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Managing Hepatitis C in Users of Illicit Drugs

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Abstract

Persons who inject illicit drugs are the group most severely affected by the hepatitis C epidemic but the least likely to receive treatment. Controlling the epidemic will require developing strategies for effectively treating drug users. A growing number of reports have shown that a substantial proportion of drug users treated for hepatitis C can achieve sustained virologic responses even if they have psychiatric comorbidity and even if they continue to use drugs while receiving hepatitis C treatment. Successfully treating hepatitis C in injection drug users requires collaboration between those with expertise in hepatitis and those with expertise in caring for substance users. Careful attention to management of adverse effects and strong links with mental health services are important. Further research is needed to better define which patients can be successfully treated and the program elements that are critical for success. In the meantime, substantial progress can be made using current knowledge if appropriate resources are brought to bear.

Introduction

Recent advances in hepatitis C treatment have made it possible to clear the hepatitis C virus (HCV) from a large proportion of treated patients [1,2]. Patients achieving a sustained virologic response (SVR), defined by an undetectable HCV RNA test 24 weeks after the completion of antiviral therapy, remain virus-free for many years and do not appear to be at risk of disease progression [3]. These successes have led recent national treatment guidelines to recommend that treatment be extended to certain groups of patients who have previously been excluded, including illicit drug users [1,2].

This recommendation is important because persons who inject illicit drugs constitute the core of the hepatitis C epidemic [4]. They are the largest group of infected persons, the group in which most new infections occur, and the group that has been the most severely affected by the epidemic. An estimated 70% to 90% of persons in the United States who have injected drugs for 10 years or more are infected with HCV [5,6], although the prevalence is considerably lower in those who started injecting after the implementation of interventions aimed at preventing the spread of HIV among injection drug users (IDUs) [7,8]. Uninfected IDUs, however, still become infected at rates of 10% to 40% per year [9,10]. Controlling the hepatitis C epidemic, therefore, will require developing, testing, and implementing strategies for the prevention, care, and treatment of hepatitis C that will be effective for illicit drug users [11]. But although a large proportion of IDUs with hepatitis C express willingness to undergo treatment, a disproportionately low number have actually received antiviral therapy [12].

Barriers to Hepatitis C Treatment in Drug Users

Caring for drug users presents special challenges to the health care team. Barriers include characteristics of patients (such as poverty, homelessness, addiction, mental health conditions, poor relationships with health providers, and unpredictable follow-through), characteristics of physicians (lack of training in substance use and addiction, inexperience, unrealistic expectations, and prejudicial attitudes), and characteristics of the health care system, which often does not provide essential services for populations in need [13]. Physicians rarely receive meaningful training in addiction medicine or effective strategies for managing the difficulties often encountered in providing care for drug users. Consequently, unrealistic expectations, coupled with judgmental attitudes, can lead to frustration and resentment for both physician and patient. Drug users, like other patients, may fail to follow their physicians' advice, may be reluctant to fully and truthfully disclose their behavior, or may experience difficulty in keeping their appointments. Physicians caring for IDUs often experience this behavior as frustrating and specifically related to drug use; they may respond with aversion, malice, or neglect [14-16]. Indeed, most physicians do not feel comfortable caring for IDUs, preferring to relegate this task to an addiction specialist or a drug treatment facility [17,18]. Physicians and other health care providers need better education about substance use and addiction and exposure to models of compassionate care to improve their understanding of problematic substance use as a treatable disorder. Fortunately, clinicians undertaking hepatitis C care can draw upon a substantial body of research and clinical experience in the prevention and management of chronic viral diseases, especially HIV infection, among IDUs [19,20]. Effective principles have been developed for engaging drug users in health care relationships (Table 1). Learning from this experience will be critical for efforts to control hepatitis C.

Medical Care for Drug Users

Successful treatment of hepatitis C in IDUs requires collaboration between those with expertise in hepatitis and those with expertise in caring for substance users to create programs specifically designed for drug users. Expertise working with drug users is available from a variety of sources, including public health and community workers with experience in HIV prevention and harm reduction, HIV treatment providers, substance use treatment providers, substance use researchers, and (probably most importantly) drug users themselves. Multidisciplinary approaches with contributions from groups such as primary care physicians, hepatologists, nurses, psychiatrists, social workers, drug counselors, and psychologists have proven most effective. Successful programs depend on a respectful approach to substance users, an understanding of the medical and behavioral sequelae of addiction, and an avoidance of moralistic judgments. A flexible attitude is necessary so that unrealistic expectations do not lead to frustration and resentment. The objective is to enable patients to be healthier, not to achieve a predetermined goal.

Data on Treating Drug Users for Hepatitis C

A growing number of reports from the United States and elsewhere have shown that a substantial proportion of drug users treated for hepatitis C can achieve SVRs even if they have psychiatric comorbidity and even if they continue to use drugs while receiving hepatitis C treatment (Table 2) [21-33,34,35,36-38]. SVR rates were modestly reduced in patients who continued using illicit drugs while receiving antiviral therapy in some studies, but differences were not statistically significant in any study, and substantial proportions of nonabstinent patients responded favorably to treatment. In most studies, patients were receiving treatment for substance use, and those who continued using illicit drugs usually were using intermittently rather than daily. Common elements of these studies were

expertise in treating hepatitis C; experience caring for drug users; careful attention to management of adverse effects, especially depression; availability of treatment for substance use, including opioid substitution therapy; and attention to the need for adjustment of methadone doses. In several studies, adherence to weekly clinic visits was used as a selection criterion [34•] or was found to be associated with treatment response [21].

In a study of 50 heroin injectors entering opiate detoxification in Munich, Germany, for example, 34 patients were treated with interferon-alfa monotherapy and 16 were treated with interferon-ribavirin combination therapy for 24 to 48 weeks, depending on HCV genotype [21]. Overall, 36% of patients achieved an SVR, a response rate comparable to that in other populations treated for hepatitis C, even though 80% of patients relapsed to drug use during the study. Patients in this study were managed by physicians who specialized in hepatology and in addiction medicine. Patients who relapsed to drug use were offered methadone maintenance therapy but were allowed to continue treatment for hepatitis C even if they continued to inject illicit drugs. Sizeable proportions of patients had an SVR, regardless of whether they relapsed to drug use (80% of patients, 33% with an SVR) or received methadone maintenance therapy (30% of patients, 53% with an SVR; $P = 0.17$).

In a study of 76 patients receiving methadone maintenance in Oakland, California, who were treated with interferon-ribavirin combination therapy, 28% had an SVR [34•]. This response rate was achieved despite the patients' relatively old age (mean, 50 years), long duration of infection (mean, 28 years), predominance of genotype 1 (60%), and quite advanced liver disease (30% had cirrhosis on biopsy or platelet counts below 75,000/ μ L)—all factors associated with reduced response rates. Patients had substantial levels of psychiatric comorbidity and substance use: 59% had a prior psychiatric diagnosis, mostly depression; 86% were receiving antidepressants by the end of treatment; 20% continued to drink alcohol during treatment, mostly in moderate quantities; and 59% used illicit drugs during treatment. Nearly half (45%) of the patients required an increase in methadone dose (median, 15 mg). Response rates were not significantly associated with the duration of abstinence from illicit drugs before treatment (less than 6 months, 22%, vs 6 months or more, 30%; $P = 0.18$) or with the use of illicit drugs other than marijuana during treatment, although there was a trend toward lower response rates in those with more frequent drug use (no drug use, 35%; occasional, 21%; daily [only eight patients], 0%; $P = 0.09$). Unexpectedly, patients who smoked marijuana were significantly more likely than others to respond to antiviral therapy [39]. These studies showed that drug users receiving treatment for substance use can be treated successfully for hepatitis C despite ongoing drug use, moderate alcohol consumption, and significant psychiatric comorbidity.

Approach to Treating Drug Users

Patients with a history of substance dependence have a high prevalence of past losses and traumas. They experience stigmatization because of their substance use and often internalize the stigma. In addition, many IDUs have had negative experiences with the health care system and harbor suspicion and mistrust towards medical providers, which present challenges to developing trusting clinical relationships. Physicians can gain trust and establish good clinical relationships with IDUs by demonstrating characteristics that challenge these assumptions. Exhibiting caring and empathy, maintaining consistency, and being reliable are key features of successful patient-provider relationships. Explicitly acknowledging and reinforcing any positive change the patient is able to make, even minor progress, provides an opportunity to strengthen the patient's sense of self-efficacy and commitment to improved health. Assessing barriers and working together with patients to generate strategies to overcome them can strengthen the clinical relationship, contribute to improved functioning, and strengthen adherence to medical care.

All patients with hepatitis C should be asked about past or current drug and alcohol use, regardless of whether they are known to have injected drugs. According to the 2005 National Survey on Drug Use and Health, 105 million housed, noninstitutionalized Americans 18 years or older report having used illicit drugs. This number represents 48.2% of the adult population—and does not include the homeless, prison inmates, institutionalized persons, or the military [40]. An estimated 67 million have used illicit drugs other than marijuana (33 million used cocaine and 3.5 million used heroin). An estimated 1.0 to 1.5 million Americans actively use illicit drugs by injection. When patients disclose illicit drug use, physicians should collaborate with them to assess their drug use and the impact it has on their health and other areas of functioning. Drug users differ widely in the drugs they use, the amounts they use, the frequency and pattern of use, the route of administration, their relationship to their use, the stability and predictability of their lifestyles, their needle hygiene, and many other factors. Many of these factors may fluctuate over time. Physicians can provide basic factual information about medical consequences of drug use, ascertain the patient's attitudes toward his or her drug use, and help the patient identify and focus on health behavior changes he or she is motivated to make. This approach can help solidify the relationship with the patient by clarifying that the physician's ultimate goal is the patient's health.

Treatment for substance use should be discussed with patients with problematic drug or alcohol use, and provisions should be made to provide competent treatment for those who want and need it. Proven, effective treatments for substance use exist. Opioid agonist therapy (eg, methadone maintenance therapy) has been shown to diminish and often eliminate illicit opiate use and to reduce transmission of many infections, including HIV [41,42]. The recent approval of buprenorphine, a partial opioid antagonist highly effective for the treatment of opioid dependence [43], has the potential to significantly expand access to opioid replacement therapy and provide physicians the means to effectively manage the complications of drug use such as hepatitis C. Physicians who complete brief training can now prescribe buprenorphine in outpatient medical settings. Alcohol treatment is also particularly important because of the strong effect of heavy alcohol intake on the progression of hepatitis C.

Physicians caring for injection drug users should consider hepatitis C in the context of the patient's overall health and life circumstances. Physicians and patients should make decisions about antiviral treatment together, taking into account the risks and benefits for the individual patient. Not all drug users will want or need antiviral therapy, given the limited efficacy of current regimens (particularly in African American patients and those with genotype 1 infection), the substantial adverse effects, and (if the disease is not advanced) the option of delaying therapy while better regimens are developed [44]. Patients may have more immediate medical or social needs that take precedence over hepatitis C treatment. Patients in whom hepatitis C treatment is most urgent are those with acute HCV infection, in whom treatment is considerably more effective [45], and those with advancing fibrosis on liver biopsy, in whom progression to cirrhosis may be imminent. Objectively evaluating the ways in which a patient's drug use impacts relevant areas of functioning can create a dialogue that will help the patient and provider assess whether hepatitis C treatment is appropriate at the present time, or whether it makes more sense to defer treatment until levels of stability and support are increased. The optimal sequence for treating hepatitis C and substance use will differ in different patients. For some, the promise of receiving hepatitis C treatment may give them the encouragement they need to cut down or stop using drugs. For others, finding ways to stabilize their life circumstances or establishing a social support system may be all they need to be ready for hepatitis C treatment.

Adherence

Physicians should discuss the importance of adhering to the prescribed regimen with any patient considering hepatitis C treatment, and together they should assess the patient's ability to adhere before embarking upon therapy. The impact of a patient's drug use should be considered objectively and without preconception. Drug use can adversely affect adherence [46]. Patients who believe they can adhere to therapy, however, can be allowed to try. Much less is lost by treating a patient who does not adhere to therapy than by letting a patient progress to cirrhosis or death without a trial of treatment because of a prior assumption that the patient would not adhere to the regimen. Barriers to adherence should be anticipated and strategies to overcome them discussed. Once treatment is under way, the patient's adherence should be monitored and supported periodically as needed.

Mental health

When considering treatment for hepatitis C in any patient, it is necessary to have a heightened awareness of the potential for mental health difficulties. Patients with hepatitis C may be at risk of psychiatric disorders for a number of reasons. First, hepatitis C may be associated with adjustment disorders and depression in response to the diagnosis itself. Common themes related to these symptoms include living with a potentially fatal infectious disease, uncertainty about future progression of the illness and about the success of hepatitis C treatment, stigma, isolation, and discrimination [47]. Second, HCV may induce neurocognitive symptoms, including decreased concentration, mental slowing, and impaired working memory, through invasion of the virus into the central nervous system [48]. These symptoms may occur early during the course of infection and appear to be independent of fatigue, depression, and stage of liver disease. Comorbid hepatitis C and HIV may place patients at even greater risk for dementia, independent of HIV or HCV disease severity [49]. Third, interferon-based treatments for hepatitis C are often complicated by neuropsychiatric adverse effects, including depression, fatigue, insomnia, irritability, and cognitive disturbances [50]. Patients are at risk for the emergence of these symptoms throughout the course of interferon treatment, and symptoms normally abate rapidly with cessation of interferon. Finally, apart from any medical comorbidity, IDUs exhibit higher rates of comorbid psychiatric disorders than the general population [51]. Depression and posttraumatic stress disorder are among the most common diagnoses. IDUs are also at risk for cognitive impairment based on the acute and chronic effects of illicit drugs, particularly psychostimulants, alcohol, and concurrent methadone treatment. Concurrent substance abuse may induce or exacerbate distress and psychiatric disorders in the context of hepatitis C.

Given these multiple levels of risk, patients should be screened for depression, fatigue, cognitive dysfunction, substance abuse, and other mental health problems before and during the course of hepatitis C treatment. Psychiatric disorders should be optimally treated before beginning hepatitis C treatment, but active symptoms do not necessarily preclude hepatitis C treatment as long as close psychiatric follow-up is available. Past episodes of depression or other psychiatric disorders are not absolute contraindications to treatment for hepatitis C. Persons with psychiatric histories may adhere to and complete hepatitis C treatment at rates as high as those of other patient groups if their mental health status is closely monitored and treated [24,34•]. Thus, strong links with on-site or community mental health services are a vital component of comprehensive health programs for IDUs and are particularly important during treatment for hepatitis C.

HIV coinfection

Drug users who have acquired hepatitis C through unsafe injection practices may have HIV infection as well. Progression of liver disease due to hepatitis C is more rapid in persons with HIV coinfection, and is a significant and increasing cause of death for HIV-infected

patients. Although hepatitis C treatment is somewhat less effective in patients with HIV coinfection, it can be effective in coinfecting drug users and is an important option in their care [32]. Treatment should be undertaken in collaboration with HIV care providers [52••].

Acute HCV infection

SVR rates approaching 100% have been achieved when HCV infection has been treated during the acute phase—much higher than in chronic infection [45]. Thus early detection and treatment of acute HCV infection should be an urgent priority [33]. Persons at high risk, such as young IDUs, in whom incidence rates as high as 40% per year have been observed [10], should be tested regularly (eg, every 3 months).

Reinfection

Drug users who are successfully treated for HCV infection can become reinfected if they inject unsafely [53]. Several small studies, however, have suggested that the risk appears low when patients are given clear, specific information about how to avoid HCV transmission [29,38,54]. Patients in these studies were educated in safe injection practices because their physicians understood that addiction is a chronic, relapsing condition; most patients entering treatment do not immediately and permanently stop injecting drugs. Patients should be advised to avoid exposure to others' blood, even apparently trivial contact, by not sharing any injection equipment, including syringes, "cookers" (containers used to dissolve drugs), "cottons" (filters used to draw up drugs), rinse water, or tourniquets, and by washing hands and injection sites before and after injecting, especially when giving an injection to another user [55]. Sterile syringes and injection equipment are available from needle exchange programs or over the counter in pharmacies, or can be prescribed by physicians [56].

Pilot Study of a Collaborative, Multidisciplinary, Integrated Care Model

At the Center for the Study of Hepatitis C, nine patients who were actively using illicit drugs have been treated with peginterferon and ribavirin in a pilot study evaluating a collaborative, multidisciplinary, integrated care model that integrates the resources and expertise of community-based needle exchange programs with those of a tertiary care hepatitis C center. One patient was lost to follow-up, one had no virologic response to the medication, and one discontinued treatment because of hepatic decompensation. All six remaining patients are HCV RNA-negative to date; four have had SVRs, one has had an end-of-treatment response and less than 24 weeks of follow-up, and one is still receiving treatment. Unexpectedly, five of the nine patients stopped their use of illicit drugs and one other patient substantially curtailed his use. All six cited the decision to start hepatitis C treatment or the news of their negative HCV RNA test as the factor motivating their decision. Although four of the nine patients had genotype 2 or 3 or acute HCV infection, factors associated with favorable outcomes, these results suggest that with appropriate support, hepatitis C treatment can be successful even for active drug users, and may serve as a bridge to healthier behaviors in other domains as well.

Need for Further Research

Although the studies reviewed in this article suggest that drug users can be successfully treated, little is known about effective methods of patient selection and management. Many of the studies reviewed here reported on small, diverse groups of sometimes highly selected patients recruited and treated in different settings with differing strategies. Data are sparse on the characteristics that distinguish those patients who can be successfully treated and the program elements that are critical for success. Larger studies that carefully describe characteristics and outcomes of patients and programs are needed to answer these questions.

It is clear that patients who are no longer using illicit drugs need access to hepatitis C treatment and can benefit from it. Much less is known, however, about patients who continue to use drugs regularly or intermittently. The need for such research is urgent, in view of the overwhelming prevalence of hepatitis C in this population, the increasing morbidity and mortality of the disease, and the limited access of IDUs to liver transplantation [4]. An estimated one million American IDUs have hepatitis C and need access to appropriate care.

A number of the studies reviewed included patients actively using illicit drugs, but nearly all reported on patients receiving opioid substitution therapy such as methadone or buprenorphine [21-33,34,35,36-38]. These studies demonstrate unequivocally that patients receiving such therapy can respond to current formulations of peginterferon and ribavirin in substantial numbers. Unfortunately, similar data will not exist for newer therapies currently under development because nearly all current trials exclude patients receiving methadone or buprenorphine. The NIH Consensus Statement on the Management of Hepatitis C [1] concluded in 2002 that methadone was not a contraindication for hepatitis C therapy and called for future research to include patients in drug treatment programs, but this call has not been heeded. As treatment regimens become more effective and more easily tolerated, the urgency of providing them to substance users will increase.

Conclusions

Illicit drug users constitute the core of the hepatitis C epidemic. Treatment strategies effective with persons who use drugs will be needed to control the epidemic. Fortunately, clinicians undertaking hepatitis C care can draw upon a substantial body of research and clinical experience in the management of chronic viral diseases among IDUs. Caring for drug users presents special challenges to the health care team, requiring patience, experience, and tolerance. Successful programs depend on a respectful approach to substance users, an understanding of the medical and behavioral sequelae of addiction, and an avoidance of moralistic judgments. Successfully treating hepatitis C in IDUs requires collaboration between those with expertise in hepatitis and those with expertise in caring for substance users. Strong links with mental health services are vital because psychiatric disturbances are associated with both hepatitis C and substance use and may be induced or exacerbated by hepatitis C treatment. Using these methods, a growing number of studies have shown that drug users can be successfully treated for hepatitis C despite psychiatric comorbidity and even intermittent, ongoing drug use. Common elements of these studies were expertise in treating hepatitis C, experience caring for drug users, careful attention to managing adverse effects (especially depression), and the availability of treatment for substance use. Further research is needed to better define the characteristics that distinguish those patients who can be successfully treated and the critical elements of successful programs. In the meantime, substantial progress can be made if existing knowledge and resources are brought to bear.

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Figure 1. Response Rates among Injection Drug Users Treated for Hepatitis C

In studies that included patients who continued using illicit drugs while receiving antiviral therapy, SVR rates were generally modestly reduced, but differences were not statistically significant in any study, and substantial proportions of nonabstinent patients still responded favorably to treatment. SVR=sustained virologic response. MMT=metadone maintenance treatment.

Table 1

Principles for managing health care relationships with substance-using patients

1. Establish a climate of mutual respect.
2. Maintain a professional approach that reflects the aim of enhancing the patient's well-being: avoid judging or blaming.
3. Recognizing that drug use is multidimensional, base recommendations on the nature and consequences of the patient's drug use rather than on preconceptions or assumptions about drug users.
4. Work with the patient to objectively assess the impact of drug use on the patient's health and functioning.
5. Recognizing that patients must set their own goals for behavior change, work with patients to achieve commitment to realistic goals for healthier behaviors.
6. Express confidence in the patient's ability to take steps toward healthier behaviors and acknowledge (commend) his or her successes.
7. Recognize that stopping drug use and sustaining abstinence are difficult and that success may take time and require multiple attempts.
8. Recognizing that abstinence is not always a realistic goal, emphasize risk-reduction measures for patients who continue to use drugs (eg, use of sterile injection equipment and safe injection practices).
9. Be consistent and dependable.
10. Educate patients about their medical status, proposed treatments, and side effects.
11. Include patients in decision making.
12. Have staff who are knowledgeable about substance use, mental health, AIDS, and hepatitis.
13. Have staff who are familiar with substance use and comfortable with users.
14. If possible, establish a multidisciplinary team consisting of primary care physicians, HIV specialists, psychiatrists, social workers, and nurses.
15. Have a single provider coordinate the care delivered by such a team to maximize consistency and continuity.
16. Define and agree on the roles and responsibilities of both the health care team and the patient.
17. Set appropriate limits and respond consistently to behavior that violates those limits.
18. Minimize barriers to participation (penalties for missed visits, etc.).
19. Be familiar with local resources for the treatment of drug users.
20. Elicit the patient's feelings about his or her drug use and interest in treatment for substance use.
21. Refer patients to competent substance use treatment programs as appropriate.

Table 2Studies of hepatitis C treatment in persons who use illicit drugs^{*}

Study	Year	Location	IDUs, N	SVR, %	Active IDUs, n
Backmund et al. [21]	2001	Munich	50	36	40 during treatment
Jowett et al. [22]	2001	England	50	36	N/A
Neri et al. [23]	2002	Italy	30	N/A	N/A
Schaefer et al. [24]	2003	Munich	49	38	N/A
Van Thiel et al. [25]	2003	Chicago	120	33	N/A
Coumot et al. [26]	2004	France	81	32	~16
Mauss et al. [27]	2004	Dusseldorf	100	49	0
Huber et al. [28]	2005	Switzerland	27	48	N/A
Dalgard [29]	2005	Norway	69	39	0
Mathews et al. [30]	2005	Australia	12	50	12
Litwin et al. [31]	2005	New York	N/A	N/A	Yes
Clanon et al. [32]	2005	Oakland	15	58	—
Bargiacchi et al. [33]	2005	Italy	12 (acute)	75	1
Sylvestre et al. [34•]	2005	Oakland	76	28	27 during treatment
Robaey et al. [35•]	2006	Belgium	98	47	21 during treatment
Mathews et al. [36]	2006	Portland	N/A	N/A	N/A
Sylvestre et al. [37]	2006	Oakland	55	37	44 during treatment
Jeffrey et al. [38]	2007	Australia	50	62	18 during treatment

IDU— injection drug user; N/A—not available; SVR—sustained virologic response.

^{*} A mix of active and previous users, some receiving and some not receiving substance abuse treatment. Regimens varied and included interferon monotherapy, interferon-ribavirin combination therapy, and peginterferon plus ribavirin.