Liver Transplantation and Opioid Dependence

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Orthotopic liver transplantation is a standard treatment for end-stage liver disease. In 1990, the United Network of Organ Sharing (UNOS) coordinated 4698 liver transplantations in 97 adult and 18 pediatric liver transplantation programs. As of May 2000, 15,258 patients were on waiting lists. Hepatitis C is the leading cause of liver transplantation (46%), followed by alcoholic liver disease (25%); both are primarily substance abuse–related diagnoses. Approximately 2.7 million persons in the United States are infected with hepatitis C virus (HCV). Twenty percent can be expected to develop cirrhosis, 10% of those with life-threatening complications. The estimated lifetime heroin-dependence prevalence increased from 1.7 to 2.3 million from 1992 to 1998. The most effective treatment is opioid replacement therapy, currently serving almost 180,000 patients in 783 programs. Studies expanding access to opioid replacement show promising results, making office-based opioid replacement likely to be approved in the near future. The prevalence of HCV in intravenous drug users in methadone maintenance therapy (MMT) is estimated at 84% to 90%. Thus, about 156,600 patients (or 5.8% of persons with HCV) are prescribed methadone. This subgroup of potential liver transplantation applicants is likely to increase.

In 1993, Levenson and Olbrisch surveyed psychosocial criteria for acceptance into transplantation programs. They found that “current use of addictive drugs” was considered an absolute contraindication for 84% of liver transplantation programs. Use of addictive drugs in the prior 6 months was not acceptable in 35.9% of the programs. They did not address MMT or policies for opiate dependence. After initial controversy, liver transplantation in alcoholic patients is now well established. However, few reports address transplantation outcomes of patients having other addictions. Available UNOS data do not provide information about substance use among patients requiring liver transplantations. Therefore, we sought to clarify general practices and policies for patients with a history of substance dependence by surveying the liver transplantation programs directly.

Methods

A survey questionnaire was mailed in March 2000 to all 97 adult liver trans-
plantation programs belonging to UNOS, followed by telephone contact. Program coordinators were asked (1) Are patients with a history of substance dependence accepted, and by whom are they evaluated (substance abuse professionals, psychiatrists, social workers)? (2) Does the program require documented abstinence and attendance in addiction treatment? (3) Is MMT acceptable or does the program require discontinuation of methadone? How many MMT patients are on waiting lists? and (4) How many MMT patients have received liver transplantations? What problems were experienced?

RESULTS

Ninety percent (87/97) of programs responded. All said they accept patients with a history of substance abuse and 86% obtain consultation by a substance abuse professional or psychiatrist. Treatment requirements are assessed individually by 60% for alcohol and by 55% for nonopioid illicit drug dependence. The most frequently required duration of abstinence was 6 months (Table 1).

Of the responding programs, 56% accept MMT patients, but 32% require that patients discontinue methadone use. Of the 28 programs requiring discontinuation, 22 obtain psychiatric/substance abuse consultations. Nine percent of programs reported that no MMT patients had applied for transplantation and had no substance abuse policies in place. Two percent gave no answer. Transplantation coordinators estimated that 102 MMT patients on a liver transplantation waiting list in 24 programs. Thirty-nine responding programs described posttransplantation experience with a total of 180 patients taking methadone. Only 9 programs have experience with more than 5 such patients (Table 2 and Table 3).

COMMENT

Our survey indicates general acceptance for liver transplantation of patients with a history of substance dependence, including opiate dependence. Criteria for listing a patient on a transplantation waiting list are fairly homogeneous. Patients currently enrolled in MMT were accepted by 56% of the programs; however, only 10% had experience with more than 5 such patients.

The number of MMT patients who underwent liver transplantation was estimated at 180, less than 0.5% of 40468 liver transplants performed since 1988. The estimated 102 MMT patients on waiting lists represent 0.7% of all patients, which seems low considering that 40% of all liver transplantations are related to HCV.

Thirty-two percent of the responding programs require discontinuation of prescribed methadone. This may indicate a clinical confusion between heroin dependence as a problem and opiate replacement therapy as a medically supervised treatment. Opiate replacement therapies are successful and well-documented long-term treatment interventions for opioid addiction. Discontinuation of methadone may result in relapse to illicit opiate use in as many as 82% of stably maintained patients. It is noteworthy that discontinuation of methadone was required despite obtaining consultation from addiction specialists in 24 of 28 programs. It is not clear if consultants advised transplantation teams for or against continuation of methadone.

We found no reports in MEDLINE about liver transplantation outcomes for opiate-dependent patients. Reports of kidney transplantation results in former heroin addicts did not indicate poor outcomes. In our survey, only 3 of 39 programs (7 MMT patients) report their outcomes as worse than for abstinent opioid addicts. Most programs report that the posttransplantation course does not seem to differ from other transplantation patients. In our survey, relapse rates for MMT patients appear low (<10%). Immunosuppressant medication noncompliance seems higher (<23%) than previously reported in alcoholics (16%). However, the 6 programs reporting some form of patient noncompliance found that transplantation outcomes were not

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<tr>
<th>Table 1. Eligibility Criteria for Minimum Abstinence Requirements (n = 87 Programs)</th>
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<tr>
<td><strong>Type of Substance Used</strong></td>
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<tr>
<td><strong>Not Answered or Not Applicable</strong></td>
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<tr>
<td>Alcohol</td>
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<td>Illicit opiates</td>
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<td>Other illicit drugs</td>
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*Includes individual assessment with routine minimum requirement of applicable months.

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<th>Table 2. Transplantation Outcomes of Methadone Maintenance Treatment (MMT) Patients*</th>
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<tr>
<td><strong>No. of Patients Treated in 39 Programs</strong></td>
</tr>
<tr>
<td><strong>No. of Programs</strong></td>
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<tr>
<td>1</td>
</tr>
<tr>
<td>2-5</td>
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<td>&gt;5</td>
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*Ellipses indicate not applicable.  
†Impression of outcomes compared with abstinent opioid addicts reported by the liver transplantation coordinator, no further data were available from the coordinators.

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necessarily affected. Long-term methadone treatment does not result in significant liver toxicity.22 Drug interactions are theoretically possible because tacrolimus and cyclosporine, the most common immunosuppressants used in liver transplantation, as well as methadone and Levomethadyl acetate hydrochloride, use the cytochrome P-450 system (CYP3A4).23,24 No program reported drug interactions, and we found no reports of significant clinical interaction in MEDLINE.

There are several limitations to this survey. No one knows the precise numbers of MMT patients who apply for or receive liver transplantation or reasons for rejection. Our survey relied on anecdotal information from the liver transplantation coordinators; comprehensive psychosocial data were not available. We did not collect information about marijuana/cannabis use, a reported reason for rejection.

Opioid dependence is a problem that is frequently encountered in liver transplantation programs. Systematic studies eventually led to greater acceptance and improved access to transplantations among patients who are dependent on alcohol.25 Interestingly, relapse rates in alcoholic transplantation patients are reported as high as 30%,25,26 but the general outcome of the transplantation is not usually affected. Alcohol relapse did not usually result in noncompliance or compromised graft function. One possible explanation may be that posttransplantation monitoring reduces the amount of alcohol patients drink due to early interventions.26 Prospective liver-transplantation outcome studies are needed for the growing population of patients with comorbid opioid dependence and HCV to identify psychosocial factors affecting the transplantation outcome and to examine the effect of addiction treatment requirements. To help shape future transplantation policies, we recommend that UNOS add addiction and MMT data to its database and monitor treatment compliance and outcomes factors.

In the meantime, there is no evidence base to support the practice of discontinuing methadone maintenance as a precondition for liver transplantation. Such a policy may induce relapse in formerly stable patients and then, because of this, may disqualify these patients for surgery.

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REFERENCES