

Criteria Grid
Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C

Best Practice/Intervention:	Redulla R. et al. (2013) Adherence and completion in hepatitis C management: a systematic review. <i>Gastroenterology Nursing</i> , 36(1):53-58.			
Date of Review:	March 2, 2015			
Reviewer(s):	Christine Hu			
Part A				
Category:	Basic Science <input type="checkbox"/> Clinical Science <input type="checkbox"/> Public Health/Epidemiology <input type="checkbox"/> Social Science <input type="checkbox"/> Programmatic Review <input checked="" type="checkbox"/>			
Best Practice/Intervention:	Focus: Hepatitis C <input checked="" type="checkbox"/> Hepatitis C/HIV <input type="checkbox"/> Other: _____ Level: Group <input checked="" type="checkbox"/> Individual <input type="checkbox"/> Other: _____ Target Population: _____ Setting: Health care setting/Clinic <input checked="" type="checkbox"/> Home <input type="checkbox"/> Other: _____ Country of Origin: <u>United States</u> Language: English <input checked="" type="checkbox"/> French <input type="checkbox"/> Other: _____			
Part B				
	YES	NO	N/A	COMMENTS
<i>Is the best practice/intervention a meta-analysis or primary research?</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Systematic review to summarize strategies available that support treatment adherence and completion in patients infected with hepatitis C
<i>The best practice/intervention has utilized an evidence-based approach to assess:</i>				
<i>Efficacy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Effectiveness</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>The best practice/intervention has been evaluated in more than one patient setting to assess:</i>				
<i>Efficacy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Effectiveness	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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	YES	NO	N/A	COMMENTS
<i>The best practice/intervention has been operationalized at a multi-country level:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>There is evidence of capacity building to engage individuals to accept treatment/diagnosis</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>There is evidence of outreach models and case studies to improve access and availability</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Methodology clearly stated
<i>Are the best practices/methodology/results described applicable in developed countries?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The summary of the various interventions in assisting patients to improve treatment outcome is applicable worldwide.
<i>Are the best practices/methodology/results described applicable in developing countries?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Evidence of manpower requirements is indicated in the best practice/intervention</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Juried journal reports of this treatment, intervention, or diagnostic test have occurred</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>Gastroenterology Nursing</i>
<i>International guideline or protocol has been established</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The strength and quality of the articles were individually reviewed using the "Johns Hopkins Evidence- Based Practice Standard Grading Tool"
<i>The best practice/intervention is easily accessed/available electronically</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Require subscription for access from http://journals.lww.com/
<i>Is there evidence of a cost effective analysis? If so, what does the evidence say?</i> Please go to Comments section	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>How is the best practice/intervention funded?</i> Please got to Comments section	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Study was no funded

<i>Other relevant information:</i> <hr/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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Adherence and Completion in Hepatitis C Management

A Systematic Review

ABSTRACT

The complexity and challenge of Hepatitis C virus (HCV) medication therapy call for a comprehensive and integrated approach in management. This article includes an appraisal of the current state of the science in HCV management and the various models that support treatment completion and adherence. The patient undergoing HCV therapy may experience a wide range of symptoms such as anemia, depression, fatigue, and flu-like symptoms. These can constantly confront the patient's adherence and compliance with treatment. The article includes an analysis of the strengths, weaknesses, and limitations of the evidence. Future directions in research were also identified.

Chronic Hepatitis C infection is a major health-care burden in the United States (Fraenkel, McGraw, Wongcharatrawee, & Garcia-Tsao, 2006). The Centers for Disease Control and Prevention reports show that there are 3.2 million persons who are chronically infected (Centers for Disease Control, 2011, para 1). Treatment entails a high level of commitment from the patient. There are many associated adverse effects ranging from flu-like symptoms, fatigue, and depression. Thus, there has been a huge focus on patients' health-related quality of life while on medication therapy. The duration and adverse effects

associated with treatment may lead to premature discontinuation of treatment or present problems related to compliance or adherence to treatment.

Health Problem

Several treatment regimens designed to reduce or eliminate the disease burden are approved by the Food and Drug Administration for Hepatitis C virus (HCV) infection. These regimens involve 24 to 48 weeks' duration of therapy. Antiviral therapy can reduce progression to cirrhosis, but there are many associated adverse effects that may range from neutropenia, thrombocytopenia, flu-like symptoms, fatigue, weight loss, and insomnia to psychological effects such as depression. These regimens require a tremendous degree of commitment from the patient, including frequent visits for laboratory evaluation at least monthly (and bimonthly during the first month). For some patients, weekly laboratory tests are indicated because of baseline elevations in laboratory values.

The decision to initiate HCV treatment requires the patient to make a trade-off between immediate risks of adverse effects and potential health gains from successful treatment (Schackman et al., 2008). More notably, treatment adherence (defined here as patient adherence to prescribed dosing, duration, and required follow-up) and completion can be challenging. It is found that 14%–22% of patients receiving the recommended combination therapy of pegylated interferon-alpha

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plus ribavirin discontinued treatment (Chou, Clark, & Helfand, 2004). Unfortunately, there has been a dearth of studies that specifically addressed strategies that support treatment adherence. No systematic reviews have been conducted to summarize or examine these studies.

Search Strategy

Five major databases were searched for articles relevant to the review: PubMed, CINAHL, Cochrane Library, MEDLINE, and Psychinfo. Because Hepatitis C is a relatively new phenomenon compared with the other types of hepatitis, no time frame was entered for the search. The intent was to capture as broad a search result as possible. The following MeSH terms were used: "Hepatitis C," "treatment adherence," "Hepatitis C management," "decision support," "patient education," and "clinical pathway."

Initially, there were 379 citations found. From these, 106 studies were considered to be relevant on the basis of titles, key words, and abstracts. A total of 24 studies met the inclusion and exclusion criteria. These were critically examined to comprise the review of the state of the evidence on the various models of intervention available that support treatment adherence and completion in HCV.

The strength and quality of the articles were individually reviewed using the "Johns Hopkins Evidence-Based Practice Standard Grading Tool" (Newhouse, Dearholt, Poe, Pugh, & White, 2007). The strength of the research evidence was graded as Level I (experimental study and meta-analysis of randomized controlled trials [RCTs]), Level II (quasi-experimental study), or Level III (nonexperimental study, qualitative study, or meta-synthesis) (see Supplemental Digital Content 1, available at: <http://links.lww.com/GNJ/A18>).

For nonresearch evidence appraisal such as systematic reviews and expert opinion, these were graded from Levels I to V. The quality of the evidence was rated using the following rating scale: A = high, B = good, and C = low/major flaw. Figure 1 provides the summary of ratings.

The two-step review process was conducted by one person only. The first review was done to confirm that the studies met the inclusion and exclusion criteria. A second review was done to complete individual grading of the studies according to standard quality and strength measures specified in the tool.

The inclusion criteria for the review were that an included study must (a) have at least an English version of the article; (b) include human data; (c) have information related to adult patients with HCV; and (d) deal with HCV treatment adherence and/or completion and HCV management. On the contrary, the following exclusion criteria were used: (a) studies related

to Hepatitis C not referring directly about the treatment and (b) studies related to Hepatitis C but referring exclusively to the evaluation of new therapies available for use.

Literature Synthesis and Review

Treatment Adherence

Twelve publications in the review addressed patient adherence to prescribed treatment regimen: 10 nonexperimental studies and 2 nonresearch studies. In a nonrandomized, prospective study by Tanioka et al. (2009), 189 of 363 patients (52%) achieved 80% adherence. Retreatment, location at a center with more patients treated, patient's age (<55 years), males, Genotype 2, and dosage of Interferon per weight were associated with achievement of 80% adherence to therapy. This was already considered a large sample size in comparison to the other studies in the review. However, a limitation identified is the consecutive enrollment of patients.

In another study, Weiss et al. (2008) assessed the treatment adherence of 180 patients. Seven percent of patients reported missing at least one injection of pegylated interferon in the last 4 weeks and 21% reported missing at least one dose of ribavirin in the last 7 days. A limitation of this work was that assessment of missed doses was done by self-report only. Also, it was a cross-sectional design assessing patients at a large range of weeks on treatment. Sylvestre and Zwebenc's study (2007) included 71 methadone-maintained patients, which showed 68% of them to be adherent. It was also found that adherent patients were more likely to achieve a sustained virologic response. The limitation was that the study was done in an addictive disorders setting and the patients might not be representative of traditional Hepatitis C patients.

Treatment Completion

Only five publications covered treatment completion and all were nonexperimental studies. In a study of 109 patients, treatment completion rates were 61% and 74% for genotypes 1 and 4, and 2 and 3, respectively. A limitation of this study was that of limited generalizability. The subjects, comprising methadone-maintained patients, are not representative of patients with substance abuse problems.

A large study of 307,437 veterans was conducted by Huckans, Loftis, Blackwell, Linke, and Hauser (2007), comparing completion rates among two groups (those with and without history of substance use disorders). Both groups were equally likely to complete interferon therapy. The retrospective review method of the electronic medical record was used.

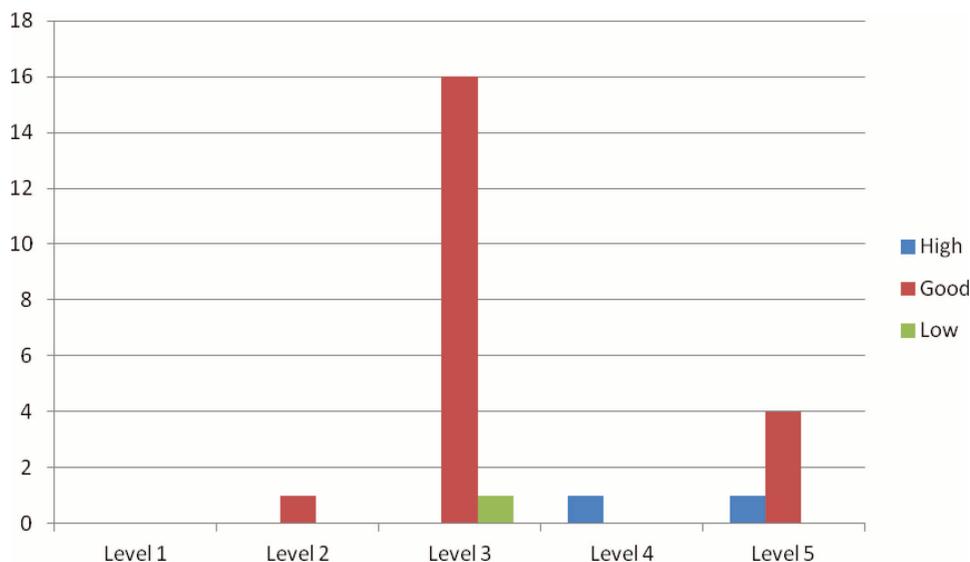


FIGURE 1. Summary of strength and quality of the evidence.

Models of Intervention in Hepatitis C Treatment

Very few studies addressed models of intervention to improve treatment adherence and completion. Notably, most of these were either qualitative design or nonresearch studies and included patients with substance abuse problems. Multidisciplinary and integrated care has been advocated in at least five studies. At least three studies recognized the importance of peer support and HCV support groups (Cormier, 2005; Mehta et al., 2008; Sylvestre & Zwebenc, 2007). One quasi-experimental study showed that attendance to a weekly support group and implementation of a multidisciplinary model of care yielded a high treatment uptake (51%). At the time of the publication, 12 of 18 patients completed the treatment. A follow-up study was done in 2010 among 204 HCV antibody-positive illicit drug users. It covered evaluation of successful HCV assessment and treatment after patients' acceptance for referral to a weekly support group. Sylvestre and Zwebenc (2007) also implemented the Organization to Achieve Solutions in Substance Abuse model, an integrated peer-based approach intervention to help facilitate successful screening and treatment among 415 drug users.

Synthesis of the Evidence

Strengths

An obvious strength of the evidence is that patient input was paramount. It is focused on their patient preferences and decisions that facilitate the translation to patient-centered interventions. In addition, the geographical sites of the studies are diverse. A majority of the studies were conducted in the United States, but

there were at least two studies in Canada, two in Australia, one in Great Britain and Belgium, four studies in Italy, one in France, and one in Israel. The recommendations in terms of supporting HCV therapy, which were advanced by the evidence, were fairly consistent throughout the review: comprehensive care strategy, case management, and peer support (Mehta et al., 2008; Sylvestre & Zwebenc, 2007); a multidisciplinary model of care (Belfiori et al., 2008; Evon et al., 2008; McLaren et al., 2008); early diagnosis and appropriate management of psychiatric adverse effects (Castera et al., 2006; Neri, Pulvirenti, & Bertino, 2006); and integration of support groups (Cormier, 2005; Grebeley, 2007).

Furthermore, two substantial systematic reviews offered important information on the management of adverse events. Hashemi, Rossi, Navarro, and Herrine (2008) concluded that if most adverse events occurring with combination therapy are anticipated and managed appropriately, there would be less incidence of premature discontinuation of therapy (evidence = grade B). Saunders and Cookman (2005) also pointed out the impact of Hepatitis C–related depression toward treatment adherence and the individual patient's quality of life (evidence = Grade A).

There was only one study that dealt with the development of a nursing service for patients with Hepatitis C. Fahey (2007) described their experience in the development and implementation of a nurse-led Hepatitis C treatment pathway in England. It was a successful innovation that follows a patient from referral for treatment to completion (evidence = Grade A). This study offered a significant contribution in the translation of the evidence using a nurse-led model.

Weaknesses

Most of the studies used nonrandomized, retrospective design. This is hugely attributed to the challenge of following patients throughout the 24- to 48-week duration of therapy. Another weakness that was noted is the inconsistent definition for and measurement of treatment adherence. In some studies, “nonadherence” refers to actual missed doses only whereas in others, it may refer to the dose reductions initiated by the clinician due to adverse effects. A literature review was done by Weiss et al. (2008), affirming this observation. However, his findings relate to the discrepancy in the use of the term “nonadherence” in the HCV and HIV literature.

Limitations

The review revealed that there are only a few RCTs conducted on Hepatitis C treatment. The majority of RCTs conducted are on the effectiveness of treatment (pegylated interferon and ribavirin). There are even fewer studies that dealt mainly with the treatment completion and adherence rates. There was one Level I study done by Neri et al. (2006), that looked into the baseline depressive symptoms of patients with chronic Hepatitis C and followed the same patients through the first 12 weeks of therapy.

There is also limited generalizability of the results. Most studies included a distinct group of subjects such as those with substance abuse problems only that does not represent the typical HCV population. The biggest sample size among the studies reviewed was 307,437 by Huckans et al. (2007) on treatment completion and virologic end-of-treatment response. However, this was limited to veterans seen in the Veterans Integrated Service Network. There were only a few studies conducted in multicenter sites.

Knowledge Gaps in the Evidence

Adherence to treatments has been linked to the improvement of treatment outcomes (Osterberg & Blaschke, 2005; Rodgers & Ruffin, 1998). Significant opportunity to address certain aspects of treatment adherence and completion remains. Evidence on treatment adherence is available but only to specific populations such as former drug users, veterans, and patients with existing psychiatric symptoms. Comparison of treatment adherence among patient subgroups and an assessment of effectiveness on the interventions implemented will need to be accomplished. Moreover, analysis of the most successful interventions that can improve treatment adherence and completion will be beneficial to clinicians. Which interventions are best to implement to specific patient subgroups and setting? What are the most common reasons for premature discontinuation of therapy?

What are indirect treatment effects that affect both treatment adherence and completion? Efforts to address these knowledge gaps should be carried out through prospective design trials composed of large sample size or multiple sites to attain reliable and valid results.

Translation of the Evidence Into Practice

Hepatitis C virus infection has become a global health burden. Its prevention and control has turned to be more exigent because of the challenge with adherence and completion of treatment. Interventions to assist the patient through every step of the treatment process have shown to improve these outcomes.

The following are key findings that will guide HCV clinicians:

1. A clear and consistent definition for treatment adherence should be established when conducting studies. Currently, wide variation exists in the definitions used. The most commonly used description appears to be the “80/80/80” rule, which is defined as greater than 80% adherence to the total number of ribavirin and interferon doses, taking greater than 80% of the required dosage of one or both drugs, for greater than 80% of the expected duration of therapy (McHutchison et al., 2002).
2. Proper patient education, peer support, multidisciplinary model of care, and comprehensive care strategy were found to be beneficial for HCV patients during treatment. Evidence-based approaches to implement these measures should be employed while combining patient preferences and values with healthcare provider input. These approaches should be constantly reexamined and revised to meet the changing needs of the HCV patient population.
3. Applicability of the various types of intervention to improve adherence and completion to specific patient subgroups and treatment settings should be sought.
4. Appropriate management of adverse effects has shown to be key in preventing premature discontinuation of therapy (Hashemi et al., 2008). Well-defined symptom management protocols will aid in meeting this goal. Nurse case managers will require up-to-date training on this area. Recent release of a new treatment protocol for Genotype 1 patients prompts more crucial consideration of adverse effects.

Future Research

The majority of the studies were done with special and mostly exclusive population groups (i.e., HCV-HIV-coinfected patients, former intravenous drug users, or a jail population); therefore, directions for future studies should include a diverse group of patients to represent the typical HCV patient population. Scope of

studies should be expanded to multisite ones or even aim at bigger geographical areas as applicable. Many of the studies reviewed were conducted in single-site centers. There were excellent qualitative studies done to elicit patients' perspectives on the treatment experience. Moving forward, efforts to apply triangulation method in research should also be considered to strengthen the validity and reliability of the results.

Summary

Appraisal of the literature has shown the role of various intervention strategies in influencing treatment adherence and completion. The challenge remains for healthcare organizations and practitioners to determine the applicability of these interventions to their patients and adopt evidence-based innovations accordingly. ✪

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