

Treating the Methadone Patient

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Injection drug users (IDUs) have the highest HCV infection rates of any behavioral risk group, and in the US, injection drug use accounts for at least 60% of new cases.¹ Approximately 70-96% of long-term injection drug users are infected with the virus.¹⁻⁶ Parenteral transmission is very efficient: as many as 65%-70% of IDUs are infected within one year of needle use, and after 5 years of injecting, as many as 90% of users are infected with HCV.^{4, 5, 7-9} For this reason, many experts estimate the length of exposure to HCV in drug users by subtracting one year from the total number of lifetime years of needle use.

Despite the remarkably high prevalence of HCV in IDUs, there is surprisingly little data about treatment in this population. Comorbid psychiatric disease¹⁰⁻¹², relapse to substance use^{13, 14}, reinfection¹⁵⁻¹⁷, and poor adherence^{18, 19} are potential obstacles that must be addressed when treating IDUs for HCV. However, severe interferon-mediated depression does not necessarily correlate with preexisting psychiatric disease, and human data on HCV reinfection after treatment is extraordinarily scant.^{14, 23} Studies to date have not shown a substantial impact of substance abuse relapse on treatment outcomes in IDUs,^{14, 23} and careful adherence data is lacking. In the light of the overwhelming prevalence of HCV in IDUs,^{3, 8} the increasing morbidity of this disease,² and the limited access of IDUs to liver transplantation,²⁴ it is imperative to develop treatment approaches for IDUs that realistically assess and surmount these barriers. An approach that focuses on more stable recovering IDUs provides an ideal opportunity to understand the impact of treating this relatively difficult population with medications that may potentially be problematic.

Methadone maintenance is currently the most effective pharmacologic treatment for chronic heroin addiction.²⁵⁻²⁷ A synthetic narcotic with actions similar to morphine and heroin, methadone has a half-life of 15-25 hours and can be dispensed as a treatment for heroin addiction only by hospital pharmacies and by federally regulated drug treatment programs.²⁵ The methadone withdrawal syndrome is qualitatively similar to that of heroin, but it differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe. It is used most effectively as a long-term maintenance treatment with ancillary psychosocial interventions.²⁸ Used appropriately, it has been shown to dramatically reduce recidivism and assist the majority of those taking it with achieving medical, psychological, and psychosocial stability.²⁵

O.A.S.I.S. (Organization to Achieve Solutions in Substance-Abuse) is a nonprofit organization located in Oakland, CA that provides medical treatment to recovering IDUs, with a focus on developing HCV treatment strategies in this population. Nearly 1,000 IDUs have been screened for HCV and approximately 100 methadone patients have been treated for the disease.²⁹ Its group treatment model is to date the most effective means of treating HCV in IDUs.^{30, 31} Current research is focusing on HCV treatment in methadone patients and understanding the impact of psychiatric disease, length of sobriety, and intervening drug and alcohol use during HCV therapy in this population.³¹

Compared to HCV patients in large worldwide studies of HCV therapy, O.A.S.I.S. methadone patients are older, more racially and sexually balanced, and are therefore more representative of HCV-infected persons in the US. The median length of HCV infection is over a decade longer than that seen in most studies, and a history of heavy alcohol use is common. The majority of patients report a previous diagnosis of psychiatric illness. Seventy-seven percent of patients exhibit current infection as determined by PCR.

In concert with the relatively lengthy exposure to the HCV virus and frequent history of comorbid alcoholism, methadone patients show substantially more advanced liver fibrosis, or scar tissue, as compared with typical non-dependent populations. Fibrosis on liver biopsies is typically graded on a scale of 0-4, with 0 being no fibrosis and 4 being severe fibrosis, or cirrhosis. The average fibrosis stage in O.A.S.I.S. methadone patients is 2.6, much higher than the scores of approximately 1.2-1.4 seen in typical treatment populations. Advanced fibrosis of stage 3 or higher was seen in 29% of O.A.S.I.S. patients, and fewer than 20% had minimal liver disease. Of those with elevated liver enzymes on blood testing, 37% showed advanced fibrosis of stage 3 or higher, and surprisingly, up to 22% of those whose liver enzyme tests remained persistently normal showed advanced fibrosis. It is obviously of great importance in these patients to proceed with a full workup, even in the presence of blood tests that many would consider reassuring.

Treatment results of the first 59 methadone patients (of 105 projected) to complete standard interferon/ribavirin combination therapy using the O.A.S.I.S. group model show a sustained response rate (SVR) of 28%, modestly lower than the 41% SVR seen in large trials of non-dependent populations. The overall dropout rate for this population is 24%, similar to the 20-21% dropout rate typically seen in HCV treatment trials. These results raise a question: what is it about the methadone patients undergoing treatment in this trial that led to a reduced treatment response? How does psychiatric disease, sobriety length, and drug or alcohol use during treatment influence response rates? Is the use of methadone while on HCV treatment problematic, and therefore should methadone patients undergo detoxification prior to HCV treatment?

Patients reporting a pre-treatment psychiatric diagnosis showed a lower SVR when compared with non-psychiatric patients, 22% vs 37%. Overall, 50% of patients in the study were taking antidepressants prior to therapy and 88% were taking such medications by treatment completion, with SSRIs like citalopram (Celexa) and paroxetine (Paxil) being the

category of medications most commonly prescribed. These results suggest that prophylactic antidepressants might need to be considered in the majority of such patients contemplating treatment.

Overall, 21% of treated patients consumed alcohol of some quantity during HCV therapy, but the patients who consumed alcohol had only a mildly reduced SVR, 25% vs 29%. Because of the low number of patients in the alcohol group, a subanalysis of the effect of larger vs smaller quantities of alcohol could not be undertaken.

An analysis of the impact of sobriety length on treatment outcomes showed that being sober at the start of treatment was important, even if that period was relatively short. Patients with sobriety lengths of less than six months exhibited virologic responses similar to those with more lengthy sobriety, 37% vs 30%, respectively. However, patients without pretreatment drug sobriety showed a decrement in treatment outcome, with an overall SVR of 17%.

Thirty-five percent of study patients used heroin, cocaine, and/or methamphetamines during HCV treatment. Those using these drugs showed an SVR of 20%, compared with 32% in abstinent patients. When analyzed by quantity of drug use, a stepwise decrement in treatment outcome was seen, with the most dramatic effect of this behavior seen in those using drugs regularly. None of these patients showed a virologic response, whereas 20% to 29% of those using drugs less frequently showed a sustained virologic response. Because a substantial proportion of patients using drugs infrequently showed acceptable virologic outcomes, relapse to drug use during HCV treatment should not prompt HCV treatment discontinuation, but rather an early and aggressive attempt to intervene before the drug use becomes regular.

Putting it all together, methadone patients undergoing HCV therapy have a host of potentially difficult barriers to treatment, including underlying psychiatric illness, alcohol use, and drug use. When treated patients without any of these characteristics are analyzed separately, their SVR is 50%, even higher than that of the published trials. Clearly, methadone use during HCV treatment is not problematic, and may indeed be protective of response rates by assisting with adherence to HCV therapy and maintaining medical stability.

These results suggest that a decision to treat HCV should not be negatively influenced by methadone therapy, and that, while substance use is associated with reduced treatment responses, a significant proportion of patients still benefit. In light of these findings, although we emphasize helping our patients avoid any substance abuse, a strategy that focuses on aggressive psychiatric intervention, side effect management, and preventing relapse to regular drug use will assist a substantial proportion of methadone patients with successfully completing therapy.

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