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## Time to Rethink Antiviral Treatment for Hepatitis C in Patients with Coexisting Mental Health/Substance Abuse Issues

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### Abstract

**Background**—A new era has dawned in the treatment of chronic hepatitis C (HCV) virus with the use of direct-acting antiviral medications augmenting combination therapy. Unfortunately, the significant impact of improvements may not be realized if antiviral treatment is not expanded to include a larger proportion of patients, many of whom have coexisting mental health and/or substance abuse issues and have been historically deferred from treatment.

**Methods**—We reviewed the extent literature on HCV treatment for individuals with co-occurring mental health and/or substance abuse issues.

**Results**—A number of empirically-based arguments exist in favor of treating HCV-infected individuals with mental health and/or substance abuse issues within the context of multidisciplinary team approaches. Integrated, collaborative, or hybrid models of care are just a few examples of multidisciplinary approaches that can combine the care of HCV treating providers with mental health and/or addictions providers to safely and effectively treat these patients. Collectively, these arguments and the empirical evidence that supports them, provides a strong rationale for why expanding antiviral therapy to these patients is critical and timely.

**Conclusions**—A decade of evidence suggests that HCV-infected individuals with mental health and/or substance abuse issues can safely and effectively undergo antiviral treatment when delivered through multidisciplinary care settings. Multidisciplinary approaches that combine HCV treating providers with mental health, addictions, and other support systems can facilitate preparation and successful treatment of these patients on antiviral therapy.

### Keywords

Psychiatric; Depression; Substance abuse; Multidisciplinary

### Introduction

It is an exciting time in the advancement of antiviral therapy for chronic hepatitis C (HCV) infection. Direct-acting antiviral medications now augment dual therapy with peginterferon and ribavirin (PEG/RBV) for patients with genotype 1, offering improved sustained virological response (SVR) rates and shorter treatment duration for many [1–3].

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Unfortunately, despite improved treatment efficacy, HCV-related deaths are expected to increase through 2020 if treatment is not expanded beyond its current proportion (e.g., 10–27 %) of the HCV population [4–6]. Treatment effectiveness, or the scope, reach, and impact of treatment on public health, will not be fully realized even with the use of new antiviral medications, as long as patients, many of whom have co-occurring mental health and/or substance abuse (MH/SA) issues, are left untreated [7]. With the dawn of new antiviral therapy comes the opportunity to rethink the risk–benefit ratio of treating patients with MH/SA comorbidities who have been previously deferred from antiviral therapy [8]. The purpose of this article is twofold. First, we provide empirically-based arguments to support the hypothesis that patients with MH/SA issues can and should be treated. Second, we provide evidence and suggestions to encourage HCV-treating providers (referred hereafter as “clinicians”) to create integrated or collaborative multidisciplinary approaches to facilitate treatment of HCV patients with MH/SA issues.

## Rationale for Treating HCV-Infected Patients with MH/SA Issues

A number of empirically-based arguments exist for why clinicians need to re-consider extending antiviral treatment to patients with MH/SA issues (Table 1). Unlike a decade ago, there is an overwhelming body of evidence from the empirical literature that HCV-infected patients with psychiatric and/or addiction comorbidities can safely and effectively undergo antiviral treatment, with similar rates of SVR, as long as such treatment is delivered within the context of a multidisciplinary setting. Collectively, these arguments and the evidence that supports them, provides a strong rationale for why expansion of antiviral therapy to these patients is critical and timely.

Clinicians are in a unique position to assist patients with MH/SA barriers to adequately prepare and engage in antiviral therapy; however, this cannot be a solitary endeavor. Substantial changes need to occur at the patient, clinician, healthcare, and public policy levels in order to improve access to HCV care and reduce HCV-related complications, costs, and deaths [9, 10]. Multidisciplinary team approaches that combine hepatology or infectious disease care with mental health, addictions, and other support systems will be key to assisting patients with MH/SA issues in preparing for, and successfully undergoing, antiviral treatment [11–16]. In addition to psychiatric services, which most often provides medication management for mental illness, other MH/SA professionals (e.g., psychologists, social workers, and certified addiction specialists) can be critical to optimizing MH/SA care for patients with HCV. These providers can conduct diagnostic psychological assessments, determine suicide risk and risk for drug or alcohol relapse, provide empirically-based non-pharmacological interventions for depression, anxiety and stress management, and enhance patient adherence to the HCV treatment regimen.

## Build a Multidisciplinary Team: Integrated, Collaborative, or Hybrid Model

Recent AASLD practice guidelines support the treatment of patients with co-existing MH/SA disorders, provided patients are able to adhere to safety and treatment protocol guidelines, and provided that patients have access to a multidisciplinary team approach that provides ongoing support from MH/SA services [17]. For many clinicians, the major sticking point in adhering to these guidelines is the lack of multidisciplinary treatment teams involved in traditional gastroenterology or hepatology clinics. However, the development of such teams will be essential to increasing the number of patients who can access and successfully undergo antiviral therapy. This fundamental principle was recently emphasized in the 2011 U.S. Department of Health and Human Services action plan for viral hepatitis, which endorsed team-based, multidisciplinary approaches that incorporate medical

specialties, primary care, and behavioral health to improve treatment access and success [18].

Comprehensive team approaches or “integrated models of care” are becoming the standard of care for many chronic illnesses (e.g., HIV, diabetes, and cancer), and are being adopted by primary care providers using the “Patient-Centered Medical Home” model [19]. Integrated models of care have been broadly defined as strategies or interventions “intended to improve the coordination of care and communication among caregivers, streamline protocols for movement across the care system, co-locate services, or deploy fully integrated service teams” [11]. Therefore, integrated care models can encompass everything from improving communication and collaboration between clinicians and MH/SA providers to a fully integrated multidisciplinary team, where MH/SA specialists are co-located in the same clinic [12, 20–22]. In general, multidisciplinary teams may be captured under three broad categories: (1) integrated; (2) collaborative; or (3) hybrid models. It is critical that clinicians consider the unique infrastructure, configuration, and staffing of their clinical environment to ensure feasibility and sustainability of multidisciplinary teams [11].

In a traditional integrated model, a MH/SA professional may be co-located within the treating clinic. This is ideal and convenient for staff and patients, as care can be streamlined and delivered under one umbrella. MH/SA providers can support a majority of their salary by billing for separate services (e.g., psychological evaluations and psychotherapy) on the same day that a patient sees a medical provider. Physicians may want to consider staffing a MH/SA professional, even if on a part-time basis, as they often have expertise in delivering behavioral and psychological treatments including, but not limited to, promotion of healthy lifestyles (e.g., diet and exercise) in patients with fatty liver disease [24–26], or treating psychosomatic-related symptoms in patients with irritable bowel syndrome [27–29].

Staffing a MH/SA provider within a community-based gastroenterology office may not be desirable or feasible. In these clinical settings, a collaborative care or hybrid model might be more feasible. A collaborative care approach implies no MH/SA services from within the HCV clinic, and depends on establishing a strong and ongoing working relationship with a community-based MH/SA practice(s). Alternatively, a “hybrid” model may utilize nursing or mid-level providers (e.g., psychiatric nurse practitioners and physician assistants) who have additional training in MH/SA care to provide brief MH/SA support and case management, while also collaborating with community MH/SA providers to provide more specialized care. In either integrated or collaborative/hybrid settings, patients may be more likely to overcome barriers, access treatment, initiate antiviral treatment, and have improved adherence to antiviral medication compared to those without such support [12, 30].

Finally, HCV-treating clinics that are imbedded in hospitals, academic medical centers, or Veteran Administration Medical Centers are ideally suited to form collaborative partnerships with service providers affiliated with psychiatry, psychology, social work, or substance abuse. We have found that putting forth effort to establish collaborations within the hospital, as well as with community MH/SA providers, can pay great dividends in the long run by increasing the number of patients who are maintained in the healthcare system, and who initiate and successfully undergo HCV treatment, as a result of optimizing pre-treatment preparation and close monitoring during antiviral therapy.

Integrated-hybrid care models have been shown to increase eligibility rates for antiviral therapy [12, 30]. We recently completed a randomized clinical trial to evaluate the impact of an integrated care intervention on treatment eligibility rates for patients originally deferred due to MH and/or SA issues [30]. The intervention employed case management (i.e., linkage to MH/SA services across the state) and motivational-enhancement counseling. The

intervention was delivered by a co-located psychologist on a monthly basis via telephone calls, and in person when patients attended their 3- and 6-month follow-up visits. The psychologist's role was to assist patients in following through with hepatologists' treatment recommendations and addressing MH/SA barriers to treatment (e.g., quit drinking or stabilize depression). Participants were randomized to enhanced medical care ( $n = 51$ ) or monthly intervention sessions with the psychologist ( $n = 50$ ), and all were scheduled for follow-up visits at 3, 6, and 9 months to be reevaluated by hepatology clinicians. In an intent to treat analysis, 42 % (21/50) of intervention participants were deemed eligible for antiviral therapy, compared to only 18 % (9/51) of participants who received standard care ( $p = 0.009$ ), RR = 2.38, 95 % CI (1.21, 4.68). Thus, participants who received additional follow-up calls, motivational enhancement counseling, and referral to community MH/SA services were 2.4 times more likely to address treatment barriers and become eligible, compared to patients who received enhanced medical care. We suspect that with some additional training, other staff members (e.g., nurses and mid-level providers), could easily deliver similar interventions in a hybrid multidisciplinary model. While the overall amount of data in support of fully integrated care approaches may be limited, the available evidence suggests that, at a minimum, utilizing parts of an integrated model (e.g., as noted in Table 1) may be advantageous and warrants future investigation [11, 12, 30].

There is no "one model fits all" approach to providing multidisciplinary care. For example, other successful paradigms may rely on teleconferencing with experts in MH/SA (e.g., Project ECHO) [15, 23]. The underlying commonality amongst these approaches is that the hepatology provider remains central to HCV care, while other providers help to address ongoing MH/SA comorbidities that might otherwise preclude them from undergoing HCV treatment. While we advocate the use of MH/SA experts to deliver specific interventions, the hepatology provider also plays a vital role in enhancing patient motivation to overcome MH/SA barriers and make positive lifestyle changes.

## Conclusions

The first generation of direct-acting antiviral agents, in combination with PEG/RBV for the treatment of genotype 1 HCV brings with it a hope of improved SVR rates and shorter treatment duration for many. It also brings with it a resurgence of patients with coexisting MH/SA issues who desire, and require, treatment. Simultaneously, enthusiasm for these new therapies may be dampened from a public health perspective as overall outcomes are not anticipated to change over the next 10+ years unless antiviral treatment is expanded to a greater proportion of the HCV-infected population [4].

The risk-benefit ratio has changed in favor of treating more patients with MH/SA issues, yet challenges remain to ensure safety and efficacy. To address these challenges, clinical trials are needed to examine the effects of newer antiviral treatments in patients representative of the broader HCV-infected population. Further, hepatology clinicians are in a powerful and unique position to help address these challenges, primarily by building multidisciplinary teams that can better prepare and support a greater number of patients for antiviral therapy. Clinicians are encouraged to explore and develop multidisciplinary teams that are befitting to their clinical setting, infrastructure, and staff. Like our colleagues in infectious disease or patient-centered medical homes, we urgently need a paradigm shift that supports novel health service models that have the potential to greatly increase access to, and successful treatment for, a vast number of HCV-infected individuals, traditionally deferred due to MH/SA issues, who still await a chance at this potentially life-saving therapy.

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## Abbreviations

<b>AASLD</b>	American Association for the Study of Liver Diseases
<b>HCV</b>	Chronic hepatitis C virus
<b>MH/SA</b>	Mental health/substance abuse
<b>SVR</b>	Sustained virological response

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**Table 1****Rationale for expanding HCV therapy to patients with mental health and/or substance abuse comorbidities**

<b>Argument</b>	<b>Evidence</b>
1. A large proportion of patients are deferred from antiviral therapy owing to MH/SA problems.	Evon et al. [8] Muir and Provenzale [31] Falck-Ytter et al. [32] Butt et al. [33]
2. Despite clinical challenges of treating patients with MH/SA issues, they can be treated safely and effectively, as long as properly supported by a multidisciplinary team that includes MH/SA services.	Schaefer et al. [34–37] Grebely et al. [38] Knott et al. [12] Sylvestre et al. [22, 39, 40] Matthews et al. [41] Freedman and Nathanson [42]
3. Patients with MH/SA problems can achieve similar SVR rates as patients without these comorbidities.	Zanini et al. [43] Bruggman et al. [44] Freedman and Nathanson [42] Bruggman et al. [45]
4. The newest antiviral therapy may reduce total duration of therapy to 6 months in nearly 2/3 of patients, thus reducing overall interferon exposure and related neuropsychiatric side effects.	Jacobsen et al. [1] Poordad et al. [3] Sherman et al. [2]
5. One out of every 30 “baby boomers” is infected with HCV. Over the next 20–30 years, a major liver disease epidemic is anticipated if treatment rates continue as usual.	Davis et al. [4] Deuffic-Burban et al. [6] Volk et al. [46] Volk [5]
6. Despite more “efficacious” drugs, if the majority of patients infected with HCV cannot access the new antiviral treatment, then the “effectiveness” of new therapies on the international HCV public health epidemic will be minimal.	Davis et al. [4] El-Serag et al. [7]
7. Patients who are “poor HCV treatment candidates” will likely face the same challenges to become suitable liver transplant candidates; thus, the prevention of disease progression in this aging cohort becomes paramount.	Lopez-Navas et al. [47] DiMartini et al. [48] Rocca et al. [49]
8. Individuals can experience significant HCV-related stigma, which can have a detrimental impact on psychological and social functioning. Advancing these patients towards antiviral treatment may mitigate these negative influences.	Butt et al. [50] Zacks et al. [51] Zickmund et al. [52]