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Reference:

Dom Geert, Wojnar M., Crunelle Cleo, Thon N., Bobes J., Preuss U.W., Addolorato G., Seitz H.K., Wurst F.M.- Assessing and treating alcohol relapse risk in liver transplantation candidates

Alcohol and alcoholism - ISSN 0735-0414 - 50:2(2015), p. 164-172

Full text (Publishers DOI): <http://dx.doi.org/doi:10.1093/alcalc/agu096>

To cite this reference: <http://hdl.handle.net/10067/1222470151162165141>

Assessing and Treating Alcohol Relapse Risk in Liver Transplantation Candidates

G. Dom^{1,*}, M. Wojnar², C.L. Crunelle³, N. Thon⁴, J. Bobes⁵, U.W. Preuss⁶, G. Addolorato⁷, H.K. Seitz⁸ and F.M. Wurst⁹

¹Collaborative Antwerp Psychiatric Research Institute (CAPRI), Antwerp University (UA), Antwerpen, Belgium, ²Medical University of Warsaw, Warszawa, Poland, ³Collaborative Antwerp Psychiatric Research Institute (CAPRI) & Department of Toxicology, Antwerp University (UA), Antwerpen, Belgium, ⁴Universitätsklinik für Psychiatrie und Psychotherapie II, Salzburg, Austria, ⁵University of Oviedo, CIBERSAM, Oviedo, Spain, ⁶Hospital of Prignitz, Perleberg, Germany, ⁷Catholic University of Rome & Gemelli Hospital, Rome, Italy, ⁸Center of Alcohol Research, Liver Disease and Nutrition, Salem Medical Center, Heidelberg, Germany and ⁹Universitätsklinik für Psychiatrie und Psychotherapie II, Christian-Doppler-Klinik & Gemeinnützige Salzburger Landeskliniken Betriebsgesellschaft mbH, Salzburg, Austria

*Corresponding author: Collaborative Antwerp Psychiatric Research Institute (CAPRI), Antwerp University (UA), Universiteitsplein 1, 2640, Wilrijk, Belgium. Tel.: +1-32-3-455-75-31; E-mail: geert.dom@uantwerpen.be

(Received 26 August 2014; first review notified 2 October 2014; in revised form 21 October 2014; accepted 28 October 2014)

Abstract — In Europe between 30 and 50% of all liver transplantations (LTX) are done within the context of chronic end-stage alcoholic liver disease (ALD). However, post-operatively 20–25% of these patients lapse or relapse into heavy alcohol use. Thus, assessment of alcohol relapse risk before enlisting and therapeutic follow-up during and after LTX is of utmost importance. However, as yet there are enormous differences between European countries and between transplant centers, with regard to the assessment methods and criteria and the implementation of therapeutic follow-up. Only the so-called ‘6-month abstinence’ rule is widely used. However, there are not much scientific data validating its use in predicting relapse. Thus, there is a clear need of a more homogeneous approach, which was the focus of a symposium of the European Federation of Addiction Societies during the 14th conference of the European Society for Biomedical Research on Alcoholism, 2013 (ESBRA), entitled ‘Liver transplantation: A European perspective’. In a follow-up on this symposium, the authors aim to sum up the evidence of psychiatric assessment criteria and psychiatric treatment interventions relevant in the context of patient selection and patient follow-up within ALD transplantation procedures. Based upon these findings, we propose elements of a procedure that can serve as a first step toward a model of good practice regarding addiction-specialist input within the pre- and post-transplantation period.

INTRODUCTION

Liver transplantation (LTX) is increasingly used as a treatment for patients with chronic end-stage alcoholic liver disease (ALD). Between 30 and 50% of all liver transplantations in Europe are done for this indication (Bruha *et al.*, 2012). Importantly, post-operatively 20–25% of these patients lapse or relapse into heavy alcohol use (Lucey, 2011). Resumption of (excessive) alcohol use after LTX has been associated with an increased risk of liver damage and mortality, specifically after many years of drinking (Rice *et al.*, 2013; Lucey, 2014). Thus, both from the point of view of patient safety and in the context of a chronic paucity of organ availability, maximal effort is justified into both screening of the most suitable candidates and helping patients to (re) gain sobriety. Theoretically, screening on relapse risk and offering personalized addiction treatment should go hand in hand when implementing a patient-centered treatment plan. However, within the current (pre) transplantation procedures, a strong emphasis has been put on the identification of the relapse risk of these patients, while much less efforts have been seen on the level of addiction treatment (Addolorato *et al.*, 2013).

Concerning relapse prediction, a wide variety of criteria and screening procedures have been developed, of which the 6-month abstinence criterion before transplantation has gained the most wide usage. It is hypothesized that patients who are able to maintain a 6-month abstinence have a lower risk of relapse than patients who are abstinent for shorter periods of time (Dew *et al.*, 2008). However, the use of this single criterion has come under debate (Addolorato *et al.*, 2007, 2013; Gramenzi *et al.*, 2011). Indeed, there are only a limited number of studies that have explored this criterion on its predictive value, and these report inconsistent findings (Rice and Lucey, 2013). Also, given the often aggressive course of end-stage ALD, the 6-month period is often too long and results in

high mortality rates. In addition, specifically for acute alcoholic hepatitis, the time frame is much shorter (Mathurin *et al.*, 2011). In addition to pre-LTX abstinence, many other clinical variables have been explored. Of note, not one (or a set) of them seems to be specific in predicting relapse (Lucey, 2014), leaving the debate open as to which is the best approach in assessing patients.

Given the importance of achieving and sustaining abstinence during both the pre- and post-LTX periods, it is highly remarkable that only a limited number of studies have explored the effect of psychiatric treatment in helping patients reduce their risk of relapse (Addolorato *et al.*, 2013). Moreover, the findings of these studies show non-consistent effects, leaving the question open as to what the best treatment interventions are that need to be offered within the comprehensive approach to ALD patients.

In view of the high rates of alcohol consumption in the European population, and still rising specifically within the Central and Eastern-European countries, ALD is of a high priority within the European health context. However, the number of indications, and the use of screening and selection procedures varies vastly between European countries, as well as between different transplant centers in the same country. Given that organ allocation is increasingly organized on a European format, there is a clear need of a more homogeneous approach in candidate screening and treatment procedures. This theme was the focus of a symposium of the European Federation of Addiction Societies (EUFAS, www.eufas.com) during the 14th conference of the European Society for Biomedical Research on Alcoholism, 2013 (ESBRA), entitled ‘Liver transplantation: A European perspective’. In follow-up of this symposium, the authors (contributors to this symposium) aim to sum up in the current review the evidence of psychiatric assessment criteria and psychiatric treatment interventions relevant in the context of patient selection and patient follow-up within ALD

transplantation procedures. Based upon these findings, we propose elements of a procedure that can serve as a first step toward a model of good practice regarding addiction-specialist input within the pre- and post-transplantation period.

METHOD

Two topics were reviewed: (a) assessment of predictors of alcohol relapse risk and (b) effect of addiction treatment interventions (ATIs). We conducted a literature search in the PubMed using the following search terms: (liver transplantation) AND (alcoholic liver disease) AND (alcohol abuse or dependence) AND (relapse or recidivism). Articles were limited to those that were in English, published in the last 10 years (up to 31 July 2014), human and original research papers. This search produced 51 articles. Out of these only 13 studies provided original data on the screening and identification of LTX candidates for the risk of alcohol relapse after LTX. In addition, six studies were found exploring the effect of a psychosocial treatment intervention for alcohol dependence among LTX patients. Together these 16 studies are included in the current review.

RESULTS

Many (psycho) social variables were explored in these studies in their relation to post-LTX alcohol relapse (Table 1). Of note, in one study (Nickels *et al.*, 2007) none of the variables under study correlated with post-LTX relapse. However, this is most likely due to the small sample size ($n = 27$), and so this study is not included in the following results.

The variables identified within the different studies can be summarized under the following broad categories: (a) pre-LTX abstinence period, (b) variables reflective of alcohol dependence severity, (c) social factors, (d) psychiatric co-morbidity, (e) treatment compliance and motivation, and (f) demographic variables. In what follows we discuss the findings under these headings.

Pre-LTX abstinence period

The duration of abstinence before enlisting on the waiting list and/or before LTX is manifestly the most frequently explored variable in relation to relapse into alcohol use post-LTX. In total, nine studies specifically explored this variable in an overall number of 1823 LTX-ALD patients. All of them found a significant negative correlation between the duration of pre-LTX abstinence and the relapse risk post-LTX. Of note, and biasing the results, is that in most studies 6-month abstinence was a prerequisite for being enlisted for LTX. So the number of patients included in these studies with a <6-month abstinence is very limited. Only Hartl *et al.* (2011) showed that abstinence <3 months was a negative factor. Overall, the longer the abstinence, the lower was the relapse risk. Tandon *et al.* (2009) calculated that for every month increment in pre-LTX abstinence there was a 5% decrease in the adjusted relapse rates.

Variables reflective of alcohol dependence severity

Four studies included variables that can be indicative of the severity of alcohol use disorder (AUD) (Kelly *et al.*, 2006; De Gottardi *et al.*, 2007; DiMartini *et al.*, 2008, 2010;

Deruytter *et al.*, 2013). Alcohol dependence diagnosis versus abuse proved a negative factor in two studies (DiMartini *et al.*, 2008, 2010). Two studies found that the duration of heavy drinking and number of drinks per drinking day was indicative of relapse (Kelly *et al.*, 2006; De Gottardi *et al.*, 2007).

A positive (first relative) family history of alcoholism (FHA) has traditionally been associated with a negative course of AUD. Three studies found a positive association between FHA+ and relapse risk (De Gottardi *et al.*, 2007; DiMartini *et al.*, 2010; Deruytter *et al.*, 2013), confirming this hypothesis.

Four studies (De Gottardi *et al.*, 2007; Gedaly *et al.*, 2008; Deruytter *et al.*, 2013; Rodrigue *et al.*, 2013b) explored whether earlier (alcohol) treatment attempts played a role. Although open for discussion, having been in contact with treatment (and subsequent failure) might be a characteristic of severity. All of the studies with the exception of Rodrigue *et al.* (2013b) found that earlier treatment contacts were associated with an increase in relapse risk after LTX. In this latter study, patients with or without treatment before LTX did not differ in alcohol relapse after LTX. Remarkably in this study ($N = 114$), patients who receive, before and after LTX, alcohol treatment did have a lower risk of relapse than those who did not. Of note, in this study Pre-LT alcohol treatment was mandatory for LT candidates with <6-month abstinence.

Overall, most studies, including 1407 patients, find that indices of AUD severity are associated with a higher risk of relapse after LTX.

Social factors

Four studies (Kelly *et al.*, 2006; De Gottardi *et al.*, 2007; Pfitzmann *et al.*, 2007; Rodrigue *et al.*, 2013b) (including overall 891 patients) identified social factors, i.e. having a stable, partner relationship and reliance on family or friend, as positive factors reducing the risk of relapse. In contrast, lack of social support and the continued engagement in alcohol-related social activities are negatively associated with relapse.

Psychiatric co-morbidity

Psychiatric co-morbidity has been shown in the addiction literature to negatively influence the outcome of AUDs. A diagnosis of and prior treatment for co-morbid psychiatric disorders was found to negatively influence post-LTX alcohol relapse in five studies (Kelly *et al.*, 2006; De Gottardi *et al.*, 2007; DiMartini *et al.*, 2010; Karim *et al.*, 2010; Egawa *et al.*, 2014) including an overall 960 patients. Although not specified in different studies, specific diagnoses like depression (Kelly *et al.*, 2006) and other substance dependence (tobacco, illicit drugs) (Kelly *et al.*, 2006; DiMartini *et al.*, 2010) are highlighted. Of importance, these are highly frequent co-morbidities with AUD.

Treatment compliance and motivational characteristics

Attitudes and behaviors toward treatment are relevant in the context of outcome, but explored in only two studies in the context of LTX. Non-acceptance of alcohol dependence diagnosis (Hartl *et al.*, 2011) and non-compliance with follow-up appointments (Egawa *et al.*, 2014) were found to negatively relate with post-LTX alcohol relapse.

Table 1. Studies on screening and identifying risk factors of relapse

Study	N	Study method	Screening method	Alcohol outcome	Predictors of relapse after LTX
<i>Kelly et al. (2006)</i>	N = 90 ALD LTX patients	Retrospective 1987–2004 follow-up 6 months after LTX	Reviewing charts	Relapse to non-harmful use 10.6% Relapse into harmful use 19%	Diagnosis of depression Lack of stable life partner Grams of alcohol/day before assessment LTX Reliance family/friends for post-LT support Smoking at time of assessment Lack of insight into alcohol etiology Age, sex, race, FH, abuse, legal, psychiatric diagnosis, SU variables = no significant differences between relapse and no relapse
<i>Nickels et al. (2007)</i>	N = 27 transplant patients with SUD (24 AUD) Inclusion No of months of pre-transplant abstinence: no data	Retrospective 1999–2004	Reviewing charts (e.g. transplant psychiatrist)	Relapse into substance use after LTX 29.6%	Age >50 Abstinence <6 months Psychiatric co-morbidity Presence of life partner High score in HRAR scale Pre-LTX abstinence < 6 months Absence of life companion Presence of young children Poor psychosomatic prognosis Pre-transplant abstinence <12 months Participation in rehabilitation program
<i>De Gottardi et al. (2007)</i>	N = 387 LTX patients for alcoholic cirrhosis Inclusion >3 m. abstinence	Longitudinal 1989–2005 Mean follow-up time 61.2 months	Psychiatric diagnosis (DSM IV) HRAR scale	Relapse into harmful alcohol use in 11.9%	Age >50 Abstinence <6 months Psychiatric co-morbidity Presence of life partner High score in HRAR scale Pre-LTX abstinence < 6 months Absence of life companion Presence of young children Poor psychosomatic prognosis Pre-transplant abstinence <12 months Participation in rehabilitation program
<i>Pfizzmann et al. (2007)</i>	N = 300	Retrospective analysis (1989–2002) Median follow-up time 89 months	Reviewing charts Patients self-report and collateral (family) information	Relapse into any drinking after LTX was 19%	Age >50 Abstinence <6 months Psychiatric co-morbidity Presence of life partner High score in HRAR scale Pre-LTX abstinence < 6 months Absence of life companion Presence of young children Poor psychosomatic prognosis Pre-transplant abstinence <12 months Participation in rehabilitation program
<i>Gedaly et al. (2008)</i>	N = 387 LT ALD = 147 (38%) Inclusion >6 m. abstinence	Retrospective 1995–2007	Reviewing charts	19% of the AUD patients returned to (any) alcohol use after LTX	Age >50 Abstinence <6 months Psychiatric co-morbidity Presence of life partner High score in HRAR scale Pre-LTX abstinence < 6 months Absence of life companion Presence of young children Poor psychosomatic prognosis Pre-transplant abstinence <12 months Participation in rehabilitation program
<i>DiMartini et al. (2008)</i>	N = 113 ALD LTX patients	Longitudinal 1998–2002	Semi-structured diagnostic interview pre-LTX TLFB every 3 m. Post-LTX	Relapse (first any use and first binge use): no overall data presented	Risk post-LTX relapse (first any use and first binge use): Alcohol dependence diagnosis FH Alcoholism Positive Use other substances Pre-LTX abstinence period was the highest discriminant factor between drinking and abstaining after LTX
<i>Tandon et al. (2009)</i>	N = 171 ALD LTX patients (53% with co-existing causes of liver dysfunction)	Retrospective mean follow-up 64.8 months	Chart review	Relapse to any drinking: 24% Relapse to problem drinking: 13%	Pre-transplant abstinence duration only independent predictor of problem drinking after transplantation. For every month increment in pre-LTX abstinence a 5% decrease in the adjusted relapse rate Relapse into alcohol use after LTX associated with: Alcohol dependence diagnosis FH Alcoholism Positive Use of other substances Pre-LTX abstinence period was the highest discriminant factor between drinking and abstaining after LTX
<i>DiMartini et al. (2010)</i>	N = 208 ALD LTX patients	Prospective Follow-up	Psychiatric interview TLFB Self-report scales Biomarkers Collateral information	Abstinence post-LTX: 54% Relapse to low amounts: 26% Relapse to moderate or heavy alcohol use: 20%	Relapse into alcohol use after LTX associated with: Alcohol dependence diagnosis FH Alcoholism Positive Use of other substances Pre-LTX abstinence period was the highest discriminant factor between drinking and abstaining after LTX
<i>Kanim et al. (2010)</i>	N = 80 ALD patients with LTX	Retrospective chart review (period 1992–2006)	Sociodemographic Psychosocial Addiction variables	Relapse to harmful drinking after LTX was 10%	Abstinence <6 months Female sex Psychiatric co-morbidity Age at transplant <50 years Personal stressors

Continued

Table 1. *Continued*

Study	N	Study method	Screening method	Alcohol outcome	Predictors of relapse after LTX
Hartl <i>et al.</i> (2011)	ALD (<i>n</i> = 68) patients who underwent LTX	Longitudinal 2003–2009 Mean follow-up 31 + 23 months	Patients' records Laboratory Interviews (patients, family and family doctor) SF-36 quality of life and self-designed questionnaire Chart analyses, questionnaires	After LTX, alcohol recidivism rate was 16%	Alcohol abstinence < 3 months Non-acceptance of having alcohol problem
Demytter <i>et al.</i> (2013)	Subjects who underwent LTX for ALD (<i>n</i> = 108)	Retrospective (inclusion between 2000 and 2008) Mean follow-up 55 months		Relapse into any drinking (29%) Relapse into problem drinking (>2 pd for women and 3 pd, men) (16%) Relapse into any alcohol use 34%	(Pre-transplant) Risk factors associated with relapse into problem drinking: shorter pre-transplant abstinence first-degree relative with alcohol abuse higher number of prior attempts to quit.
Rodríguez <i>et al.</i> (2013a)	<i>N</i> = 114 ALD LTX patients	Retrospective May 2002–February 2011. Single center	Medical charts		Continued alcohol use after liver disease diagnosis Low motivation for alcohol treatment Poor stress management skills No rehabilitation relationship Limited social support Lack of non-medical behavioral consequences Continued engagement in alcohol-related social activities
Egawa <i>et al.</i> (2014)	Subjects who underwent LTX for ALD (<i>n</i> = 195)	Retrospective	Chart analysis, interview, HRAR scale	Incidence of alcohol consumption after LTX: 22.9%	History of treatment for psychological disorders other than alcoholism before LTX Non-compliance with clinic visits after LTX Smoking after LTX

SUDs, substance use disorders; SU, substance use; AUDs, alcohol use disorders; LTX, liver transplant patients; ALD, alcoholic liver disease; LT, liver transplantation; DSM, Diagnostic and Statistical Manual of Psychiatric Disorders; HRAR, High-Risk Alcoholism Relapse Scale; ATLFB, Alcohol Time Line Follow Back.

Demographic variables

Age at LTX has revealed inconsistent results. Two smaller studies (overall $N=95$) (Karim *et al.*, 2010; Grat *et al.*, 2014) found that younger age at LTX (<50 year) was associated with a higher risk of relapse. Two studies including a larger sample (overall 687 patients) found age at LTX not an independent predictor for relapse (De Gottardi *et al.*, 2007; Pfitzmann *et al.*, 2007). Finally, female gender was a negative factor in one study (Karim *et al.*, 2010) ($N=80$), while no gender effect was found in a larger study (Pfitzmann *et al.*, 2007) ($N=300$). Overall, only a limited number of demographic variables have been studied and findings are clearly not consistent.

Alcohol addiction treatment

Given that both pre-LTX and post-LTX alcohol abstinence is crucial, helping patients to obtain and sustain abstinence is important. Strangely, only very few studies have explored the effectiveness of adding specific addiction treatments, both pharmacological and psychosocial, within LTX protocol. Although many factors may be in play, one that has been recorded multiple times is that patients listed for LTX show lower interest for alcoholism treatment than non-transplant AUD patients (Addolorato *et al.*, 2013) (Table 2).

Psychosocial treatment

Five studies explored the effectiveness of adding some form of addiction treatment intervention (ATI). Bjornsson *et al.* (2005) showed that active addiction treatment ('structured management') in the period before the transplant operation could reduce the number of relapsing patients after LTX by more than half (from 48 to 22%). No treatment seemed to be offered in the post-operative period. Erim *et al.* (2006) in a non-randomized study showed similar findings; fewer patients had alcohol recidivism post-LTX after a 6-month (pre-LTX) group psycho-educational therapy. In a more recent randomized study, motivational enhancement therapy (MET) with contingency management (CM) (two well-known and evidence-based addiction interventions) was compared with treatment as usual (TAU) with AA attendance. The active treatment group reported fewer drinks per drinking day during the waiting list period. Unfortunately, no data of the post-LTX drinking status were reported in this study (Weinrieb *et al.*, 2011).

Recently, in a retrospective study, Addolorato *et al.* (2013) compared the alcohol outcomes of patients being offered addiction counseling by a provider outside the transplant unit versus those who received treatment by addiction specialists integrated within the transplant unit. The latter group showed less alcohol recidivism and lower mortality rates. Although it can be argued that progression from outside counseling to a system of integrated addiction specialists within the unit is reflective of a growing specialization and expertise in treating ALD patients, results of this study clearly indicate the effects of integrated treatment efforts. Recently, Rodrigue *et al.* (2013b) showed that patients following up for different types of psychosocial substance abuse (SA) treatment before LTX had the same post-LTX alcohol relapse (any alcohol use) as patients who did not follow up SA treatment. Only those patients who followed up before and after LTX SA treatment had significantly reduced alcohol relapse rates. Several factors in this study make interpretation of the findings difficult. First,

for some, but not all, of the patients pre-LTX SA treatment was mandatory before LTX listing. Next, treatment after LTX was not mandatory. Finally, only a minority of the patients followed up for treatment before and after LTX (32 out of 112 participants); so this may represent a highly motivated subgroup. Nevertheless, findings of this study underline the importance of timing when SA treatment is offered. Of interest, pre-LTX abstinence of >24 months and post-LTX SA treatment proved to be independent, significant predictors of post-LTX alcohol use in this study. Finally, in a large retrospective British study, Masson *et al.* (2014) compared the effect of using an 'abstinence contract' with the patients. They found no differences between relapse rates between patient cohorts that subscribed such a contract and those that did not. However, in this study, a contract was not used as an intervention type, merely as an addition within the standard care package that was introduced from a certain time point (2007). Thus, conclusions on patient outcomes before and after 2007, as presented in this study, need to be looked upon very cautiously.

Pharmacological treatment

In patients with ALD, pharmacological treatments should take severe liver dysfunction into account. Up to date, only a few studies provide information on feasibility, safety and effectiveness of using relapse-prevention medication in these patients. Based upon their pharmacological characteristics, specifically medications that do not involve hepatic metabolizing should be valuable candidates, e.g. acamprosate, baclofen and topiramate. However, hitherto, only baclofen has been evaluated in an RCT in patients with end-stage ALD, showing both safety and positive effects (continuous days of abstinence, craving) versus placebo (Addolorato *et al.*, 2007).

DISCUSSION

The nineteen studies included in this review explored a broad variety of clinical variables in their relation with post-LTX alcohol relapse. With the exception of the demographical variables age and gender, results are overall consistent, showing an increased risk of relapse. However, no specific variable stands out as unique in its predictive power. In addition, remarkably few studies were found that explored the effect of a form of standardized alcohol treatment. Results of these studies indicate the importance of integrating standard addiction treatment within transplant programs.

There is no doubt that it is important to reduce alcohol use relapse in alcoholic patients after LTX. Alcohol recidivism negatively influences survival (Faure *et al.*, 2012), and is associated with graft loss (Schmeding *et al.*, 2011) and overall medical complications requiring additional care and re-hospitalization (Addolorato *et al.*, 2013). However, excluding patients from a life-saving transplantation procedure because of a high risk of alcohol relapse represents a serious ethical debate, a debate that is highly relevant to the society as a whole. Indeed, in many countries this debate is already broadening on how to deal with (and who is going to pay for) the health consequences of behavioral disorders (e.g. cigarette smoking, eating patterns and obesity) (van Baal *et al.*, 2008),

Table 2. Addiction treatments and outcome for patients with ADL pre- and post-LTX

Author	Sample	Control	Intervention design	Variables/measures	Outcome
Psychosocial interventions					
Bjornsson <i>et al.</i> (2005)	58 ALD patients receiving structured management therapy before LTX	40 ALD patients receiving TAU before LTX	Retrospective: Structured management by addiction specialist versus TAU before LTX		Relapse to alcohol use post-LTX: 22% in the active treatment group versus 48% in TAU ($P = 0.003$)
Erim <i>et al.</i> (2006) (paper in German)	48 ALD patients receiving manualized group psycho-educational therapy for 6 months	22 ALD with no active treatment	Manualized group psycho-education for 6 months versus TAU No randomization	Breathalyzer (BAC)	Lower rates of alcohol recidivism in active treatment
Weinrieb <i>et al.</i> (2011)	ALD patients enlisted on waiting list for LTX $N = 46$	ALD patients enlisted on waiting list for LTX $N = 45$	At enlistment waiting list patients were randomized to either: 7 individual sessions MET&CM and AA TAU and AA	Addictive behavior: TLFB, ASI, breathalyzer, stages of readiness scale Mood: Beck Depression and Anxiety Inventory General health: Medical Outcomes Study Short Form-12 (MOS SF-12)	25% of the sample drank after randomization, before LTX. Patients receiving MET had significantly fewer drinks per drinking day vs. TAU. However, no differences on other variables.
Addolorato <i>et al.</i> (2013)	$N = 92$ ALD Cirrhosis patients	Retrospective	Treated by a Alcohol Addiction Unit (AAU) within the transplant center ($n = 55$; 2002–2010) (counseling, baclofen, AA, medical management) versus treated by an addiction specialist external to the transplant center ($n = 37$; 1995–2002) (psychological support every month)	Recidivism = any alcohol use (lapse) or relapse	Patients treated with AAU: Lower prevalence of recidivism (16.4 versus 35.1%) Lower mortality (14.5 vs. 37.8%) <6 months abstinence not associated with alcohol recidivism rates.
Rodrigue <i>et al.</i> (2013b)	Adults who underwent LTX for ALD ($n = 118$)	Single-Center, retrospective (May 2002—February 2011)	Different psychosocial substance abuse (SA) interventions before and after LTX. Interventions before LTX were mandatory	Relapse to any alcohol use in 34% of the patients.	Patients with ($n = 61$; 52%) or without ($n = 57$; 48%) SA treatment before LTX no significant differences in relapse after LTX. Patients who received SA treatment before & after LTX had significantly lower alcohol relapse (16%) than those without treatment (41%) or treatment only before LTX (45%) Predictors of abstinence after LTX: pre-LTX abstinence >24 months, post-LTX SA treatment.
Masson <i>et al.</i> (2014)	Adults, UK, who underwent LTX for ALD during 1996–2011 ($n = 140$)	Retrospective	The study explored the effect of the (standard) introduction of an abstinence contract with the patients. This was introduced as standard in February 2007. Patient outcomes without contract ($n = 96$) were compared with those with contract ($n = 44$)		Overall, 37% of patients returned to drinking alcohol. No significant difference in the rate of returns or pattern of drinking between patients with (34%) and without contract (39%).

in which some genetic and neurobiological vulnerability plays a significant role (Volkow *et al.*, 2013).

In view of this delicate decision-making, the authors of the current paper stress the importance of developing standard procedures that are, at a maximum, based upon scientific evidence and, ideally, have the potential of becoming standard ingredients in the transplant programs across different European countries. Three main features need to be included in these procedures: (a) selection and assessment of the risk of relapse into alcohol use, (b) monitoring of abstinence and (c) therapeutic interventions. Within this framework, there is a central role for addiction specialists.

The different studies on relapse risk in ALD/LTX patients included in the current review reveal that the same clinical factors that predict relapse in post-LTX patients are known also to be associated with good clinical outcomes in (non-ALD) AUD patients. Identifying clinical characteristics that allow a prediction, on an individual AUD patient's level, of the probability of acquiring abstinence and maintaining remission is highly important. Indeed, the course of AUDs across a lifetime is highly variable and AUDs are shown to have only moderate levels of diagnostic stability over a lifetime. For example, Boschloo *et al.* (2012) observed across a 2-year period a recurrence rate of 15% among those who were initially in remission and a 41% persistence rate among those who were initially diagnosed. Knowing which patients will have a high risk on relapse will allow a better targeting of the (scarce) treatment resources.

Throughout the research literature, the following clinical characteristics of AUD patients are consistently associated with a better outcome: (a) less intense substance use problems (Tuithof *et al.*, 2014), (b) more stable life functioning, (c) higher incomes, (d) a spouse who encourages change, (e) greater overall social support, (f) a later onset of regular drinking, (g) no concomitant psychiatric diagnosis and (h) recent history of seeking help for drinking problems (Aguir *et al.*, 2012; Trim *et al.*, 2013). Of importance, none of these variables stands out as the single most decisive, and their predictive power regarding relapse remains modest. Recently, a number of studies have been done looking for biomarkers that have better predictive power. Specifically, neurocognitive and neuroimaging variables have proved promising in this field (De Wilde *et al.*, 2013; Seo *et al.*, 2013; Volkow and Baler, 2013; Charlet *et al.*, 2014). These characteristics, which are hypothesized to relate better with the underlying pathogenic processes of AUD, do indeed seem to provide a more powerful way to predict relapse risk. However, and although promising, an important caveat remains related to their practical implementation in standard clinical practice (Volkow and Baler, 2013).

Within the liver transplantation literature a great emphasis has been put upon the length of the pre-enlisted abstinence. This is, to a certain degree, supported by the data. Indeed, both the results of the current review as the broader course of AUDs suggest that the longer the abstinence, the smaller is the risk on consecutive relapse. In his ground-breaking longitudinal study Vaillant indicates that stable remission from AUD can be expected after 5 years of abstinence (Vaillant, 1996). Clearly, most patients with end-stage ALD do not have that amount of time. Although a substantial period of abstinence is warranted specifically allowing for spontaneous recuperation of liver functionality (EASL Guideline, 2012), length of abstinence as a single criterion is not a powerful predictor

of relapse into harmful alcohol use after LTX for ALD patients. Specifically, the 6-month period of abstinence, which is currently the 'golden rule' in many transplant centers, is not supported by the outcome studies. Taken together, the authors of the current guidance paper suggest that patients with a shorter period of abstinence (e.g. 3 months, period after which further recuperation of liver functionality is not likely) should also be considered as valuable candidates. Extending this period for longer most probably results in losing more patients while gaining (not substantially) in predictive power when assessing relapse risk after ALD. A shorter period of abstinence (<6 months) may include a higher risk of post-LTX relapse, but should not be a reason for non-inclusion, but instead should be considered an indication to start active addiction treatment in order to reduce relapse risk.

Overall, this review confirms that not one single clinical variable can be used to assess a patient's alcohol relapse risk. This means, in each single patient's case, a comprehensive assessment performed by an addiction specialist (or team) evaluating the different clinical and social variables, which have been associated with an increase of relapse risk. Throughout the last years some groups have proposed different scoring systems (De Gottardi *et al.*, 2007; Dom *et al.*, 2010; Rodrigue *et al.*, 2013a), attaching a score for the different clinical variables. Although of interest, a systematic, multicenter evaluation of these scores is still lacking.

Only six studies could be identified to explore the effect of specific addiction intervention in improving ALD patients' alcohol outcome. Most of these studies show a positive effect on alcohol outcome post-LTX. Of importance, both the setting and the intensity of treatment offered seem important. Integrating addiction treatment within the comprehensive transplant team did improve the outcome significantly (Addolorato *et al.*, 2013). This finding is in line with other findings that indicate that, for patients with multiple complex co-occurring disorders, integrating treatment interventions does improve outcome (Mueser *et al.*, 2001). Next, more intense treatment (i.e. before and after LTX, or specific interventions versus only a single alcohol contract) also gives a better outcome (Rodrigue *et al.*, 2013b; Masson *et al.*, 2014). This is also in line with previous findings that with more chronic and severer alcohol problems, more intense treatment approaches are warranted.

Finally, although not the focus of this review, it needs to be stressed that throughout all pre- and post-operative follow-ups a close monitoring of alcohol use is warranted. Within this context, the importance of biomarkers is increasingly recognized. Several recent studies suggest, in this respect, ethyl glucuronide in hair samples (hEtG) as promising. Indeed, traditional alcohol markers in blood and urine have narrow detection windows (hours to days), while hair serves for long-term storage of EtG, allowing much broader time frames (months). Moreover, obtaining samples is non-invasive and storage is easy. Most importantly, recent analyzing techniques allow distinguishing between chronic, excessive, moderate alcohol use and abstinence (Society of Hair Testing; www.soht.org) (Crunelle *et al.*, 2014a,b; Neels *et al.*, 2014). Specifically among LTX patients, several studies evaluated hEtG and show it to be a highly specific and practically implementable tool for monitoring alcohol use, superior to traditional markers (Morini *et al.*, 2011; Staufer *et al.*, 2011; Sterneck *et al.*, 2013; Piano *et al.*, 2014).

This review has several limitations. First, we limited our focus to chronic end-stage ALD, excluding studies on patients

with acute alcoholic hepatitis. In recent studies, feasibility of early LTX and its favorable outcomes in severe alcoholic hepatitis both on risk of alcohol relapse and survival were reported (Mathurin *et al.*, 2011). Of interest, the (psychosocial) criteria upon which candidates in this study were selected are very similar to the ones described above for chronic ALD. Second, although this review focused on alcohol, it needs to be noted that increasingly patients present for transplantation with a history of both alcohol and illicit drug abuse, e.g. heroine. Reasons are multiple, i.e. the frequent transition of heroine users to alcohol dependence and the association of intravenous drug use with hepatitis C and subsequent cirrhosis (Nickels *et al.*, 2007). As a consequence, a sizeable portion of patients that might be in need of a life-saving LTX is using maintenance therapy (MT) (methadone, buprenorphine). In contrast with 'pure' alcohol LTX candidates, comorbid illicit substance use is often considered an absolute contraindication for LTX. In addition, LTX candidates on MT often are required to taper off their medication before considering LTX (Jiao *et al.*, 2010). Clearly, developing evidence-based procedures for transplant candidates with a history of illicit drug use and/or maintenance therapy is urgently needed.

CONCLUSIONS AND RECOMMENDATIONS

ALD is one of the most common indications for LTX in many European countries. Importantly, survival rates after LTX of ALD patients are at least as good as for patients with other LTX indications. However, continued longstanding alcohol use and cigarette smoking increase the risk of developing malignancies, cardiovascular disorders, liver damage and reduced survival. Given that 20–30% of the ALD patients return to heavy drinking after LTX, a careful assessment as to which patients are at high risk is warranted. Currently, there are no arguments to maintain a strict 6-month abstinence period as a (single) criterion when deciding over in or exclusion for LTX. A sizeable period of abstinence (e.g. 3-month) remains important, specifically for allowing hepatic function recovery. Every patient should be assessed and regularly re-assessed by an addiction specialist or team, evaluating the risk of alcohol relapse based upon a standard set of clinical criteria. Every patient identified at risk for relapse needs to be offered (pre- and post-LTX) addiction treatment, focusing on alcohol and tobacco abstinence. This treatment should be integrated within the transplant team and continued for at least one-year post-transplantation.

Conflict of interest statement. None declared.

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