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Treating Chronic Hepatitis C in Recovering Opiate Addicts: Yes, We Can

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Commentary

Hepatitis was a major problem identified in intravenous drug users (IDUs) since the 1950s. Pioneering research leading to methadone maintenance treatment as effective pharmacotherapy of opiate addiction was conducted among IDUs in New York City in the 1960s; prospective studies conducted between 1964 and 1972 reported that 60 to 70% of all heroin addicts entering methadone treatment had evidence of liver disease.[1] At the time, it was ascertained that many of these patients had hepatitis B virus (HBV) infection, a disorder then only recently characterized. However, it was quite clear that other forms of "non-A non-B hepatitis" and alcoholic liver disease were also present among these patients. By the end of 1980s, studies from several laboratories identified that the major risk group for contracting the newly identified hepatitis C virus (HCV) infection were parenteral opiate and cocaine abusers.[2] It is now well known that a history of intravenous drug use is the single strongest risk factor for acquiring HCV infection and that prevalence of HCV, particularly in IDUs greater than 40 years of age, is over 70%.[3-5]

Methadone or buprenorphine maintenance treatment can be equated to a long-term therapy for opiate addiction equivalent to that employed for other chronic diseases (i.e., diabetes, hypertension); however stigma toward patients receiving treatment for addiction is still widespread, both in the general public as well as among physicians and health providers. In this issue of *Digestive and Liver Disease*, the study by Belfiori et al. demonstrates that IDUs treated with pegylated interferon and ribavirin can achieve sustained virological response rates that are equivalent to those obtained in registration trials using these therapies. To obtain these responses, IDUs were treated by a multidisciplinary group consisting of infectious disease physicians, addiction medicine specialists, and psychiatrists. The success of their approach raises the question: why so many former opiate addicts are still not considered suitable candidates for antiviral therapy?

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Why is antiviral treatment withheld?

An active IDU is not likely to comply with a long-term treatment program fraught with numerous possible adverse effects, such as a 48-week course of pegylated interferon and ribavirin. To embark on such a regimen in a patient who is actively abusing opiates or other drugs is often an exercise in futility. However, once an opiate addict is successfully treated with agonist pharmacotherapy (methadone or buprenorphine), drug-seeking behavior is abolished and the patient can be considered for treatment of medical co-morbidities, such as viral hepatitis. It is, however, commonplace for methadone- or buprenorphine-maintained subjects to be stigmatized when seeking medical care in settings other than the addiction clinic due to the limited education of medical personnel regarding these addiction treatments, which are still often viewed as “drug substitution” rather than an effective pharmacotherapy.

The issue of adherence to difficult-to-tolerate interferon-based HCV treatment regimens remains a concern. However, IDUs in methadone or buprenorphine maintenance treatment programs usually have immediate access to psychiatric and psychological treatment personnel. In addition, the diagnoses of depressive symptoms or depression have frequently been made prior to the initiation of interferon, which itself can cause or exacerbate such side effects. However, personnel who treat addiction are frequently more fearful of hepatitis treatment than they are of treatment for depression.

The American perspective

In the United States, there has always been reticence on the part of most physicians, except a few involved directly in the treatment of addiction, to address the problems of viral hepatitis in former opiate addicts. Even HBV vaccination was not conducted in this population until a persuasive study showing both adherence and response to the three-dose hepatitis B vaccination was published.[6] Despite the fact that by the 1990s hundreds of thousands of persons were successfully treated for heroin addiction with methadone maintenance and that the HCV seroprevalence was known to be 70%-90% in these patients, antiviral treatment was virtually precluded to this population.[7]

Essentially every pharmaceutical company developing therapies for HCV infection included in their exclusion criteria all persons with a history of drug abuse, addiction and even those in effective pharmacotherapy of heroin addiction. Thus, hepatologists systematically ignored treatment of HCV in methadone-maintained patients. With so few former drug users in effective treatment for addiction receiving antiviral treatment for HCV, it is not surprising that many progressed to end-stage liver disease requiring liver transplantation. Nevertheless, despite published reports of successful hepatic transplantation in former addicts on effective pharmacotherapy, many transplantation centers throughout the U.S. have remained reluctant or unwilling to perform this procedure in recovering opiate addicts receiving methadone, or more recently buprenorphine, maintenance therapy.[5]

The guidelines regarding treatment of HCV infection among IDUs have been liberalized in the U.S. over the past ten years. In 1997, the United States National Institutes of Health HCV Consensus Conference discouraged treatment of HCV in IDUs.[8] Five years later, the 2002 Consensus Conference revised its recommendation to suggest that IDUs be offered HCV treatment on a case-by-case basis.[9] Despite the relaxation of these rules and increased treatment of HCV among IDUs in Europe, IDUs remain the largest subgroup with untreated HCV infection in the United States.

To overcome the limited availability of antiviral treatment for methadone-maintained patients infected with HCV, we developed an “HCV-addiction medicine co-localization model” and applied the model to IDUs enrolled in a methadone maintenance treatment program in New

York City between 2006 and 2008.[10] All individuals who desired to initiate treatment for HCV in the methadone clinic were eligible for participation. Prior to initiation of treatment for HCV, all individuals underwent a comprehensive evaluation, which included a liver biopsy. Among our patients, 39% underwent liver biopsy and one half of those who underwent biopsy have initiated anti-HCV therapy. In future studies to improve treatment adherence in this population, non-invasive assessments of hepatic fibrosis may be an appropriate substitute to liver biopsy.

The Italian perspective

Since 1990, treatment of substance abuse in Italy is managed by the National Health System Addiction Service outpatient clinics (Servizi pubblici per Tossicodipendenze, SerT). In 2006, 10,000 opiate-dependant patients received treatment for addiction in over 500 SerTs nationwide. Both methadone and buprenorphine are approved drugs for pharmacotherapy of addiction, although methadone is prescribed in over 80% of cases [11], and each regional government oversees policy on dispensation and dosing schedules. Few studies have investigated the efficacy of regional SerTs regarding retention in treatment and relapse to drug use; however, a recent survey of 115 SerTs reported that in 80% of clinics, the average dose of methadone for maintenance treatment was < 60 mg/day, lower than that recommended by international guidelines.[12] Furthermore, rapid methadone detoxification treatments, which increase the risk of relapse to drug use, outnumbered methadone maintenance treatments. [13]

The high prevalence (> 70%) of chronic HCV infection among former opiate addicts receiving agonist pharmacotherapy with methadone or buprenorphine in Italy raises the issue of obtaining antiviral treatment in this population, which, as described for the United States, is also largely underserved in this regard. [5,11] There is convincing evidence provided by Sylvestre and colleagues that when antiviral treatment is managed in cooperation with the staff of a methadone (or buprenorphine) maintenance program, compliance is maximized and outcome is comparable to that of non-opiate-maintained HCV patients.[14]

The Belfiori et al. study is the first published Italian experience of treating chronic hepatitis C in the SerT setting; the authors describe an integrated approach with a multidisciplinary team to manage psychiatric co-morbidities, opiate pharmacotherapy, and antiviral treatment in 52 patients. Standard dual antiviral treatment with pegylated interferon alpha and ribavirin was administered, and the intention-to-treat rate of sustained virological response was 50% overall. Compliance to antiviral therapy was indeed higher in this study than that reported in non opiate-maintained HCV patients, with only 7% of patients discontinuing treatment prematurely; this demonstrates that treatment of chronic HCV infection is not only feasible in this population, but successful as well.

Take-home messages

Former opiate addicts receiving methadone or buprenorphine maintenance treatment can comply and respond to a standard course of pegylated interferon and ribavirin for eradication of HCV infection. The ideal treatment setting for former addicts is the methadone or buprenorphine maintenance clinic, which is the primary care site for treatment of addiction, with a multidisciplinary team composed of the addiction specialist, hepatologist or infectious disease specialist, and psychiatrist. Treatment of opiate addiction with adequate doses of methadone or buprenorphine to eliminate drug craving, with appropriate increases to counteract side effects from pegylated interferon therapy, is essential to ensure maximum compliance to antiviral treatment.

The optimization of methadone or buprenorphine dose and the availability of antiviral treatment for chronic hepatitis C among opiate-maintained patients remain largely unmet clinical needs; the integrated multidisciplinary approach to HCV treatment utilized in the study by Belfiori et al. is therefore a welcome contribution to the growing body of literature on this topic.

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