment adherence is low (<4% at 5 years) and 5-year patient and graft survival rates are similar to those found for other indications [11–13]. Guidelines and listing criteria for ALD have been agreed [14].

To date, there has been much less public debate surrounding liver transplantation in the context of illicit drug use, even though alcohol and illicit drug use have, in this context, many features in common (Table 1). This could be attributed to a lack of public awareness of the issues involved and perhaps reluctance on the part of the transplant community to raise awareness, which may further affect the low rates of organ donation. However, all healthcare professionals involved with liver transplantation have a duty of care to all potential liver transplant candidates and need to balance the often competing demands of equity, justice and utility, values that may conflict with public opinion [5].

In recent years, the transplantation rates for viral hepatitis C (HCV) have risen to around 40% in both Europe

Table 1. Alcohol and/or other drug issues in the context of liver disease and transplantation.

	Alcohol use	Illicit drug use
Perceived as 'self-induced'	++	++
Associated with a dependence syndrome	++	+/–
Associated with direct liver damage	++	+/–
Associated with other physical pathology	+++	++
Associated with poor programme compliance	+	+

and the USA (http://www.ustransplant.org/annual_reports/current/chapter_vi_AR_cd.htm, accessed 18th February 2008; http://www.eltr.org/publi/results.php3?id_rubrique=448, accessed 18th February 2008), and within this population there is a significant cohort of patients whose source of infection is intravenous drug use (IVDU) [15]. Indeed IVDU is the source of transmission in over 90% of HCV cases within the UK [16]. With the increase in numbers of people with end-stage liver disease from HCV referred for liver transplant assessment and the lack of a corresponding increase in the number of donor livers, there is an inevitable increase in the competition for a graft, there is now a need to develop guidelines for selection of such patients for transplantation. The time is prescient to consider issues of graft loss pertaining to both treatment adherence and potentially harmful drug use, including alcohol, post-transplant. It is also important to acknowledge that there are patterns of poly drug use which incorporate drug use in those with ALD as well as alcohol use in those with HCV and a history of illicit drug use.

Published experience

There is limited information in this group of liver allograft recipients. Two US based studies have reported successful transplantation of patients on maintenance methadone therapy (MMT) for previous illicit opiate IVDU. Post-transplant survival and treatment adherence was good and it was suggested that transplantation for patients with an IVDU history (including those still receiving MMT) should be considered where they meet the same psychosocial requirements as those with ALD [17,18]. It should be noted that both studies described only small numbers and there may be reluctance for centres to report those instances where outcomes have been less good. A more recent meta-analysis examining relapse to substance use across solid organ transplantation reported low illicit drug use postliver transplantation [15]. Therefore, it would appear reasonable to conclude that there is no clear evidence for automatic exclusion from transplantation in cases where there is an illicit drug history or where there is ongoing substitute opiate prescribing (commonly MMT, but increasingly Buprenorphine [19]).

Illicit drug use is not the same as alcohol misuse

Although many of the issues surrounding transplantation in the context of alcohol and illicit drug use are similar (Table 1), clearly there are also significant differences. A social drinker who becomes a heavy social drinker may develop ALD, but has no other untoward psychosocial consequences and may thus grasp long-term abstinence with conviction when the consequences of excessive alcohol consumption become apparent. However, an injecting drug user with a history of poly substance misuse may understand the principle of HCV liver damage, yet remain enmeshed in a social subculture of ongoing illicit drug use and be exposed to the longstanding psychosocial and physical consequences of this lifestyle.

Conversely, a potential transplant candidate with a diagnosis of ALD on the back of a longstanding history of alcohol dependence may well have become absorbed into a drinking culture at both psychological and social levels, and thus have limited insight, opportunity and peer support when being challenged to adopt a life of longstanding abstinence. Compare this to a patient with HCV secondary to IVDU, which may have been a singular event during youth, and replaced only with, for example, a tendency to regular recreational use of cannabis. Herein lies the dilemma: on one hand, the medical/transplant community seeks to ensure that the cause of liver disease has been addressed to minimize the possibility of a recurrence or noncompliance through a chaotic relapse; on the other hand, from the psychosocial perspective, the addiction community seek also to identify patterns of substance use in an attempt to articulate levels of risk, depending upon variables shown in Table 2. Indeed, criticism has occurred from within the transplant community in cases where it has been argued that patients have been denied a transplant based on a moral argument surrounding drug use, rather than an objective assessment of risk within carefully agreed guidelines [20].

A recent meta-analysis of 54 studies (including 50 liver) examined cases of nonadherence to medical treatment and relapse rates to substance use [15]. Once again, criticism is levelled at the lack of longitudinal or prospective studies, in addition to some vagueness in the clarity of data collection (for example, lack of definition of what constitutes a slip to alcohol or drug use or a full relapse or dependent use). Nonadherence to medical treatment in the study group appears reassuringly low, yet comparative studies with a control group have not been undertaken [15,21].

Table 2. Factors that may influence the future pattern of substance misuse.

Drug use	The type of substance used
Route of administration	Whether the drug is injected; risk of method of use
Career history	How long drug use has been for; periods of abstinence
Frequency	How often the drug(s) is/are taken
Diagnosis	Is there a diagnosis of dependence (see Table 3)
Context	How and why the drugs are used; alone or in a group
Social	Is there a support network; are family or partners using drugs
Treatment	History and context of treatment engagement
Forensic	Nature and extent of criminal history i.e. drink-driving, acquisitive crime, possession or violent crime
Persistent use	Ongoing use despite serious consequences (i.e. medical or legal)
Maintenance therapy	Context and stability of a programme (i.e. Methadone or Subutex)
Motivation	Substance and lifestyle goals of patient; insight and motivation

Much has been written in recent years of the 'drug using career' describing the often extensive process of drug use, from initiation followed by escalation, often with increasing untoward effects, and the extended cycles of slips, relapses and cessation, which often occur over an extensive period [22,23]. This pattern is a familiar one within substance misuse treatment services where clinicians have learned to take the longer-term view. The principles of harm reduction are underpinned in the need to keep an element of stability and safety for patients whilst ongoing drug use is likely to be maintained (such as needle exchange programmes and hepatitis B vaccination programmes). This approach intends to enable as normal a transition into mainstream society, and non-using lifestyles, as possible and with the minimum of untoward legacies. Likewise, it is now clear that for some drug users, opiate addiction is a lifelong pattern with associated untoward consequences on both the health and social domains [24]. Parameters have been defined to reflect the multiple dimensions of addiction and treatment careers and are outlined in Table 3 [22].

Thus, the aim of abstinence from the transplant physicians' point of view can be in conflict with the harm minimization approach adopted by substance misuse services. In a study of over 8000 US citizens aged 15–54 years, using one of five substances (tobacco; heroin; cocaine; alcohol and cannabis), less than one-third progressed to substance dependence, with tobacco having the highest graduation rate from lifetime use to dependence [25]. There may be a clearer role for smoking cessation therapy in the transplant population [15,26].

There is also a difference in approach adopted within the United Kingdom and the United States in terms of working up patients with a substance misuse history for transplantation. This difference is as likely to reflect differences in addiction services and models of treatment. Abstinence-based programmes are much more readily available in the US and access to a residential rehabilitation programme for a period of abstinence and stability much more likely to be offered. Whether this is likely to provide a significant long-term therapeutic benefit, as opposed to simply helping to sustain the 6 months of required abstinence, requires further investigation.

A survey of all 97 US transplant programmes associated with UNOS revealed that all units accepted referrals for patients with a substance abuse history, with 86% of units requiring consultation from a substance abuse specialist or psychiatrist. Six-month abstinence remained the most common stated requirement (although anecdotal evidence suggests that this rule is not fully implemented) [27].

Table 3. Parameters that are associated with the drug using career (Hser *et al.*[22]).

Career parameters (Hser *et al.*[22])		
Participation	Involvement in periods of drug use	Involvement in periods of treatment
Frequency	The number of times an individual engages in drug use	The number of times an individual enters treatment
Type	The types and numbers of different drugs used	The types of drug treatment modalities entered (i.e. inpatient detox, outpatient clinic, community drug team or residential rehabilitation)
Length	Total number of years of drug use	Total length of periods of treatment engagement
Intensity	The intensity measure is the ratio between time spent in active drug use and time spent engaged in drug treatment over the course of the career	
Perception and attitude	Of drug use	Of treatment involvement

Although more than half of 87 transplant centres accepted patients on a methadone maintenance programme, a third required that patients discontinue methadone as part of the listing requirement. Ten centres did not respond to the survey [24].

Concern should certainly be raised in cases where transplantation is to be considered in exchange for detoxification from methadone maintenance therapy. Where an opiate misusing patient has stabilized their use through a recognized programme (often addressing chaotic/injecting behaviour and facilitating treatment engagement and concordance), insistence on leaving such a programme could be construed as akin to treatment sabotage and is not unlikely to precipitate a relapse to illicit opiate use [18,28]. Indeed, unlike in alcohol dependence, complete abstinence from opiates is less important than stability, and maintenance therapy is a recognized effective treatment for the management of opiate dependence [19,29].

Alcohol misuse is a common problem in opiate misusers attending for MMT. One third of drug users entering community based or residential treatment programmes in the UK are likely to be drinking significantly above the recommended levels of alcohol and a substantial proportion are likely to continue to do so when reviewed at 1-year follow-up [30]. Opiate users are often likely to substitute opiates with alcohol upon cessation of use; alcohol use (even within the recommended 'safe limits') will exacerbate liver damage associated with other causes and this is notable in the context of HCV infection as a consequence of IVDU where alcohol has supplemented or replaced other drugs of misuse [31]. It is therefore necessary to consider poly-drug use and the switching of drugs when assessing risks of disease recurrence and programme compliance in the context of transplantation. This is easy to state but much harder to define in terms of what constitutes risk. A patient with ALD who is abstinent from alcohol but smokes an occasional cannabis joint is unlikely to pose a risk to the graft post-transplant, but if the level of cannabis use is sufficient, it may become a substance of psychological reliance, perhaps for the purposes of relaxation, escapism or peer integration, and may in turn increase the likelihood of switching the substance of choice back to alcohol. The same argument can also be made of the ex-IVDU patient who occasionally smokes cannabis and may then consider smoking heroin once again, which in turn is a significant risk to a resumption of IVDU as tolerance to opiates returns and dependence to the drug is re-established (Table 4). Much has been written and debated on the subject of 'gateway' drugs, particularly cannabis, with some evidence of relationship between regular cannabis use and heroin use, and the age of first drug use linking with likelihood of use of further drugs [32].

Assessment and evaluation of drug misusing transplant candidates

So then, in terms of reducing risk to the allograft, the intention should be abstinence from all substances of potential abuse. This would clearly include alcohol, cannabis and tobacco, although there are many patients who have ceased opiate use when HCV positive, or alcohol when diagnosed with ALD they continue to smoke tobacco or cannabis in a recreational way but without untoward consequences. Therefore the aim must be to incorporate patterns of all substances of use into the overall psychosocial assessment in a way in which such factors can be taken into account in a considered manner. This would identify potential risks as well as absolute contraindications to listing (such as alcohol consumption

Table 4. The ICD-10 classification for the dependence syndrome.

F1x.2 Dependence syndrome
Three or more of the following manifestations should have occurred together for at least 1 month or, if persisting for periods of <1 month, should have occurred together repeatedly within a 12-month period:
1 A strong desire or sense of compulsion to take the substance
2 Impaired capacity to control substance-taking behaviour in terms of its onset, termination, or levels of use, as evidenced by: the substance being often taken in larger amounts or over a longer period than intended; or by a persistent desire or unsuccessful efforts to reduce or control substance use
3 A physiological withdrawal state when substance use is reduced or ceased, as evidenced by the characteristic withdrawal syndrome for the substance, or by use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms
4 Evidence of tolerance to the effects of the substance, such that there is a need for significantly increased amounts of the substance to achieve intoxication or the desired effect, or a markedly diminished effect with continued use of the same amount of the substance
5 Preoccupation with substance use, as manifested by important alternative pleasures or interests being given up or reduced because of substance use; or a great deal of time being spent in activities necessary to obtain, take, or recover from the effects of the substance
6 Persistent substance use despite clear evidence of harmful consequences, as evidenced by continued use when the individual is actually aware, or may be expected to be aware, of the nature and extent of harm

Table 5. UK Liver Advisory Group guidelines.

Assessment

Patients admitted for a transplant assessment irrespective of diagnosis should be screened for current and past illicit substance use as part of the clinical interview. This should include misuse of over the counter medications (OTCs) and apparent misuse of pain relief medication

Any patient considered to have a significant drug taking history should be assessed by a specialist in substance misuse; the term 'significant' must be interpreted by the clinical, multi-disciplinary team

Adequate time and resources should be made available to allow this specialist to undertake this process

Assessment should include problematic or dependent use as well as recent use. It should also identify substance use and stability within the patient's wider social support network, and take into account mental health and criminal justice issues as appropriate

Services should endeavour to develop and implement joint screening and assessment protocols between hepatology and substance misuse services to ensure effective care pathways are in place

Contra indications

I. Current ongoing intravenous use of illicit or nonprescribed substances
II. Two or more recent (within 2 years) incidences of unexplained and significant noncompliance with treatment – not necessarily confined to the management of liver disease
III. Current failure to comply with the assessment and treatment process for transplantation, including refusal to provide consent for gaining access to information pertaining to drug treatment and prescribing
IV. Recent past history of cross dependency (substituting from one drug to harmful/problematic use of another), within the last 2 years; this requirement could be relaxed for patients who have switched drugs within 2 years but have been stable since maintaining engagement in substance misuse services

Length of abstinence should be 2 years ideally, but not <6 months, where a patient has been dependent on a drug. The patient should have the opportunity to engage in an optimum substance misuse treatment programme

Potential contra indications

Potential contraindications allow issues of concern to be factored in without necessarily attempting to weight issues against one another in the absence of good evidence. The importance of potential contraindications should be discussed between the transplant team and substance misuse specialist and interpreted with clinical judgement on a case by case basis

I. Current legally prescribed intravenous drug use (i.e. Diamorphine or Physeptone). Some patients are long term yet stable IVDUs and their use of prescribed IVDU opiates is as part of a long term agreed treatment plan. Others may be more recent presentations who have failed on an optimum treatment programme but are a high risk group. Assessment here needs to be done by a specialist
II. Insufficient social support network to remain abstinent from illicit drugs, and where it is not possible to work with the patient to facilitate a suitable and acceptable social support package
III. Lack of motivation to move away from drug using culture/area, within the confines of opportunity
IV. Current illegal drug use
V. Past history of cross dependency (substituting from one drug to harmful or problematic use of another, within the last 2–5 years
VI. Reluctance to agree to drug treatment and after-care or to sign a treatment agreement

Active ongoing alcohol use in the presence of HCV, where there is clear evidence of medical advice to become abstinent

in the ALD group and IVDU in the HCV group) whilst also tackling arguably relative risks such as regular cannabis use in the patient with ALD and the smoking of heroin in the patient with HCV. Pretransplant psychosocial and behavioural risk profiles may be comparable among heart, lung and liver transplant populations (although with more nicotine use in the pretransplant liver population and more alcohol use in the prelung transplant population) [33]. Such data support the benefit of a generic screening protocol, which would incorporate screening for substance use.

There appears to be sufficient doubt about unacceptable outcomes for drug users to be excluded from transplantation [15,17,18,21,23]. However, in an era of donor shortage it is acceptable to scrutinize organ allocation to ensure effective utilization [6]. Dew *et al.* [15] suggest 3.7 (1.9 in liver only) cases per 100 PPY (patients per year) of illicit drug use post-transplant. This is encouraging, yet questions remain about the effective screening and assessment of illicit drug use as well as the long term cumulative drug use in this cohort. Furthermore, the UK drug treatment programme has expanded significantly over the last decade with increased access to, and understanding of, effective treatment [19,29,34], and acknowledgement that in the past, drug misusers might have been afforded treatment of limited effectiveness. Such patients may be the ones now presenting for transplant assessment and as such, current LAG guidelines ask clinicians to take this into account (http://www.uktransplant.org.uk/ukt/; accessed 28th February 2008).

When there is a perception that organs are used inappropriately (such as the transplantation in the case of George Best, the UK soccer player) there may be a reduction in organ donation; development and publication of guidelines should allay the fears of the public and ensure that all potential liver allograft recipients are treated, and seen to be treated, with fairness and equity. Whilst the issues are not as clear cut as those around alcohol, it is important to

agree and adopt evidence-based, publicly debated and agreed guidelines for the transplantation in the case of patients with a significant history of illicit drug use.

The UK has agreed and published guidelines for the assessment of those transplant candidates with a history of substance abuse (http://www.uktransplant.org.uk/ukt/; accessed 28th February 2008). These are summarized in Table 5, where there are both absolute and relative contra-indications for transplantation. It is likely that such guidelines may require modification between healthcare systems and over time.

In the interests of equity and justice and because organs donated from deceased donors are a national rather than local resource, all guidelines can only be useful where there is both intra and inter-unit reliability as well as regular local and national clinical audit within an effective clinical governance framework. In addition, there should be commitment to prospective multi-centre longitudinal studies [15,21] with modification of guidelines in the light of experience; such approaches must be supported by ready and affordable access to effective substance misuse treatment for patients both pre and post-transplant [19,21].

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