Hepat Mon. 2011;**11**(7):513-518

KOWSAR

Hepatitis Monthly

Journal home page: www.HepatMon.com

Barriers to receiving hepatitis C treatment for people who inject drugs: Myths and evidence

Peter Higgs [1, 2, 3*], Rachel Sacks-Davis [2, 3], Judy Gold [2, 3], Margaret Hellard [2, 3]

[1] National Center in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia
[2] Center for Population Health, Burnet Institute, Melbourne, Australia
[3] School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

ARTICLE INFO

Article Type:
Review Article

Article history:
Received: 25 Aug 2010
Revised: 18 Feb 2011
Accepted: 06 Apr 2011

Keywords:
Hepatitis C virus
Interferon
Drug users
Alcohol
Mental disorder

ABSTRACT

Background: Alcohol consumption, current injecting drug use, and pre-existing mental illness have been identified as 3 of the main reasons for excluding patients from treatment for hepatitis C.
Objectives: We reviewed the literature to obtain an evidence base for these common exclusion criteria.
Materials and Methods: We reviewed original research and meta-analyses investigating the effects of alcohol consumption, current injecting drug use, and pre-existing mental illness.
Results: We identified 66 study reports relevant to the review, but found only limited evidence to support withholding of treatment on the basis of the 3 previously mentioned exclusion criteria.
Conclusions: Currently, there is a lack of evidence for many of the barriers faced by patients in availing treatment for hepatitis C. Adherence to treatment routine was found to be a better predictor of sustained virological response than injecting drug or alcohol consumption during treatment period or the presence of a pre-existing mental disorder. Although several challenges remain, we need to ensure that treatment decisions are based on the best available evidence and the treatment is performed appropriately on a case-by-case basis.

▸ *Implication for health policy/practice/research/medical education:*
Making evidence-based HCV treatment decisions rather than ones based on preconceived ideas about people who deserve treatment for HCV is essential. Those involved in deciding to offer HCV treatment would do well to consider the results of this study which show that patient centred treatment is crucial.

▸ *Please cite this paper as:*
Higgs P, Sacks-Davis R, Gold J, Hellard M. Barriers to recivieng hepatitis C treatment for people who inject drugs: Myths and evidence. *Hepat Mon*. 2011;**11**(7):513-8.

1. Background

In developed countries, people who inject drugs (PWID) are at the greatest risk of infection with hepatitis C virus (HCV) (1, 2). Despite the lack of evidence, throughout the 1990s, regulations restricting PWIDs' access to referral for specialist treatment for their chronic HCV infection has existed in a number of western countries (3, 4). The 2005 special issue (40, supplement 5) of Clinical Infectious Diseases was dedicated to HCV infection, managing opiate dependence, and developing models of integrated care for HCV-positive people. The summary in the special issue concluded that there remained important knowledge gaps on the providing the best health-care and treatment for HCV infection in current injecting drug users and stated that further research

* *Corresponding author at:* Peter Higgs, National Center in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia. Tel: +61-392822195, Fax: +61-392822100.
E-mail: p.higgs@unsw.edu.au

would be required to specifically address this issue (5).

A recent review on HCV treatment for PWID in patient groups with and without a history of injecting drug use showed that the group with a history of injecting drug use was able to successfully complete treatment with minor variations in treatment outcomes (6). Presently, a number of international research studies conducted in different treatment settings show that it is possible to successfully provide HCV treatment to current injectors (7-10). Previous research has shown that there are individual (both the patient and provider) and structural barriers to HCV treatment (11-13). During a previous literature review on hepatitis C antiviral treatment in PWID, we identified 3 barriers that may on an individual level, affect the treatment in injecting drug users and were commonly cited as the formal exclusion criteria for, or predictors of exclusion from, the antiviral therapy: continued injecting drug use, alcohol use, and pre-existing mental disorders (11, 14-21).

2. Objectives

Although we observed that individual barriers were not the only ones that prevented injecting drug users from accessing treatment, we limited our review on this to focus more on the above-mentioned 3 barriers. For each barrier, we delineated a myth that underlay the exclusion of affected HCV-positive patients from receiving treatment. In the context of our study, a myth was defined as a commonly held belief that may or may not have been consistent with the available evidence.

3. Materials and Methods

A literature review was undertaken on the effects of alcohol consumption, mental disorder, and current injecting drug use on hepatitis C antiviral treatment to evaluate the extent to which the 3 myths were evidence-based. The literature searches were conducted from 2008 to July 2010. By using Ovid MEDLINE®, we searched the entries in the database from 1996 to the present with daily update, and keyword mapping identified the following subject headings to be used as search terms: "hepatitis C", "hepacvirus", "antiviral agents", "alcohol-related disorders", "alcohol drinking", "mood disorders", and "substance use, intravenous". Various combinations and sub-categories of the above subject headings were used in the searchers. We also used the "explode" function in Medline, which allows broad searching of a term while simultaneously narrowing the searches for all other terms in the subject heading. Reference lists in the identified articles were also searched for obtaining any relevant information. We included articles in English that described results from original research or meta-analyses that measure the outcomes of continuous alcohol consumption, a pre-existing mental illness, and/or current injecting drug use in patients receiving hepatitis C antiviral therapy, or articles that reported a successful follow-up for measuring the rates of reinfection of patients who received antiviral therapy.

4. Results

Over 400 articles were filtered through the database searches, and 66 were included in this review. In the next section of the paper, we include a critical review of the 3 myths identified.

4.1. Myth 1: Illicit use of drugs during HCV treatment may cause complications and increase the chance of reinfection

Few studies, all with small samples (N < 75), have investigated the impact that current injecting drug use during HCV treatment has on the rates of sustained virological response (SVR). Four studies have found similar SVR rates among participants who reported injecting drug during the treatment period and those who had a history of injecting use but had reported no drug use during the treatment (8, 10, 22, 23). Participants of 2 studies who injected regularly (at least once in every 2 days for a prolonged period during the treatment) were observed to have lower SVR rates than those who abstained from injecting or injected less frequently during the treatment, even though the differences did not reach a statistically significant value (22, 23).

Several studies have found that those who continued injecting drug use during treatment were less likely to comply with the treatment regimen and hence did not complete treatment (24, 25). However, 2 other studies showed that frequent injecting drug use during treatment did not affect the probability of attaining an SVR as long as the treatment regimen was completed (8, 26). Few studies have conducted a systematic follow-up of the participants after HCV treatment, and those studies have shown low rates of reinfection (27). Although there are cases of posttreatment reinfection in the literature (28-30), the incidence of such cases is less frequent than the incidence of HCV infection (31) or reinfection (32, 33) in community-based studies.

4.1.1. Implications

Adherence to treatment appears to be a stronger predictor of whether injectors with chronic HCV infection will achieve SVR than whether or at what levels they inject drugs during the treatment period. The less clear part is how the complex social and environmental factors can be managed so that individuals could have strategies that can help ensure adherence to the treatment regimen. This includes management of side effects that may occur during treatment. Although follow-up after treatment to measure the reinfection rates have been done in a lesser number of participants, to date the reinfection rates that have been observed after treatment are far lower than those observed after spontaneous clearance. Therefore,

there is no evidence showing that the potential for posttreatment HCV reinfection is a sound reason for not offering treatment to PWID.

4.2. Myth 2: Alcohol consumption before and/or during treatment has major implications for the successful treatment of HCV

The biological mechanisms by which alcohol might affect HCV treatment outcomes have been researched (34-37). Alcohol consumption has been found to increase the likelihood of histological steatosis and to accelerate hepatic fibrosis and inflammation in patients with HCV infection (38-42). Some studies have found that alcohol consumption raises the HCV viral load (41); however, a meta-analysis of the effect of alcohol consumption on HCV replication failed to show any association between alcohol consumption and HCV viral load (38). Some studies have reported that a history of alcohol consumption has an adverse effect on HCV treatment outcomes by reducing the probability of attaining SVR (43-46). An earlier study had reported a weak dose–response relationship between the quantity of alcohol ever consumed and the likelihood of failing treatment (45). However, other studies have reported that the weak dose–response effect can be reversed by observing a lengthy period of pretreatment abstinence from alcohol consumption (47, 48). Some other studies have found an association between pretreatment alcohol consumption and treatment outcome; however, a univariate analysis performed after adjusting for other factors in these studies failed to establish any such association (41).

The effect of alcohol consumption during treatment independent of the effect of a history of alcohol consumption, on treatment efficacy remains unclear. Some studies have shown that alcohol consumption during treatment has a negative impact on the treatment outcome moreover, a dose–response effect has been observed during a univariate analysis performed in 1 study (41). However, some other studies have reported successful treatment outcomes among patients who have continued to consume moderate amounts of alcohol (up to 24 grams per day) during treatment (49, 50). A study in Canada found that participants who had consumed alcohol 6 months prior to treatment were less likely to complete the treatment regimen and were less likely to attain an SVR; however, even in this study, no association could be found between alcohol consumption during treatment and the treatment outcomes (51). Therefore, in studies where alcohol consumption has been associated with a decrease in SVR, it is unclear if the effect was due to alcohol consumption or a reduced adherence to treatment (40, 49). Indeed, in a treatment study in which continuous alcohol consumption was considered an exclusion criteria for receiving treatment, consuming an average of more than 3 alcoholic drink per day within a year prior to treatment was an independent predictor of early treatment discontinuation after adjusting for factors of race, illicit substance use, and income; however, alcohol consumption itself was not associated with attaining an SVR (52).

Overall, we found that many of the studies on the effect of alcohol on treatment response did not admit heavy drinkers into treatment; therefore, we could only examine the effects of prior alcohol consumption on the treatment outcome (42, 43, 46-48). Among those studies that did investigate alcohol consumption during treatment, the participant numbers were small, and many studies were on interferon monotherapy, which is a relatively ineffective treatment regimen compared to the latest treatment regimens, and most do not account for potential ambiguity in the outcome (41, 45, 51).

4.2.1. Implications

Until further studies can establish the direct effect of alcohol consumption on treatment success, while adjusting for adherence to HCV treatment, it seems reasonable to advise patients to decrease their level of alcohol consumption before and during HCV treatment. However, given that some patients have successfully completed treatment without abstaining from alcohol consumption, a patient's inability to abstain from alcohol consumption before and during therapy should not be seen as an automatic exclusion criterion for receiving HCV treatment.

4.3. Myth 3: Pre-existing mental health problems among PWID lead to HCV treatment being unviable

Depression is one of the most common side-effects of HCV treatment (53); a review reported that up to 40% of the people being treated with interferon experience a mild to moderate depression (54). Several studies have investigated the relationship between depression (judging by either a history of depression or a depression score when commencing the treatment) and treatment outcomes. All studies except 1 have observed no significant relationship between depression and treatment adherence (55), treatment completion (55-57), early or end of treatment response (55, 58), or SVR (56). A larger study found that patients with depression were significantly less likely to complete treatment; however, there was no significant difference in SVR (59). One study examined the difference in treatment outcomes between patients with and without schizophrenia and found no difference in the treatment completion or end-of-treatment response, but the patients with schizophrenia were significantly more likely to achieve an SVR (60).

Other studies have involved a combined analysis of various psychiatric disorders on the treatment outcomes. One study found no difference in treatment completion among patients with current or past mood or anxiety disorders (61). Two studies found no difference in treatment completion, end-of-treatment response, or SVR among patients with a current or past psychiatric

disorder and those without (62, 63). One study found no difference in end of treatment response or SVR between patients with a history of mental health issues and/or drug use and those patients without (64)

Notably, 8 of 10 studies listed above involved fewer than 100 individuals, and many studies did not perform multivariate analysis (56, 58-64), were conducted retrospectively (56, 60, 63, 64), and/or had various exclusion criteria relating to ongoing or uncontrolled psychiatric illness (58, 59, 63, 64). Multiple studies have found an association between a lifetime history of depression, or high depression scores at baseline, and development of depression during HCV treatment (57, 59, 64-67). One study found no difference in the symptoms of depression, schizophrenia, or mania between those with and without schizophrenia at baseline (68). Similarly, no difference was found in the development of symptoms during treatment when a group of patients with various psychiatric disorders was compared to a group of patients without any psychiatric disorders (69) or when a group of patients with a history of psychiatric disorders and/or illicit drug use was compared to a group of patients without any of these (63). However, similar to the studies investigating the relationship between pre-existing mental health problems and treatment outcomes, 8 of 11 studies involved fewer than 100 participants, and 2 studies were conducted retrospectively (60, 64).

4.3.1. Implications

Although, there is some evidence to suggest that having a history of depression or a high depression score when commencing treatment increases the likelihood of an individual developing depression during HCV treatment and potentially affecting treatment completion, there is no evidence to suggest that a pre-existing psychiatric disorder could adversely affect the likelihood of attaining an end-of-treatment response or SVR. Evidence also suggests that people experience a number of side effects from their HCV treatment. These results suggest that rather than automatically excluding individuals with pre-existing psychiatric disorders from treatment, they should receive appropriate care for their psychiatric disorder before, during, and after HCV treatment.

5. Conclusion

In most developing countries, formal policies restricting PWID from accessing HCV treatment have been lifted over the past 10 years. Although some PWID now receive treatment, the rates remain low; many PWID are still being excluded from treatment because of concerns about their continuous alcohol consumption, injecting drug use, and pre-existing mental illness. Our review highlights the lack of evidence supporting these exclusions. Many of the studies that we reviewed included only a small number of participants and failed to adjust their findings to account for potential ambiguity. Our evidence suggests that a patient's likelihood of attaining SVR is impacted more by the adherence to treatment than by the frequency of drug injecting during the treatment period. Likewise, although there is evidences showing that a pre-existing mental illness may increase the likelihood of experiencing depression as a side effect of the treatment, from our review, it appears that the patients with pre-existing mental illnesses who complete the treatment are just as likely as other patients to attain SVR; this highlights the role of concurrent management of mental health problems with HCV treatment.

To ensure that alcohol consumption does not have a direct effect on treatment efficacy, continued counseling should be offered to patients on reducing their alcohol consumption before and during treatment. However, as some patients have successfully completed treatment even while continuing to consume moderate amounts of alcohol, alcohol consumption should not be seen as an automatic exclusion criterion for HCV treatment. The decision to treat HCV should be patient centered and made on a case-by-case basis with foremost attention to the needs and interests of the person seeking treatment. The research in this area is ongoing, and as the number of studies increases, we will be able to pool more data on a range of indicators, which may help understand the factor that has the greatest impact on the HCV treatment outcome. At present, there is no compelling evidence for restricting access to PWID seeking HCV treatment. We consider this the right time for making evidence-based decisions rather than making decisions based on pre-conceived ideas about patients who deserve treatment for HCV, and we hope that those involved in deciding to offer HCV treatment would consider the results of our study.

Financial support

None declared.

Conflict of interest

None declared.

References

1. Aceijas C, Rhodes T. Global estimates of prevalence of HCV infection among injecting drug users. *Int J Drug Policy*. 2007;**18**(5):352-8.
2. Te HS, Jensen DM. Epidemiology of hepatitis B and C viruses: a global overview. *Clin Liver Dis*. 2010;**14**(1):1-21.
3. Edlin BR. Hepatitis C prevention and treatment for substance users in the United States: acknowledging the elephant in the living room. *Int J Drug Policy*. 2004;**15**(2):81-91.
4. Mehta S, Genberg B, Astemborski J, Kavasery R, Kirk G, Vlahov D, et al. Limited Uptake of Hepatitis C Treatment Among Injection Drug Users. *J Community Health*. 2008;**33**(3):126-33.
5. Kresina TF, Khalsa J, Cesari H, Francis H. Hepatitis C virus infection and substance abuse: medical management and developing models of integrated care–an introduction. *Clin Infect Dis*. 2005;**40**(Suppl 5):S259-62.
6. Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. *Clin*

Infect Dis. 2009;**49**(4):561-73.
7. Belfiori B, Ciliegi P, Chiodera A, Bacosi D, Tosti A, Baldelli F, et al. Peginterferon plus Ribavirin for chronic hepatitis C in opiate addicts on methadone/buprenorphine maintenance therapy. *Digest Liver Dis*. 2009;**41**(4):303-7.
8. Dore GJ, Hellard M, Matthews GV, Grebely J, Haber PS, Petoumenos K, et al. Effective treatment of injecting drug users with recently acquired hepatitis C virus infection. *Gastroenterology*. 2010;**138**(1):123-35 e1-2.
9. Ebner N, Wanner C, Winklbaur B, Matzenauer C, Jachmann CA, Thau K, et al. Retention rate and side effects in a prospective trial on hepatitis C treatment with pegylated interferon alpha-2a and ribavirin in opioid-dependent patients. *Addict Biol*. 2009;**14**(2):227-37.
10. Litwin AH, Harris KA, Nahvi S, Zamor PJ, Soloway IJ, Tenore PL, et al. Successful treatment of chronic hepatitis C with pegylated interferon in combination with ribavirin in a methadone maintenance treatment program. *J Subst Abuse Treat*. 2009;**37**(1):32-40.
11. Morrill JA, Shrestha M, Grant RW. Barriers to the treatment of hepatitis C. Patient, provider, and system factors. *J Gen Intern Med*. 2005;**20**(8):754-8.
12. Sylvestre D, Loftis J, Hauser P, Genser S, Cesari H, Borek N, et al. Co-occurring hepatitis C, substance use, and psychiatric illness: Treatment issues and developing integrated models of care. *J Urban Health*. 2004;**81**(4):719-34.
13. Watson B, Conigrave KM, Wallace C, Whitfield JB, Wurst F, Haber PS. Hazardous alcohol consumption and other barriers to antiviral treatment among hepatitis C positive people receiving opioid maintenance treatment. *Drug Alcohol Rev*. 2007;**26**(3):231-9.
14. Falck-Ytter Y, Kale H, Mullen KD, Sarbah SA, Sorescu L, McCullough AJ. Surprisingly small effect of antiviral treatment in patients with hepatitis C. *Ann Intern Med*. 2002;**136**(4):288-92.
15. Fleming CA, Craven DE, Thornton D, Tumilty S, Nunes D. Hepatitis C virus and human immunodeficiency virus coinfection in an urban population: low eligibility for interferon treatment. *Clin Infect Dis*. 2003;**36**(1):97-100.
16. Hagan H, Latka MH, Campbell JV, Golub ET, Garfein RS, Thomas DA, et al. Eligibility for treatment of hepatitis C virus infection among young injection drug users in 3 US cities. *Clin Infect Dis*. 2006;**42**(5):669-72.
17. Hatem C, Minello A, Bresson-Hadni S, Jooste V, Evrard P, Obert B, et al. Is the management of hepatitis C patients appropriate? A population-based study. *Aliment Pharmacol Ther*. 2005;**21**(8):1007-15.
18. Muir AJ, Provenzale D. A descriptive evaluation of eligibility for therapy among veterans with chronic hepatitis C virus infection. *J Clin Gastroenterol*. 2002;**34**(3):268-71.
19. Restrepo A, Johnson TC, Widjaja D, Yarmus L, Meyer K, Clain DJ, et al. The rate of treatment of chronic hepatitis C in patients co-infected with HIV in an urban medical centre. *J Viral Hepat*. 2005;**12**(1):86-90.
20. Stoove MA, Gifford SM, Dore GJ. The impact of injecting drug use status on hepatitis C-related referral and treatment. *Drug Alcohol Depend*. 2005;**77**(1):81-6.
21. Yawn BP, Wollan P, Gazzuola L, Kim WR. Diagnosis and 10-year follow-up of a community-based hepatitis C cohort. *J Fam Pract*. 2002;**51**(2):135-40.
22. Grebely J, Raffa JD, Meagher C, Duncan F, Genoway KA, Khara M, et al. Directly observed therapy for the treatment of hepatitis C virus infection in current and former injection drug users. *J Gastroenterol Hepatol*. 2007;**22**(9):1519-25.
23. Sylvestre DL, Litwin AH, Clements BJ, Gourevitch MN. The impact of barriers to hepatitis C virus treatment in recovering heroin users maintained on methadone. *J Subst Abuse Treat*. 2005;**29**(3):159-65.
24. Belfiori B, Chiodera A, Ciliegi P, Tosti A, Baldelli F, Stagni G, et al. Treatment for hepatitis C virus in injection drug users on opioid replacement therapy: a prospective multicentre study. *Eur J Gastroenterol Hepatol*. 2007;**19**(8):731-2.
25. Sylvestre DL, Clements BJ. Adherence to hepatitis C treatment in recovering heroin users maintained on methadone. *Eur J Gastroenterol Hepatol*. 2007;**19**(9):741-7.
26. Jeffrey GP, MacQuillan G, Chua F, Galhenage S, Bull J, Young E, et al. Hepatitis C virus eradication in intravenous drug users maintained with subcutaneous naltrexone implants. *Hepatology*. 2007;**45**(1):111-7.
27. Dalgard O. Follow-Up Studies of Treatment for Hepatitis C Virus Infection among Injection Drug Users. *Clin Infect Dis*. 2005;**40**(Suppl 5):S336-8.
28. Asselah T, Vidaud D, Doloy A, Boyer N, Martinot M, Vidaud M, et al. Second infection with a different hepatitis C virus genotype in a intravenous drug user during interferon therapy. *Gut*. 2003;**52**(6):900-2.
29. Backmund M, Meyer K, Edlin BR. Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users. *Clin Infect Dis*. 2004;**39**(10):1540-3.
30. Dalgard O, Bjoro K, Hellum K, Myrvang B, Skaug K, Gutigard B, et al. Treatment of chronic hepatitis C in injecting drug users: 5 years' follow-up. *Eur Addict Res*. 2002;**8**(1):45-9.
31. Grebely J, Knight E, Ngai T, Genoway KA, Raffa JD, Storms M, et al. Reinfection with hepatitis C virus following sustained virological response in injection drug users. *J Gastroenterol Hepatol*. 2010;**25**(7):1281-4.
32. Aitken CK, Lewis J, Tracy SL, Spelman T, Bowden DS, Bharadwaj M, et al. High incidence of hepatitis C virus reinfection in a cohort of injecting drug users. *Hepatology*. 2008;**48**(6):1746-52.
33. van de Laar TJ, Molenkamp R, van den Berg C, Schinkel J, Beld MG, Prins M, et al. Frequent HCV reinfection and superinfection in a cohort of injecting drug users in Amsterdam. *J Hepatol*. 2009;**51**(4):667-74.
34. Fujita N, Sugimoto R, Urawa N, Araki J, Mifuji R, Yamamoto M, et al. Hepatic iron accumulation is associated with disease progression and resistance to interferon/ribavirin combination therapy in chronic hepatitis C. *J Gastroenterol Hepatol*. 2007;**22**(11):1886-93.
35. Izumi N, Enomoto N, Uchihara M, Murakami T, Ono K, Noguchi O, et al. Hepatic iron contents and response to interferon-alpha in patients with chronic hepatitis C. Relationship to genotypes of hepatitis C virus. *Dig Dis Sci*. 1996;**41**(5):989-94.
36. Ono K, Sata M, Murashima S, Fukuizumi K, Suzuki H, Tanikawa K. Biological responses to administered interferon in alcoholics. *Alcohol Clin Exp Res*. 1996;**20**(9):1560-3.
37. Zylberberg H, Fontaine H, Thepot V, Nalpas B, Brechot C, Pol S. Triggering of acute alcoholic hepatitis by alpha-interferon therapy. *J Hepatol*. 1999;**30**(4):722-5.
38. Anand BS, Thornby J. Alcohol has no effect on hepatitis C virus replication: a meta-analysis. *Gut*. 2005;**54**(10):1468-72.
39. Bhattacharya R, Shuhart MC. Hepatitis C and alcohol: interactions, outcomes, and implications. *J Clin Gastroenterol*. 2003;**36**(3):242-52.
40. Cooper CL. Obstacles to successful HCV treatment in substance addicted patients. *J Addict Dis*. 2008;**27**(2):61-8.
41. Loguercio C, Di Pierro M, Di Marino MP, Federico A, Disalvo D, Crafa E, et al. Drinking habits of subjects with hepatitis C virus-related chronic liver disease: prevalence and effect on clinical, virological and pathological aspects. *Alcohol Alcohol*. 2000;**35**(3):296-301.
42. Oshita M, Hayashi N, Kasahara A, Hagiwara H, Mita E, Naito M, et al. Increased serum hepatitis C virus RNA levels among alcoholic patients with chronic hepatitis C. *Hepatology*. 1994;**20**(5):1115-20.
43. Chang A, Skole K, Gautam M, Schmutz J, Black M, Thomas R, et al. The impact of past alcohol use on treatment response rates in patients with chronic hepatitis C. *Aliment Pharmacol Ther*. 2005;**22**(8):701-6.
44. Chen CM, Yoon YH, Yi HY, Lucas DL. Alcohol and hepatitis C mortality among males and females in the United States: a life table analysis. *Alcohol Clin Exp Res*. 2007;**31**(2):285-92.
45. Mochida S, Ohnishi K, Matsuo S, Kakihara K, Fujiwara K. Effect of alcohol intake on the efficacy of interferon therapy in patients with chronic hepatitis C as evaluated by multivariate logistic regression analysis. *Alcohol Clin Exp Res*. 1996;**20**(9 Suppl):371A-7A.
46. Tabone M, Sidoli L, Laudi C, Pellegrino S, Rocca G, Della Monica P, et al. Alcohol abstinence does not offset the strong negative effect of lifetime alcohol consumption on the outcome of interferon therapy. *J Viral Hepat*. 2002;**9**(4):288-94.

47. Anand BS, Currie S, Dieperink E, Bini EJ, Shen H, Ho SB, et al. Alcohol use and treatment of hepatitis C virus: results of a national multicenter study. *Gastroenterology*. 2006;**130**(6):1607-16.
48. Ohnishi K, Matsuo S, Matsutani K, Itahashi M, Kakihara K, Suzuki K, et al. Interferon therapy for chronic hepatitis C in habitual drinkers: comparison with chronic hepatitis C in infrequent drinkers. *Am J Gastroenterol*. 1996;**91**(7):1374-9.
49. Bruggmann P, Dampz M, Gerlach T, Kravecz L, Falcato L. Treatment outcome in relation to alcohol consumption during hepatitis C therapy: an analysis of the Swiss Hepatitis C Cohort Study. *Drug Alcohol Depend*. 2010;**110**(1-2):167-71.
50. Edlin BR. Prevention and treatment of hepatitis C in injection drug users. *Hepatology*. 2002;**36**(5 Suppl 1):S210-9.
51. John-Baptiste A, Varenbut M, Lingley M, Nedd-Roderique T, Teplin D, Tomlinson G, et al. Treatment of hepatitis C infection for current or former substance abusers in a community setting. *J Viral Hepat*. 2009;**16**(8):557-67.
52. Seal KH, Currie SL, Shen H, Anand BS, Bini EJ, Brau N, et al. Hepatitis C treatment candidacy and outcomes among 4318 US veterans with chronic hepatitis C virus infection: does a history of injection drug use matter? *J Clin Gastroenterol*. 2007;**41**(2):199-205.
53. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. *N Engl J Med*. 1998;**339**(21):1485-92.
54. Mistler LA, Brunette MF, Marsh BJ, Vidaver RM, Luckoor R, Rosenberg SD. Hepatitis C Treatment for People With Severe Mental Illness. *Psychosomatics*. 2006;**47**(2):93-107.
55. Guadagnino V, Trotta MP, Carioti J, Caroleo B, Antinori A. Does depression symptomatology affect medication compliance during the first weeks of anti-HCV therapy in intravenous drug users? *Dig Liver Dis*. 2006;**38**(2):119-24.
56. Hauser P, Morasco BJ, Linke A, Bjornson D, Ruimy S, Matthews A, et al. Antiviral completion rates and sustained viral response in hepatitis C patients with and without preexisting major depressive disorder. *Psychosomatics*. 2009;**50**(5):500-5.
57. Reichenberg A, Gorman JM, Dieterich DT. Interferon-induced depression and cognitive impairment in hepatitis C virus patients: a 72 week prospective study. *AIDS*. 2005;**19**(Suppl 3):S174-8.
58. Loftis JM, Socherman RE, Howell CD, Whitehead AJ, Hill JA, Dominitz JA, et al. Association of interferon-alpha-induced depression and improved treatment response in patients with hepatitis C. *Neurosci Lett*. 2004;**365**(2):87-91.
59. Evon DM, Ramcharran D, Belle SH, Terrault NA, Fontana RJ, Fried MW. Prospective analysis of depression during peginterferon and ribavirin therapy of chronic hepatitis C: results of the Virahep-C study. *Am J Gastroenterol*. 2009;**104**(12):2949-58.
60. Huckans M, Mitchell A, Ruimy S, Loftis J, Hauser P. Antiviral therapy completion and response rates among hepatitis C patients with and without schizophrenia. *Schizophr Bull*. 2010;**36**(1):165-72.
61. Pariante CM, Orru MG, Baita A, Farci MG, Carpiniello B. Treatment with interferon-alpha in patients with chronic hepatitis and mood or anxiety disorders. *Lancet*. 1999;**354**(9173):131-2.
62. Schaefer M, Schmidt F, Folwaczny C, Lorenz R, Martin G, Schindlbeck N, et al. Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. *Hepatology*. 2003;**37**(2):443-51.
63. Chainuvati S, Khalid SK, Kancir S, Shea M, Edwards J, Sernyak M, et al. Comparison of hepatitis C treatment patterns in patients with and without psychiatric and/or substance use disorders. *J Viral Hepat*. 2006;**13**(4):235-41.
64. Ho SB, Nguyen H, Tetrick LL, Opitz GA, Basara ML, Dieperink E. Influence of psychiatric diagnoses on interferon-alpha treatment for chronic hepatitis C in a veteran population. *Am J Gastroenterol*. 2001;**96**(1):157-64.
65. Dell'Osso L, Pini S, Maggi L, Rucci P, Del Debbio A, Carlini M, et al. Subthreshold mania as predictor of depression during interferon treatment in HCV+ patients without current or lifetime psychiatric disorders. *J Psychosom Res*. 2007;**62**(3):349-55.
66. Raison CL, Borisov AS, Broadwell SD, Capuron L, Woolwine BJ, Jacobson IM, et al. Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. *J Clin Psychiat*. 2005;**66**(1):41-8.
67. Fransen Van De Putte DE, Fischer K, Posthouwer D, Van Erpecum K, Mauser-Bunschoten EP. Occurrence, course and risk factors of depression during antiviral treatment for chronic hepatitis C in patients with inherited bleeding disorders: a prospective study. *Haemophilia*. 2009;**15**(2):544-51.
68. Huckans M, Mitchell A, Pavawalla S, Morasco BJ, Ruimy S, Loftis JM, et al. The influence of antiviral therapy on psychiatric symptoms among patients with hepatitis C and schizophrenia. *Antiviral Therapy*. 2010;**15**(1):111-9.
69. Schaefer M, Schwaiger M, Garkisch AS, Pich M, Hinzpeter A, Uebelhack R, et al. Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C. *J Hepatol*. 2005;**42**(6):793-8.