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**What psychiatric screening and monitoring might be needed with the new generation of hepatitis C treatments?**

Rowan PJ. Psychiatric monitoring with newer HCV therapies

Paul J Rowan

**Paul J Rowan,** University of Texas Health Sciences Center at Houston School of Public Health, Houston, TX 77030, United States

**Author contributions:** Rowan PJ contributed to this paper.

**Correspondence to: Paul J Rowan, PhD, MPH,** University of Texas Health Sciences Center at Houston School of Public Health, 1200 Herman Pressler Drive, Houston, TX, 77030, United States. prowan@uth.tmc.edu

**Telephone:** +1-713-5009183 **Fax:** +1-713-5009181

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**Abstract**

Psychiatric difficulties, including depression and alcohol use disorders, pose a challenge to treatment decision-making for chronic hepatitis C. This is especially made worse because interferon-alpha, as part of the standard of care, may exacerbate depressive symptoms and cause suicidal symptoms to appear. This requires a treatment setting that has the capacity to carry out psychiatric assessment and monitoring, and the capability to deliver patient education regarding these aspects of care. Psychiatric comorbidities create a challenging decision-making situation, especially since success rates for the most common hepatitis C genotype, genotype 1, hover around 40%. In recent years, new treatments have emerged. These significantly boost the likelihood of sustained viral response, including for genotype 1, and do not seem to have the side effects of interferon-alpha or ribavirin. Relevant data are reviewed to assess the degree that these new treatments might reduce the portion not eligible for treatment due to psychiatric comorbidities, and might reduce the emergence of psychiatric symptoms during treatment. Several organizations have recently released evidence-based treatment recommendation guidelines. It is apparent that interferon-alpha continues to be a standard of care, with the new drugs added to this recognized regimen in order to shorten treatment and to boost efficacy. Clinical settings must continue to assess appropriateness for treatment, including current or recent psychiatric comorbidities, and must continue to closely monitor patients for the emergence of psychiatric side effects. The newly developed hepatitis C treatments may affect the metabolism of several categories of psychiatric drugs, and so drug-drug interactions must also be considered and monitored. With many promising drugs under development, an all-pill regimen, with no interferon-alpha and no ribavirin, may emerge in the near future. This will greatly change the challenge of treatment decision-making, and should expand the portion of patients able to successfully complete a treatment regimen.

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**Core tip:** Emerging Hepatitis C treatment regimens, which include newer medications such as boceprevir, telaprevir, sofosbuvir, and simeprevir, hold promise to reduce the need for psychosocial screening and monitoring. Thus far, these medications do not seem to have the same psychiatric side effect profile as interferon-alpha.

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Based upon genotype prevalence data and efficacy data, several recently emerging treatment guidelines continue to call for first-line treatment that includes interferon-alpha in combination with one or more of these newer medications. Therefore, the need for psychiatric screening, monitoring, and support continues.

As interferon-alpha became a recognized standard-of-care treatment for chronic hepatitis C, it became apparent that psychiatric side effects complicated treatment decision-making[1]. Specifically, current or recent depression has been considered a contra-indication for interferon-based regimens because the interferon-alpha can provoke or increase depressive symptoms in those with depression or a history of depression[2]. The effect is possibly attributable to interferon’s effect on serotonin pathways, but is more likely due to interferon-alpha’s function as one of the many inflammatory cytokines which are recognized to cause flu-like symptoms and also cause “sickness behavior,” experienced as depression[3,4]. It is hypothesized that acute inflammatory responses occur in response to infection and occur when tissue repair is needed, and that the cytokine-induced activation of anhedonia and low motivation serves the organism by allowing the body to devote physiological efforts to rest and healing rather than other activities[5].

Part of the interferon-induced depression phenomenology may include suicidality, making suicidality a treatment consideration before beginning therapy, and requires close monitoring during therapy[4]. Current or recent alcohol use has been another contra-indication: efficacy may be reduced in those drinking during treatment[6]and because those with a drinking history are perceived as having high risk of relapse under the distress of treatment[7].

Additionally, interferon therapies require that social circumstances needed to be assessed. This includes an appraisal of the ability of the patient to adhere to a challenging regimen across six or more months, the possible need to take leave from employment when experiencing side effects, and the need for stable residence, since interferon-alpha requires refrigeration. The revelation of the boosted efficacy of joint interferon-alpha and ribavirin treatment, circa 1994, brought more treatment success, but did not change this psychiatric aspect of the treatment decision matrix. Neither did the advent of pegylated interferon-alpha, circa 1998. Treatment guidelines have recommended a psychosocial evaluation for interferon-alpha candidates, with a period such as six months before re-assessment[8].

Because of these difficulties of treatment, and because chronic hepatitis C is a slowly progressing disease, the clinical decision often is to delay treatment, and “watch-and-wait.” In the pegylated-interferon/ribavirin era, outcomes evaluations have determined that approximately 70% of otherwise eligible patients do not begin interferon-alpha treatment due to contra-indications, with a significant portion of reasons being psychiatric[9,10].

Further complicating the clinical picture is the fact that ribavirin, while boosting rates of sustained viral response when combined with interferon-alpha, is a teratogen. Therefore, great care and attention must be used when considering hepatitis C treatment for women of child-bearing age, and when delivering this treatment. Before beginning therapy, a pregnancy test must be conducted, and the woman must decide whether she will be able to maintain two types of birth control throughout treatment, and to conduct repeat pregnancy tests, as well as maintaining adherence to the interferon-alpha/ribavirin regimen[11].

For quite some time, the standard of care has been to carefully consider the psychiatric profile of a potential interferon-alpha candidate. Patients with current or recent psychiatric difficulties can be referred for a course of psychiatric treatment, perhaps with re-assessment in six months, or be started on interferon-alpha therapy as long as supportive care and monitoring are in place. This requires a great deal of the hepatology or gastroenterology clinical setting: these settings must have the capacity or resources to carry out psychiatric evaluations, to provide psychiatric treatment or link a patient with psychiatric care, and to monitor psychiatric symptoms throughout therapy. Patients must also be willing to accept the treatment decision to not begin a potentially curative therapy, and follow other medical advice such as abstention from alcohol.

Across time, clinicians have become more confident in treating patients who had current or recent psychiatric difficulties. Risks have been addressed by using a multidisciplinary team[12-14], by conducting regular psychiatric monitoring[15], and by prophylactic antidepressant treatment[16]. Although clinicians have become competent at detecting and addressing these complicating factors, the inherent difficulties have driven the development of newer drugs that do not carry these challenges.

In recent years, many newer drugs have been developed. In the spring of 2011, boceprevir and telaprevir received Food and Drug Administration (FDA) approval for hepatitis C virus (HCV) treatment. In winter 2013, sofosbuvir and simeprevir received FDA approval. Daclatasvir has been approved as of July 2014 by the European Medicines Agency, and an application for approval of ledipasvir was submitted to the FDA in February 2014.

These drugs, and others under investigation, may resolve the difficulties of interferon-alpha-based therapy. Generally, since they do not behave as inflammatory cytokines, they do not share the side effect of inducing flu-like symptoms, depression, or suicidality. The new drugs do not require refrigeration, and they are not known to have the teratogenic risk of ribavirin. FDA prescribing information for the recent drugs that are thus far FDA-approved, including sofosbuvir, simeprevir, telaprevir, and boceprevir, do not note psychiatric symptoms as recognized side effects. Since they can be used in combination with interferon-alpha and with ribavirin, or both, the prescribing information for each of these new medications does note the risks associated with the entire regimen, as approved.

Will these newer therapies make the focus upon psychiatric status a thing of the past? Will the new therapies make the psychiatric assessments and psychiatric care, and lifestyle assessments, such as the assessment of residential stability or pregnancy monitoring, a thing of the past? Ideally, the new generation of medications would eliminate these challenging treatment considerations, and far fewer treatment candidates should be delayed by psychiatric concerns.

This question can be answered by reviewing recently updated treatment guidelines. In March 2014, a guideline was develop and released jointly by the American Association for the Study of Liver Disease and the Infectious Diseases Society of America[17]. In April 2014, guidelines were released by the World Health Organization[18] and the European Association for the Study of the Liver[11]. The Veterans Affairs (VA) National Hepatitis C Resource Center and Office of Public Health released a treatment consideration guide in March 2014, with an update in May 2013[19].

These guidelines incorporate recent efficacy evidence for hepatitis C treatment. At this point in time, recommended care has not yet reached the point of being able to decrease concerns over psychiatric or social factors.

The guidelines are very consistent in recommending that the majority of patients with chronic hepatitis C, who are candidates for treatment, should still be treated with a regimen that includes interferon-alpha. The innovation provided by the recently developed medications is that one or more of these should be added in order to boost the likelihood of achieving a sustained viral response. The most common hepatitis C genotype is type 1, at possibly 46% of cases worldwide[20]. Genotype 3 may account for approximately 30% of cases world-wide, genotype 2 may account for approximately 9% of cases, genotype 4 may account for 8%, and genotype 6 may account for 5% of cases.

The VA guideline is organized by genotype, then by other parameters such as whether the patient is treatment-naïve, and whether or not cirrhosis is present. This guideline suggests that treatment-naïve patients with genotype 1 and no notable contra-indications be treated with a regimen of pegylated interferon-alpha combined with ribavirin, and also combined with either sofosbuvir or simeprevir.

Thus, the greatest numbers of patients coming under consideration, those with genotype 1 who are treatment naïve, are still advised to receive a regimen that includes interferon-alpha and ribavirin, and so includes the treatment challenges inherent with those regimens. Treatment-naive patients with genotype 3 may be started on a regimen of ribavirin combined with sofosbuvir for 24 wk, with an alternative, 12-wk regimen including pegylated interferon along with the ribavirin and the sofosbuvir. Therefore, for genotype 3, the second-most prevalent genotype, the concern about pregnancy remains when following recommended care. It thus remains the case that, for a majority of treatment-naïve patients, a hepatitis C treatment setting must have the capacity to carry out psychosocial assessment, education, intervention, and monitoring, even though a new generation of much more benign drugs have been developed and are receiving FDA approval.

One problem affecting some of these new drugs is that they may affect the metabolism of psychiatric drugs[21]. Because of this possibility, the clinical care team will need to monitor for any drug-drug interactions for drugs that the patient may have already been prescribed, or may consider taking while being treated for hepatitis C. For example, FDA prescribing information notes that sofosbuvir may interact with anti-epileptic medications, such as carbamazepine and phenytoin, which are both used for the treatment of bipolar disorder and other psychiatric conditions. Telaprevir has a longer list of potential interactions with psychiatric drugs, including ant-epileptics, some antidepressants, and some benzodiazapenes. Kiser *et al*[21] note possible interactions with some of the atypical anti-psychotics, as well. Treatment may call for close monitoring, or the patient may want to discontinue a drug for the length of hepatitis C treatment, or the patient might switch to another drug, with no interaction risk, for the noted indication.

Drawing upon the same set of available efficacy data, the Veterans Affairs guidelines are very concordant with those from the other noted organizations. Overall, when considering the epidemiology of hepatitis C genotype and the first line of treatment suggested by recently developed guideline statements, interferon-alpha with ribavirin continues to be a mainstay of treatment, with the innovation being the boosted rates of sustained viral response when adding the newly approved drugs.

Since interferon-alpha and ribavirin will continue to be mainstays of care, treatment settings will continue to be required to accommodate the problem of psychiatric comorbidities in their clinical populations, and to be able to address treatment-based psychiatric side effects including depressive symptoms and suicidality. A strong emphasis on patient education continues to be required to convey information regarding regimen adherence, dosing, timing, drug-drug interactions, and the problem of the teratogeneity of ribavirin.

The AASLD/IDSA 2014 recommendations[17] note that “evaluation by a practitioner who is prepared to provide comprehensive management, including consideration of antiviral therapy, is recommended for all persons with current (active) HCV infection.” They proceed further on this issue to note that such comprehensive care is not common for settings diagnosing and treating liver disease, but strategies, such as co-localization of care and collaborative care arrangements, can be developed to meet this recommended style of comprehensive care.

At the same time, evaluation of new drugs, including combinations of new drugs, is actively being pursued, largely with the goal of an all-pill regimen that avoids interferon-alpha, and also avoids, where possible, ribavirin. With FDA approval for four new drugs thus far, and several more under evaluation, the pragmatics of providing effective, evidence-based treatment for chronic hepatitis C, with a much more benign patient experience, may be much easier in the near future. In many cases, a “watch-and-wait” approach remains appropriate, as the treatment options may soon increase dramatically. “Watch-and-wait” may be acceptable for much of the patient population as long as the decision-making process has been patient-centered[22].

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