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Number 91

Interventions To Improve Patient Adherence to Hepatitis C Treatment: Comparative Effectiveness



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Interventions To Improve Patient Adherence to Hepatitis C Treatment: Comparative Effectiveness

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Interventions To Improve Patient Adherence to Hepatitis C Treatment: Comparative Effectiveness

Structured Abstract

Objectives. Patients with chronic hepatitis C often have difficulties adhering to antiviral therapy due to the complexities of treatment and the adverse events commonly experienced. This Comparative Effectiveness Review (CER) systematically assesses the comparative benefits and harms of treatment adherence interventions for adults receiving combination antiviral therapy for chronic hepatitis C.

Data sources. We searched MEDLINE[®], PubMed[®], CENTRAL, PsycInfo, Embase, and CINAHL from 2001 through June 20, 2012, as well as reference lists of relevant review articles.

Review methods. We developed the review protocol, including the analytic framework and Key Questions, with input from Key Informants and technical experts. Two investigators independently assessed titles and abstracts for eligibility against predefined inclusion/exclusion criteria. Two investigators reviewed full-text articles and independently quality-rated those meeting inclusion criteria. One reviewer abstracted data from all included studies; these data were verified by another reviewer. We summarized data qualitatively grouped by intervention type.

Results. We included 12 studies from 1,629 identified reports. These studies included six randomized controlled trials (RCTs) and six cohort studies. All the studies enrolled patients receiving combination therapy of peginterferon- α and ribavirin. The RCTs were generally of poor quality and had small sample sizes (21 to 250). While two good-quality cohort studies included relatively large numbers of patients (674 and 1,560), the remaining studies had serious methodological limitations and small sample sizes. None of the studies reported data on important health outcomes, such as liver complications, mortality, and hepatitis C virus (HCV) transmission. The interventions and patient populations for these studies differed substantially. Although quality of life appeared to improve with interventions in two studies, no statistical significance was reported. In the eight studies reporting sustained viral response (SVR), two showed a statistically significantly higher proportion of patients achieving SVR compared with usual care, and three of the other six showed a tendency toward an improvement in SVR. Four of the eight studies reporting adherence showed statistically significant improvement in adherence, and two others achieved nonsignificant improvement. Two studies reported no harms associated with the interventions.

Conclusions. Adherence interventions might improve patient adherence and viral response in patients with chronic hepatitis C. The strength of evidence from these interventions, however, is low. More adequately powered and rigorously conducted RCTs are needed to test HCV adherence interventions on intermediate and health outcomes, as well as in genotype 1 patients receiving triple therapy. Researchers must also adequately report details about the study's design and conduct, including adopting a standard definition of adherence.

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Executive Summary

Background

Hepatitis C virus (HCV) is the most common chronic blood-borne infectious disease in the United States.^{1,2} The Centers for Disease Control and Prevention estimated that 16,000 Americans were newly infected in 2009, and between 2.7 and 3.9 million community-dwelling people were living with chronic HCV infection.² The primary goal of chronic HCV detection and treatment is to prevent complications and death from HCV infection.

Response to HCV treatment is typically defined by surrogate virological measures, such as sustained viral response (SVR) and early viral response (EVR). Studies have shown that a variety of factors affect treatment response, including viral or disease-related factors; treatment-related factors, such as the dose and duration of treatment and treatment history; and patient-related factors, such as age, race/ethnicity, comorbidities, and presence of fibrosis.³⁻⁷ Genotyping is among the best ways to predict viral response to treatment and is used to determine treatment type and duration.⁸ Until early 2011, a combination of pegylated interferon-alpha (pegIFN- α) administered once-weekly by subcutaneous injection in combination with twice-daily oral ribavirin (so-called dual therapy) was the standard antiviral therapy for chronic HCV infection. Dual therapy is typically administered for 24 weeks in patients infected with HCV genotype 2 or 3 and for 48 weeks in patients with HCV genotype 1 or 4.^{8,9} In May 2011, the Food and Drug Administration (FDA) approved two protease inhibitors to treat chronic HCV infection. The 2011 American Association for the Study of Liver Diseases Practice Guideline recommends that protease inhibitors be used in combination with existing antiviral drugs (so-called triple therapy) for genotype 1 HCV-infected patients.³

Randomized evidence has demonstrated that antiviral therapies are efficacious in the treatment of chronic HCV infection.⁴ When it comes to effectiveness and quality of care, however, a number of issues, including treatment adherence, need to be addressed. Adherence to HCV treatment is challenging because of the lengthy duration, complex treatment regimen, and frequent adverse events. Adherence challenges are likely to become even more significant with the introduction of triple therapy. Several observational studies have examined the association between adherence and treatment outcomes, particularly SVR, in hepatitis C patients.¹⁰⁻¹² The existing body of literature consistently shows that increasing adherence to dual therapy is associated with improved likelihood of achieving SVR. Therefore, efforts are needed to improve treatment adherence in HCV.

Adherence, in the context of HCV treatment, includes patient adherence to both the medication regimen and the overall medical plan. *Medication* adherence is defined as the patient's use of antiviral agents according to the prescribed dose, duration, frequency, and timing. In contrast, *medical plan* adherence indicates that patients complete followup visits, laboratory tests, or other medical procedures according to the physician's directions. In this report, we refer to adherence to medication and adherence to the overall medical plan during HCV treatment as patient adherence, or "adherence" more generally.

Nonadherence to HCV treatment may be associated with a lack of management of adverse events,^{5,10} higher pill burden and lengthy treatment,¹³ limited provider experience,^{14,15} active substance use,^{5,7,16} lack of social support,^{13,17} and presence of cirrhosis.¹⁵ Interventions for improving adherence can be categorized according to the primary risk factor they target: (1) policy-level interventions, (2) system-level interventions, (3) provider-level interventions, (4) regimen- or therapy-related interventions, (5) patient-level interventions, or (6) interventions

designed to help manage adverse events. The final category may be particularly relevant to chronic hepatitis C patients receiving antiviral therapy, given the noted adverse events. These adherence interventions are often multifaceted and can be used alone or in combination.

Scope and Key Questions

We identified no systematically reviewed evidence addressing the impact of HCV treatment adherence interventions on health outcomes, intermediate outcomes, or adherence. This report assesses the comparative effectiveness of treatment adherence interventions for adults receiving antiviral therapy for chronic HCV infection. The outcomes of interest include the final health outcomes of morbidity, all-cause mortality and HCV-specific mortality, liver complications (cirrhosis, liver failure, and liver cancer), quality of life (QOL), and transmission of HCV; intermediate outcomes of sustained and early viral response, biochemical response (e.g., alanine transaminase [ALT] level), histological response, and patient adherence; and harms related to adherence interventions. Screening and treatment of HCV are addressed in separate reviews forthcoming from the Effective Health Care Program.^{18,19}

We developed our analytic framework to guide our review (Figure A). The Key Questions for this review are as follows.

Key Question 1. In adult patients with chronic HCV infection undergoing antiviral therapy, what is the comparative effectiveness of treatment adherence interventions in improving intermediate (e.g., sustained viral response, histological changes, drug resistance, relapse rates, and treatment side effects) and health outcomes (e.g., disease-specific morbidity, mortality, QOL, transmission of HCV)?

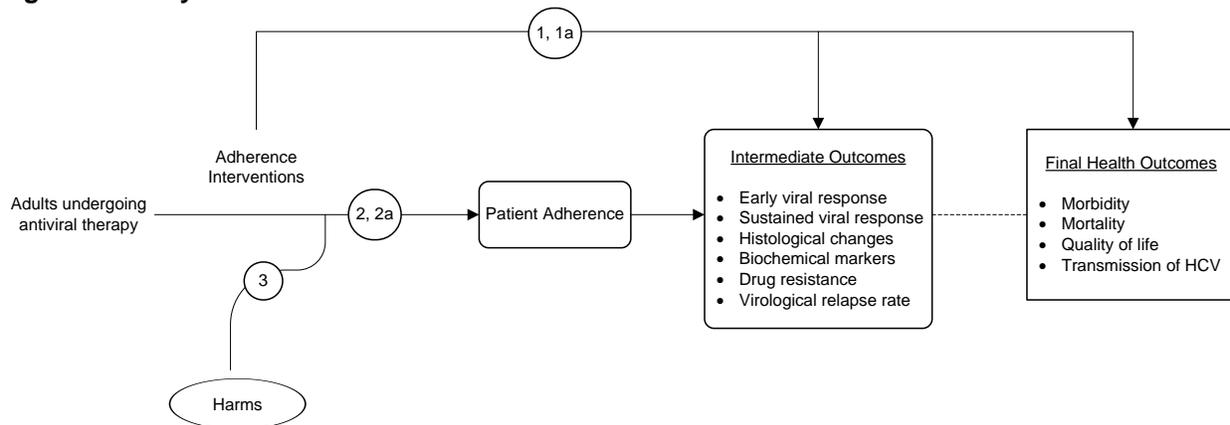
- a. Does the comparative effectiveness of treatment adherence interventions differ by patient subgroups?

Key Question 2. What is the comparative effectiveness of treatment adherence interventions in improving treatment adherence (e.g., medication adherence, medical plan adherence)?

- a. Does the comparative effectiveness of treatment adherence interventions in improving treatment adherence differ by patient subgroups?

Key Question 3. What are the harms associated with hepatitis C antiviral treatment adherence interventions?

Figure A. Analytic framework



HCV = hepatitis C virus

Note: Numbers in circles refer to Key Questions.

Methods

The Evidence-based Practice Center drafted a topic refinement document that included the proposed Key Questions. This was completed in consultation with Key Informants. The public was invited to comment on these Key Questions during a 4-week period. The Agency for Healthcare Research and Quality (AHRQ) approved the final Key Questions after reviewing the public commentary.

We drafted a study protocol and recruited a Technical Expert Panel (TEP) that included five individuals who specialized in HCV treatment, treatment adherence, and systematic review methodology. The TEP was established to ensure scientific rigor, reliability, and the methodological soundness of the research. A full draft report was reviewed by experts and posted for public commentary from July 11, 2012, through August 8, 2012. Comments received either from invited peer reviewers or through the public-comment Web site were compiled and addressed in a disposition-of-comments table.

Literature Search Strategy

A research librarian searched MEDLINE[®] (accessed via Ovid), PubMed[®], Cochrane Central Register of Controlled Trials (CENTRAL), PsycInfo, Embase, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) for relevant articles. We restricted searches to those published between January 2001 and June 20, 2012. We chose 2001 because pegIFN- α received FDA approval in 2001. We manually searched reference lists of relevant review articles and asked TEP members to share potentially relevant studies. We also searched ClinicalTrials.gov to identify any trials currently underway that may meet our inclusion criteria once the results are available. Finally, we sent a request to the manufacturer of RibaPak[®] for scientific information that might be relevant to our review.

We included a study if it met all of the following criteria:

- The study was a randomized controlled trial (RCT), a cohort study, or a case-control study published in the English language
- Adult patients were diagnosed with chronic hepatitis C and received a combination of pegIFN- α and ribavirin (dual therapy) or pegIFN- α and ribavirin plus a protease inhibitor (triple therapy) for recommended durations

- An adherence intervention was compared with usual care or another intervention
- The study reported data on any health outcomes (i.e., all-cause mortality, HCV-specific mortality, QOL, transmission of HCV, liver transplants, liver complications); intermediate outcomes (i.e., change of HCV DNA from baseline, liver function, histological response, EVR, SVR, HCV relapse rates); treatment adherence (i.e., frequency, dosage, duration, timing); or adverse events
- The study included followup at 12 weeks or later

Two members of the research team independently screened titles and abstracts for potential eligibility. We reviewed full-text articles of all potentially eligible studies according to the predetermined inclusion/exclusion criteria. We resolved disagreements through discussion.

Quality Assessment of Individual Studies

We used predefined criteria developed by the U.S. Preventive Services Task Force²⁰ and the Newcastle-Ottawa Quality Assessment Scale²¹ (specific to cohort studies) to assess the included studies' methodological quality. Two independent reviewers assigned a quality rating for each study. We resolved disagreements through discussion and consensus. We assigned a rating of "good," "fair," or "poor" to each study using predefined criteria for studies meeting inclusion criteria. For RCTs, specific areas assessed included:

- Adequate randomization, including allocation concealment and whether potential confounders were comparable among groups
- Measurements: equal, reliable, and valid
- Blinding of patients, providers, and outcome assessors
- Adequacy of followup
- Intervention fidelity and compliance with the intervention
- Appropriate analysis (i.e., intention to treat)

For cohort studies, specific areas assessed included:

- Selection of the nonexposed cohort
- Ascertainment of exposure
- Demonstration that the outcome of interest was not present at start of study
- Measurements: equal, reliable, and valid (including blinding of outcome assessment)
- Adequacy of followup of cohorts
- Adjustment for potential confounders

We used these items to evaluate the risk of bias. Generally, a good-quality study met all major criteria. It was possible to get a good rating if an item was not reported (so could not be assessed) but the remaining methods were judged to be good. A fair-quality study did not meet all criteria but was judged to have no flaws so serious that they invalidated the results. A poor-quality study contained a serious flaw in design, analysis, or execution, such as differential attrition, or some other flaw judged serious enough to cast doubt on the results' validity. All studies were included in the data synthesis and results.

Data Synthesis

We abstracted data from all included studies into a standard evidence table. One investigator abstracted the data, and a second checked these data. Discrepancies regarding data abstraction were resolved by re-review and discussion. Key information abstracted included study design; recruitment setting and approach; inclusion/exclusion criteria; demographic and health

characteristics of the sample, including baseline HCV severity; description of intervention and control arms (or exposed and nonexposed cohorts); sample retention; and outcome data (patient adherence, definition and method of adherence measurement, EVR, SVR, histological and biochemical responses, QOL, and adverse events).

We summarized all included studies in narrative form as well as in summary tables that present the important features of the study populations, design, intervention, outcomes, and results. We reported odds ratios (ORs) for dichotomous outcomes. When studies did not report effect estimates but provided sufficient raw data, we calculated ORs using an approximation method.²² We did not conduct any pooled analysis because of the significant clinical and methodological heterogeneity of studies and poor reporting of results. We conducted a qualitative analysis for all Key Questions and stratified the comparisons into four groups based on the primary intervention focus: (1) system-level interventions versus usual care, (2) regimen/therapy-related interventions versus usual care, (3) patient-level interventions versus usual care, and (4) adverse event management interventions versus usual care or placebo. We developed this classification system based on two previous systematic reviews that evaluated the effect of adherence interventions for various disease conditions.^{19,23} We discuss outcomes for each of the four groups separately.

Strength of the Body of Evidence

We graded the strength of the evidence for primary outcomes using the standard process of the Evidence-based Practice Centers outlined in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.²⁴ Specifically, we assessed the strength of evidence for QOL, morbidity/mortality, harms, intermediate outcomes of SVR and EVR, and adherence. The grade of evidence is based on four major domains: (1) risk of bias, (2) consistency, (3) directness, and (4) precision. We assigned an overall strength-of-evidence grade based on the ratings for these four individual domains for each key outcome and for each comparison of interest. The overall strength of evidence was rated using four basic grades (as described in the AHRQ Methods Guide): high, moderate, low, or insufficient.²⁴ We rated the evidence as insufficient when no studies were available for an outcome or comparison of interest, or the evidence was limited to small trials that were methodologically flawed and/or highly heterogeneous. Ratings were assigned based on our judgment of how likely it was that the evidence reflected the true effect for the major comparisons of interest.

Applicability

For each study, we reviewed the population studied, the intervention and comparator, the outcomes measured, settings (including cultural context), and timing of assessments to identify specific issues that may limit the applicability of individual studies or the body of evidence to the U.S. health care setting, as recommended in the AHRQ Methods Guide.²⁵

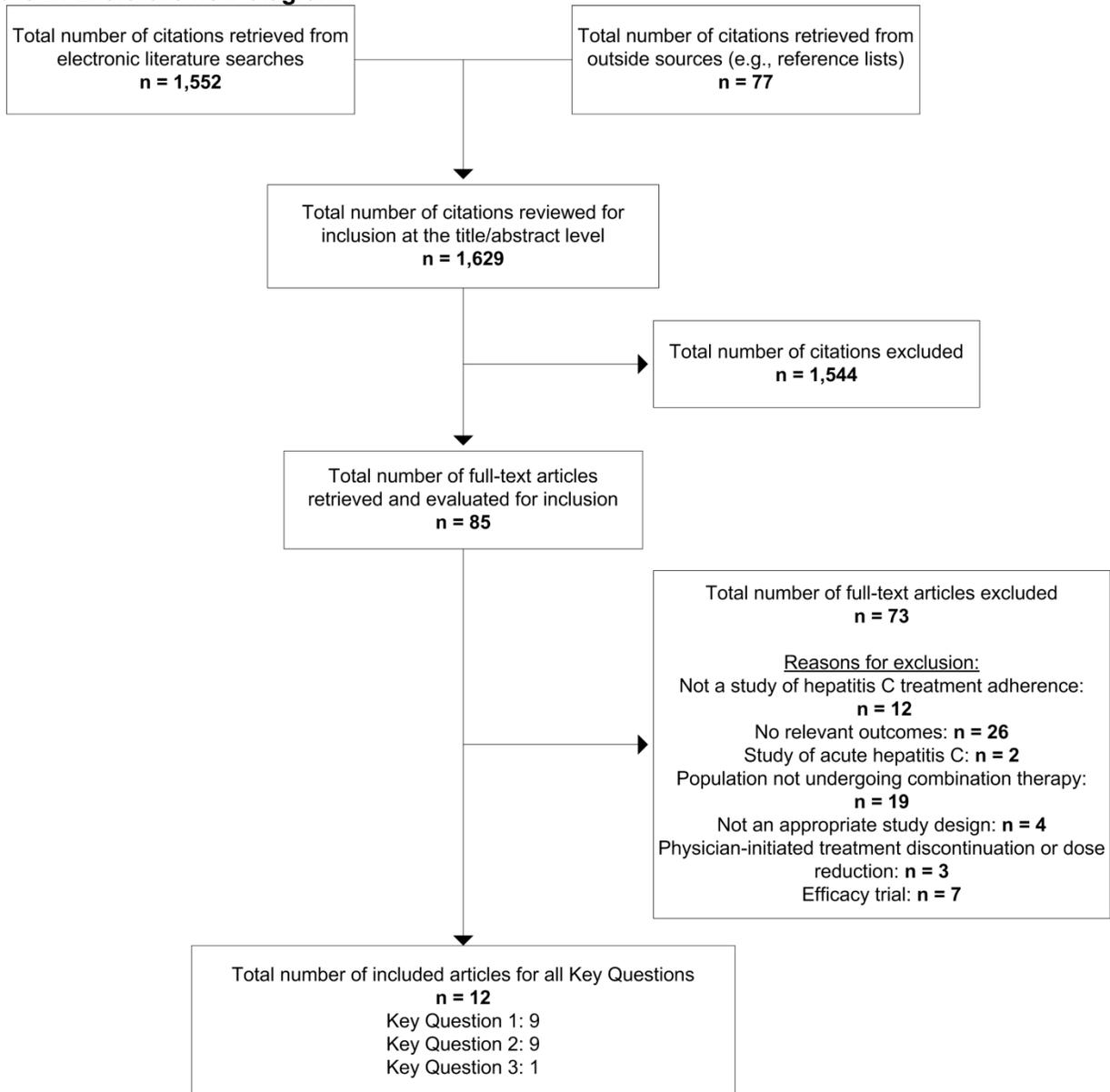
Results

Literature Search

Our search of English-language publications yielded 1,629 citations. From this body of literature, we provisionally included 85 articles for full-text review based on abstracts and titles (Figure B). After screening full-text articles against our inclusion/exclusion criteria, we excluded

73 for various reasons, such as having no relevant outcomes (k=26), including a population not undergoing combination therapy of pegIFN- α plus ribavirin (k=19), or not evaluating hepatitis C treatment adherence (k=12). While we also searched for non-English publications and identified 99 potentially relevant studies, evaluating these non-English studies was not within the scope of this review.

Figure B. Literature flow diagram



Characteristics of Included Studies

Twelve studies²⁶⁻³⁷ met the inclusion criteria for at least one of our Key Questions. Half of these studies were RCTs of fair³⁶ or poor quality.^{27,28,33,35,37} The remaining studies were cohort studies rated as good^{29,32} fair,^{26,30} or poor quality.^{31,34} Most of these studies were conducted in the United States in clinic-based settings, although two were conducted in hospital-based settings in Italy and two were multisite studies conducted in France. Six primarily poor-quality studies had

sample sizes less than 50,^{28,31,34-37} while three poor- or fair-quality studies enrolled 100 to 250 patients.^{26,27,29,30,32} Only two studies measured patient-important health outcomes,^{27,28} while the remaining studies measured intermediate disease management outcomes (e.g., EVR, SVR) and/or treatment adherence.

We included studies that evaluated a variety of adherence approaches, including one fair- and two poor-quality studies examining interventions targeting system-level factors,^{28,30,37} one fair-quality study targeting regimen- or therapy-related factors,²⁶ two good- and two poor-quality studies addressing patient-level factors,^{29,31-33} and three fair- and one poor-quality study accessing the direct management of adverse events.^{27,34-36} No studies were included that tested the effects of policy- or provider-level interventions. All of the trials except one³⁵ compared an adherence intervention with usual care. None of the studies defined what “usual care” consisted of in the study’s setting. Even though there were three to four studies comparing intervention approaches within one intervention category (e.g., system-level or adverse event management interventions), none of these within-category studies tested the same adherence interventions. Thus, the body of evidence is generally limited to single studies of different intervention types and is further limited by the noncomparability of enrolled study populations.

Study participants varied widely across studies in important ways that may impact the probability of treatment response (i.e., SVR) and/or affect treatment adherence, which were the main outcomes available from these studies. Most studies included several HCV genotypes (with varying probabilities of response to dual therapy)^{28,30,31,33-37} or did not report HCV genotypes.³² Three studies limited their study participants to a single genotype (e.g., genotype 1)^{26,27} or to genotypes 2 or 3, which are similarly responsive to treatment.²⁹ Two of the larger studies targeted those naive to treatment, who are most likely to respond to treatment,^{29,30} and many did not report this important participant characteristic.^{27,31,32,35,37} Other characteristics that may affect likelihood of treatment adherence were similarly variable across studies.

Results of Included Studies

We discuss the results of the four different types of comparisons separately: system-level interventions compared with usual care, regimen-related interventions compared with usual care, patient-level interventions compared with usual care, and adverse event management interventions compared with usual care. Studies reported highly variable outcomes. In addition, the definition each study used for adherence and the specific methods for measuring adherence varied. We did not include reports that clearly reflected discontinuation or dose reductions initiated by a physician. In terms of health outcomes, no studies reported morbidity, mortality, or HCV transmission. Only two studies^{27,28} reported QOL outcomes. Additionally, only two studies reported harms related to the adherence intervention.^{27,35} We present the results of Key Question 1 (intermediate and health outcomes) and Key Question 2 (adherence) together due to the paucity of data for all outcomes.

Key Question 1 (Intermediate and Health Outcomes) and Key Question 2 (Treatment Adherence)

Key Question 1. In adult patients with chronic HCV infection undergoing antiviral therapy, what is the comparative effectiveness of treatment adherence interventions in improving intermediate (e.g., sustained viral response, histological changes, drug resistance, relapse rates,

and treatment side effects) and health outcomes (e.g., disease-specific morbidity, mortality, QOL, transmission of HCV)?

Key Question 2. What is the comparative effectiveness of treatment adherence interventions in improving treatment adherence (e.g., medication adherence, medical plan adherence)?

System-Level Interventions Versus Usual Care

Key Points

- Three small fair- or poor-quality studies compared the effectiveness of system-level HCV treatment adherence interventions versus usual care, and none of these reported on important health outcomes (e.g., morbidity, mortality, or the transmission of HCV). (Strength of evidence = insufficient)
- One poor-quality trial evaluated how a system-level treatment adherence intervention affected health-related QOL. Hepatitis-specific limitations and distress improved over time in the intervention group, but not in the control group. Data were insufficient to draw conclusions, however, due to high risk of bias and no statistical test of group differences. (Strength of evidence = insufficient)
- Three studies examined the effectiveness of system-level treatment adherence interventions compared with usual care on SVR, adherence, or both. System-level interventions had an imprecise impact on SVR. In two studies, more methadone-maintenance patients receiving directly observed therapy (DOT) achieved SVR compared with controls, while fewer patients receiving care at a specialty pharmacy achieved SVR than those receiving usual pharmacy care. However, no results were statistically significant. Findings were further limited by moderate to high study-level risk-of-bias and the fact that we could not compare interventions across studies. (Strength of evidence = insufficient)
- One fair-quality cohort study reported no benefit of specialty pharmacy care compared with usual pharmacy care for patient self-discontinuation of treatment. (Strength of evidence = insufficient)

Three studies evaluated a system-level intervention's effect on QOL, SVR, EVR, and/or adherence compared with usual care. A fair-quality retrospective cohort study by Cohen and colleagues³⁰ included 197 patients and compared the effects of patients' use of specialty care pharmacies (n=95) with patients' use of standard retail pharmacies (n=102) on SVR and adherence. A poor-quality RCT by Bonkovsky and colleagues²⁸ randomized 48 patients who were enrolled in methadone maintenance programs for at least 3 months to receive supervised (i.e., DOT) pegIFN- α 2a (alpha 2a) at methadone clinics once weekly (n=24) compared with self-administration of pegIFN- α 2a (n=24). The other poor-quality RCT, by Bruce and colleagues,³⁷ presented preliminary data from 21 patients who were randomized to receive modified DOT of pegIFN- α 2a and ribavirin at methadone clinics once weekly (n=12) or self-administration of HCV therapy (n=9).

Quality of Life

The poor-quality RCT²⁸ was the only study that reported QOL outcomes. This study found an improvement in hepatitis-specific limitations mean score from baseline in the supervised DOT treatment group (84.2 at the end of followup vs. 74.5 at baseline), whereas these self-reported limitations became worse in the self-administered control group (mean score of 68.9 at followup

vs. 76.8 at baseline). Similarly, the mean score on self-reported health distress improved at followup in the intervention group from baseline (81.6 vs. 63.8). There was a very small change in the self-administered treatment group (67.3 vs. 69.8). The study did not report statistical tests of changes over time or of differences between groups.

Sustained Viral Response

All three studies reported the adherence intervention's effect on SVR with imprecise nondefinitive results. In the cohort study,³⁰ 48 percent (46/95) of patients using specialty pharmacies achieved SVR, compared with 56 percent (56/102) of those using a standard retail pharmacy. This difference was not statistically significant in unadjusted or adjusted analysis that accounted for age, sex, ethnicity, genotype, and prior treatment (adjusted odds ratio [OR_{adj}], 0.69; 95% confidence interval [CI], 0.37 to 1.30). One poor-quality RCT²⁸ reported a higher achievement of SVR in 54 percent (13/24) of patients enrolled in the supervised DOT treatment, compared with 33 percent (8/24) using self-administered treatment (unadjusted OR, 2.36; 95% CI, 0.73 to 7.60). Among genotype 1 patients, SVR rate did not differ between groups. However, among patients with genotypes 2 or 3, SVR was achieved in 91 percent (10/11) of patients in the DOT group as opposed to 25 percent (2/8) of patients in the self-administration group. The other RCT found that 6 out of 12 patients (50%) receiving modified DOT of pegIFN- α 2a and ribavirin versus 1 out of 9 patients (11%) randomized to the self-administered group achieved SVR, although the result was not statistically significant. Five patients in the control group did not initiate HCV treatment.³⁷

Early Viral Response

Only one poor-quality RCT³⁷ reported data on EVR. In this study, 10 out of 12 patients (83%) in the modified DOT group versus 3 out of 9 patients (33%) in the control group achieved early viral response.

Adherence

Neither RCT reported adherence data.^{28,37} The cohort study³⁰ included 10 patients in the specialty pharmacy group who self-discontinued treatment, compared with 4 in the control group (calculated OR, 0.35; 95% CI, 0.11 to 1.15). Physician-directed reasons for discontinuation of therapy included nonresponse or breakthrough.

Regimen-Related Interventions Versus Usual Care

Key Points

- No studies evaluated the effect of regimen-related interventions on health outcomes or the intermediate outcomes of SVR or EVR. (Strength of evidence = insufficient)
- A single fair-quality cohort study that compared packaging to reduce pill burden for ribavirin (RibaPak) with regular ribavirin reported the intervention effects on adherence, which the study measured three ways (duration of treatment, proportion of prescribed doses taken, and proportion taking at least 80% of prescribed doses). This study reported improved adherence in the reduced-pill-burden intervention on all three measures at 24 weeks and on two of three measures at 12 weeks. (Strength of evidence = low)

One fair-quality prospective cohort study²⁶ addressed the effect of regimen-related interventions on adherence and reported no other outcomes. The study evaluated the treatment

adherence of patients who were prescribed RibaPak, available in 400 mg and 600 mg ribavirin tablets (i.e., reduced pill burden), compared with patients prescribed 200 mg ribavirin tablets. Five hundred and three patients with genotype 1 were enrolled at a ratio of 3:1 (RibaPak vs. regular ribavirin).

Adherence

Adherence was assessed in three ways: (1) the proportion of patients remaining on treatment at each followup, (2) the proportion of prescribed doses taken among those remaining on treatment, and (3) the proportion of patients who took at least 80 percent of their prescribed dose. The proportion of prescribed doses taken was measured objectively based on pill counts at each visit. Leftover pills were counted by site personnel and were compared with the number of pills that should have been left over based on the prescribed daily dose and the number of days in the treatment period.

A greater proportion of RibaPak patients than patients taking traditional ribavirin remained on treatment at both 12 weeks (86.4% compared with 77.7%; $p=0.01$) and 24 weeks (71.4% compared with 62.4%; $p=0.045$). There was no significant difference between the groups in the mean number of doses missed at 12 weeks. At 24 weeks, there was a statistically significantly greater mean number of missed doses among the traditional ribavirin patients (1.12 missed doses) than the RibaPak patients (0.36 missed doses) ($p=0.01$). At both 12 and 24 weeks, patients using RibaPak were statistically significantly more likely to have taken at least 80 percent of their prescribed medication than those using traditional ribavirin (12 weeks: 94% vs. 84%; OR, 2.28; 95% CI, 1.54 to 3.38; 24 weeks: 98% vs. 89%; OR, 1.90; 95% CI, 1.30 to 2.78).

Patient-Level Interventions Versus Usual Care

Key Points

- No patient-level adherence intervention studies reported health outcomes. (Strength of evidence = insufficient)
- Three studies (one good-quality cohort, one poor-quality cohort, and one poor-quality RCT) comparing patient-level adherence interventions with usual care all tended toward increased proportions achieving SVR among patients receiving enhanced patient education and support, although no differences were statistically significant. (Strength of evidence = low)
- Four studies (two good-quality cohort studies, one poor-quality RCT, and one poor-quality cohort study) comparing patient-level adherence interventions with usual care all tended toward better adherence at the end of treatment among patients receiving the adherence interventions. (Strength of evidence = moderate)

Three studies^{29,31,32} compared the effect of a patient-level intervention with usual care among adults with HCV on SVR and adherence. One good-quality prospective cohort study²⁹ in France included 674 HCV patients with genotype 2 or 3. This study compared patients according to whether they received therapeutic education from a third party (health care professional other than the prescribing physician) ($n=370$) or no therapeutic education (usual care) ($n=304$). A good-quality retrospective cohort study including 1,560 patients³² used propensity scoring methods to compare the “Be in Charge” (BIC) program, a patient-support program provided by the manufacturer of pegIFN- α 2b (alpha 2b), with usual care. The BIC program was designed to improve patient adherence. Patients enrolled in the program received personalized nursing

support by telephone and/or mailed educational materials and motivational letters throughout therapy. The poor-quality RCT³³ took place in France. Two-hundred fifty patients were randomized to either therapeutic education with a nurse (n=123) or conventional clinical followup with the investigating physician (i.e., usual care) (n=121). The intervention included regular consultation with a nurse, who evaluated the patients' understanding of the disease and side effects of treatment and aimed to increase adherence. Finally, one poor-quality prospective cohort study,³¹ conducted in Italy, evaluated the Together To Take Care (TTTC) program, a multidisciplinary educational intervention in which patients who had a history of substance abuse received counseling on the risks of HCV infection and psychological support to help them modify their behavior. This study included a total of 48 patients: 16 patients in addiction therapy who received the TTTC intervention and 32 control group patients, also in addiction therapy, who were consecutively pair matched 2:1 for age, sex, and time of HCV infection at enrollment.

Sustained Viral Response

Three studies^{29,31,33} consistently showed that patients enrolled in interventions targeting patient-level factors (e.g., therapeutic education) achieved a higher level of SVR than patients receiving usual care. The difference was statistically significant in the poor-quality RCT evaluating a nurse-led therapeutic education intervention compared with usual care (38.2% vs. 24.8%; unadjusted OR, 1.88; 95% CI, 1.08 to 3.25),³³ but not in the prospective observational study of therapeutic education (77% vs. 70%; ORadj, 1.54; 95% CI, 0.99 to 2.40)²⁹ or the multidisciplinary patient-support program (68.7% vs. 45.8%; OR, 2.6; 95% CI, 0.69 to 9.81).³¹

Early Viral Response

Of the four studies included in this group, only the RCT reported data on EVR. This study reported that patients enrolled in the nurse education intervention were more likely to achieve EVR (72.8% vs. 57.6%; $p < 0.01$).³³

Adherence

All four studies consistently showed that patient-level interventions improved adherence, despite variability in study designs, study quality, adherence definitions, and analytical techniques. Patients in the intervention groups had approximately 50-percent higher odds of adhering to therapy or continuing with treatment at 24-48 weeks compared with control groups. One poor-quality study³¹ showed a statistically significant OR of 4.38 when comparing the intervention group with usual care.

Adverse Event Management Interventions Versus Usual Care/Placebo

Key Points

- There were no studies of the effects of adverse event management interventions on health outcomes besides QOL. (Strength of evidence = insufficient)
- One small fair-quality RCT found greater improvements in QOL (as measured by increased energy and activity) in dual-therapy-treated, genotype 1 HCV patients with anemia who received epoetin, an agent to reduce anemia, compared with those whose anemia was managed by a reduction in ribavirin. Patients receiving epoetin showed a significant increase in hemoglobin serum levels over the course of treatment, whereas those just receiving a reduction in ribavirin did not. Improvement in SVR was also

reported in the epoetin-treated group compared with the ribavirin-reduction group. (Strength of evidence = insufficient)

- Two studies of depression prevention (citalopram, an antidepressant) or management (antidepressants for documented symptoms) to improve adherence in dual-therapy-treated HCV patients did not provide clear evidence about the effect on SVR due to reporting or risk-of-bias limitations. The study of prophylactic citalopram found greater EVR at 12 weeks, particularly in genotype 1 patients. (Strength of evidence = insufficient)
- One study comparing prophylactic citalopram with placebo and one study comparing cognitive behavioral therapy (CBT) with usual care showed no statistical difference between groups in terms of treatment completion or adherence. The CBT intervention participants were less likely to be adherent to their pegIFN- α therapy than control participants, although the difference was not significant. (Strength of evidence = insufficient)

Four studies^{27,34-36} assessed the effect of interventions to prevent or manage adverse events (e.g., anemia, depression) related to HCV treatment on health outcomes (i.e., QOL) or intermediate outcomes (i.e., SVR, EVR, and/or adherence). The first, a fair-quality RCT,³⁶ randomized 29 HCV-treatment-naïve patients enrolled in a methadone maintenance treatment program to receive either eight 50-minute individual sessions of CBT in addition to standard HCV dual therapy or usual care. In the second, a poor-quality RCT,²⁷ 134 HCV-infected, genotype 1 patients treated with dual therapy who were experiencing a therapy-induced reduction in hemoglobin levels (i.e., anemia) were randomized to receive epoetin alpha (epoetin) (group 1, n=67) or to receive a reduction of ribavirin (800-1,000 mg/day) (group 2, n=67) for 48 weeks. The third, a poor-quality RCT,³⁵ evaluated the efficacy of taking citalopram in preventing the development of pegIFN- α -induced depression and improving treatment completion among HCV patients. Thirty-nine patients with HCV genotypes 1, 2, or 3 were randomized to receive prophylactic citalopram (20 mg tablets) (n=19) or placebo pills (n=20). The poor-quality retrospective cohort study³⁴ examined the effect of on-demand psychiatric therapy involving antidepressant use (n=25) compared with no antidepressant treatment (n=17) among patients experiencing HCV-treatment-related depression.

Quality of Life

One study²⁷ assessed the change in energy- and activity-related QOL from baseline in patients using epoetin compared with those receiving a reduction in ribavirin. At 36 weeks, improvements were apparent in both scores from baseline in group one, patients using epoetin (energy score change, 18 ± 17.3 ; activity score change, 20 ± 18.5), and in group two, patients with weight-based reduction in ribavirin (energy score change, 12.2 ± 21.6 ; activity score change, 7 ± 18.7). These changes were statistically significantly larger in the epoetin group ($p < 0.05$ for energy score and $p < 0.01$ for activity score) than the ribavirin-reduction comparison group.

Sustained Viral Response

Three studies^{27,34,35} reported SVR. Of these, one RCT³⁵ did not report sufficient data to allow calculation of effect estimates. In the comparative effectiveness trial that compared epoetin with a reduction of ribavirin dosing, patients on epoetin were statistically significantly more likely to achieve SVR (59.7% vs. 34.4%; OR, 2.83; 95% CI, 1.40 to 5.72).²⁷ While the use of

antidepressants appeared to reduce SVR when compared with usual care (36% vs. 53%; OR, 0.5; 95% CI, 0.14 to 1.75),³⁴ this result was based on a poor retrospective study.

Early Viral Response

One study³⁵ reported EVR for genotype 1 and genotypes 2/3. In both patient genotype cohorts, a higher proportion of patients on citalopram than patients receiving a placebo achieved EVR (75% vs. 44.4% in genotype 1; 85.7% vs. 81.8% in genotypes 2/3). These differences, however, were not statistically significant.

Adherence

Two studies^{35,36} reported adherence outcomes. In the study by Morasco and colleagues,³⁵ 84.2 percent of patients receiving citalopram completed their recommended course of treatment, compared with 75.0 percent of patients receiving placebo, although this difference was not statistically significant (OR, 2.13; 95% CI, 0.34 to 13.24). The reasons patients did not finish recommended treatment did not differ between the two groups and included medical factors (n=3) and noncompliance (n=1). In the RCT by Ramsey and colleagues,³⁶ 50 percent of the CBT-intervention group were considered to be adherent (i.e., received at least 24 pegIFN- α injections over the course of their therapy), compared with 80 percent of the control group. Again, this was not a statistically significant difference (ORadj, 0.19; 95% CI, 0.03 to 1.15).

Key Questions 1a and 2a. Patient Subgroups

Key Questions 1a and 2a. Does the comparative effectiveness of treatment adherence interventions differ by patient subgroups?

None of the included studies assessed whether the comparative effectiveness of adherence interventions on adherence differed by patient subgroups.

Key Question 3. Harms

Key Question 3. What are the harms associated with hepatitis C antiviral treatment adherence interventions?

Only two poor-quality RCTs^{27,35} reported information on harms related to an adherence intervention. Both studies evaluated the use of medications (i.e., epoetin and citalopram) to prevent or manage the side effects related to antiviral treatment. Although neither study found adverse events associated with the use of epoetin or citalopram, both studies were quite small and had brief study periods. In addition, the relatively small trial (n=29) comparing the effect of CBT with usual care found that more participants in the usual-care control group than in the intervention group received at least 24 pegIFN- α injections at 24 weeks (i.e., were considered adherent). This effect was also not statistically significant.

Discussion

Key Findings

We identified 12 studies—6 RCTs and 6 cohort studies—that addressed the comparative effectiveness of adherence interventions on health outcomes, intermediate outcomes, and patient

adherence in hepatitis C patients treated with the standard dual combination viral therapy. This existing body of literature, however, had substantial methodological and clinical heterogeneity.

The six included RCTs were rated as primarily poor quality, with small sample sizes (21–250). While two good-quality cohort studies^{29,32} included a relatively large number of patients (674 and 1,560), the remaining cohort studies had serious methodological limitations and generally had small sample sizes. We also found important variations in patient populations in all of the included studies, such as including patients with differing genotypes, history of substance abuse, and history of antiviral treatment. These factors may represent potentially important risk factors for treatment response and/or adherence. Patient populations also differed in racial and ethnic distribution, as well as patient comorbidities.

While studies are grouped into four general categories, studies within a single category often investigated interventions that differed in their components and intensity. The most consistent grouping was the four patient-level interventions that enhanced patient education and/or support in order to improve adherence. Despite this, we were not able to identify the most successful intervention components, given the lack of detailed descriptions, differences in intervention providers (e.g., nurses vs. physicians vs. psychologists), and differences in approaches in the various interventions.

The included studies rarely reported health outcomes, which hampered our ability to directly interpret the evidence. In addition, we were unable to pool intermediate outcomes due to differing definitions and measurement methods for adherence. Although the completion of HCV treatment is a commonly used definition, studies used different thresholds for defining treatment completion. We encountered additional issues in cross-trial comparisons for these studies, including studies that may target the completion of different antiviral agents (i.e., ribavirin vs. pegIFN- α vs. both) or fail to clarify which antiviral agents they measured.

There is a paucity of evidence assessing the effect of adherence interventions on health outcomes. Only two small poor-quality studies^{27,28} reported data on QOL. Both studies suggested a tendency toward improved QOL in the adherence intervention groups compared with usual care, despite the interventions' reflecting completely different approaches in very different patient populations.

The association of adherence interventions with viral response, particularly SVR, was the most commonly investigated outcome in the available literature. In general, adherence interventions tended to result in greater proportions of patients achieving SVR (and EVR, where reported), but few studies showed statistically significant differences between groups.

Almost all included studies measuring adherence showed that interventions tended to improve adherence, despite the varying quality, interventions, definitions, and measurements. The existing body of literature offers little information about the harms associated with adherence interventions.

Strength of Evidence

We present the strength of the evidence for *health outcomes* for all studies by intervention group in Table A. The strength of the evidence for *intermediate outcomes* for all studies by intervention group is presented in Table B. We summarize this information by outcome and intervention group in narrative below.

Health Outcomes

Overall, we found insufficient evidence to determine the effect of adherence interventions on health outcomes. No studies reported morbidity, all-cause mortality, or HCV-specific mortality. In addition, no studies reported on HCV transmission. One poor-quality RCT and one poor-quality cohort study provided evidence for QOL improvements that resulted from patient adherence interventions, but it was insufficient due to risk of bias, imprecision, and lack of a sufficient number of studies.

Two poor-quality RCTs with a high risk of bias provided insufficient evidence for harms related to adherence interventions. Both of these studies tested the effect of medications (e.g., epoetin and citalopram) to help manage side effects related to HCV treatment. Both studies reported that no patients showed adverse events related to the use of these medications but provided no additional details.

Intermediate Outcomes

The strength of evidence is insufficient to low for SVR achievement through adherence interventions that manage adverse events, provide patient education and support, or directly oversee HCV therapy in patients at high risk for nonadherence (methadone maintenance clinic patients). This rating is due to medium to high risk of bias, imprecision, and lack of sufficient numbers of comparable studies.

We also found insufficient evidence on how interventions affected EVR based on three RCTs with high risk of bias. One study presented inadequate data, which precluded determination of estimates of overall consistency and precision.

We deemed the strength of evidence to be insufficient (based on one fair- and two poor-quality RCTs) or low (based on five primarily fair- to good-quality cohort studies) for improved adherence as a result of various types of interventions. In general, the cohort studies found that adherence interventions had a consistent benefit on patient adherence.

System-Level Interventions Versus Usual Care

We found insufficient evidence regarding the impact of system-level interventions on QOL, SVR, EVR, or adherence. No evidence exists regarding mortality and morbidity.

Regimen-Related Interventions Versus Usual Care

We found insufficient evidence on the association between regimen-related interventions and patient adherence. We found no evidence about other outcomes.

Patient-Level Interventions Versus Usual Care

We judged the strength of evidence for the association between patient-level interventions and the achievement of SVR to be low. We made this valuation based on a medium risk of bias across three studies with consistent effects, despite imprecise estimates and the fact that these outcomes were indirect.

The studies provided generally consistent and precise effect estimates related to patient adherence. We judged the strength of evidence to be moderate given the relatively few studies (four) with overall medium risk of bias and the indirectness of the outcome. More research in this area may affect this estimate and our confidence in the effect estimate. Only one study

examined the effect of a patient-level intervention on EVR. As a result, we found the strength of evidence to be insufficient. There was no evidence regarding health outcomes, including harms related to patient-level adherence interventions.

Adverse Event Management Interventions Versus Usual Care/Placebo

The strength of evidence on QOL was found to be insufficient based on a relatively small poor-quality RCT. The evidence on harms was also insufficient given the high risk of bias and the lack of detail provided. Similarly, we judged the evidence on SVR, EVR, and adherence to be insufficient due to high risk of bias, the inconsistency and imprecision of the effects, and the indirectness of the outcomes. Again, no evidence addressed the effects of the intervention on mortality or morbidity.

Table A. Strength of evidence for health outcomes

Outcome	Group	Number of Studies	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence
Key Question 1: Quality of Life	All interventions vs. control	2 RCTs	High	Unknown	Direct	Imprecise	Insufficient
	System-level intervention vs. control	1	High	Unknown	Direct	Imprecise	Insufficient
	Regimen-related intervention vs. control	0	--	--	--	--	Insufficient
	Patient-related intervention vs. control	0	--	--	--	--	Insufficient
	Adverse event management intervention vs. control	1	High	Unknown	Direct	Imprecise	Insufficient
Key Question 1: Mortality and Morbidity	All interventions vs. control	0	--	--	--	--	Insufficient
	System-level intervention vs. control	0	--	--	--	--	Insufficient
	Regimen-related intervention vs. control	0	--	--	--	--	Insufficient
	Patient-related intervention vs. control	0	--	--	--	--	Insufficient
	Adverse event management intervention vs. control	0	--	--	--	--	Insufficient
Key Question 3: Harms	All interventions vs. control	2 RCTs	High	Unknown	Unknown ^a	Unknown ^a	Insufficient
	System-level intervention vs. control	0	--	--	--	--	Insufficient
	Regimen-related intervention vs. control	0	--	--	--	--	Insufficient
	Patient-related intervention vs. control	0	--	--	--	--	Insufficient
	Adverse event management intervention vs. control	2	High	Unknown ^a	Unknown ^a	Unknown ^a	Insufficient

RCT = randomized controlled trial

^aNo reported adverse events related to intervention without further detail. Thus, the consistency, directness, and precision of the outcomes are unknown.

Table B. Strength of evidence for intermediate outcomes

Outcome	Group	Number of Studies	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence
Key Question 1: SVR	All interventions vs. control	5 RCTs	High	Consistent	Indirect	Imprecise	Low
		4 Cohort	Medium	Inconsistent	Indirect	Imprecise	Insufficient
	System-level intervention vs. control	3	High	Inconsistent	Indirect	Imprecise	Insufficient
	Regimen-related intervention vs. control	0	--	--	--	--	Insufficient
	Patient-level intervention vs. control	3	Medium	Consistent	Indirect	Imprecise	Low
	Adverse event management intervention vs. control	3	High	Inconsistent	Indirect	Imprecise	Insufficient
Key Question 1: EVR	All interventions vs. control	3 RCTs	High	Unknown	Indirect	Unknown	Insufficient
	System-level intervention vs. control	1	High	Unknown	Indirect	Unknown	Insufficient
	Regimen-related intervention vs. control	0	--	--	--	--	Insufficient
	Patient-level intervention vs. control	1	High	Unknown	Indirect	Precise	Insufficient
	Adverse event management intervention vs. control	1	High	Unknown	Indirect	Unknown	Insufficient
Key Question 2: Adherence	All interventions vs. control	3 RCTs	High	Inconsistent	Indirect	Imprecise	Insufficient
		5 Cohort	Medium	Consistent	Indirect	Precise	Low
	System-level intervention vs. control	1	Medium	Unknown	Indirect	Imprecise	Insufficient
	Regimen-related intervention vs. control	1	Medium	Unknown	Indirect	Precise	Low
	Patient-level intervention vs. control	4	Medium	Consistent	Indirect	Precise	Moderate
	Adverse event management intervention vs. control	2	Medium	Inconsistent	Indirect	Imprecise	Insufficient

EVR = early viral response; RCT = randomized controlled trial; SVR = sustained viral response

Applicability

The included studies have generally good applicability to HCV patients in the United States who are receiving standard (dual) combination therapy of pegIFN- α and ribavirin. However, the available evidence is unlikely to be directly applicable to the present patients with genotype 1 HCV, which represents the preponderance of HCV infections in the United States,³⁸ who are now recommended to add protease inhibitors to the existing combination therapy. In particular, adding a third agent administered multiple times per day is likely to further impact patients' ability and likelihood of complying with treatment.

Eight of the 12 included studies were conducted in the United States. The remaining trials were conducted in France (k=2) or Italy (k=2). These studies recruited patients from various clinical settings, including primary care, specialized hepatology units, addiction management centers, and multiple clinics. Most studies had wide inclusion criteria, although a number of studies excluded those presumed to be less responsive to therapy (i.e., with coexisting infections or previous history of HCV treatment) or those at risk for poor adherence (i.e., with psychological illnesses or current or previous substance abuse).

Patients in the included studies exclusively used standard doses of combination antiviral therapy of pegIFN- α and ribavirin. The intended duration of treatment in all studies was 48 weeks for patients with genotypes 1 and 4, and 24 weeks for those with genotypes 2 and 3.

A wide variety of adherence interventions were investigated in the included studies. We found no studies that directly compared the effectiveness of one type of intervention with that of another type of intervention. Very little detail was given in the majority of the studies regarding the specific intervention components, messages, frequency, and duration. Thus, it is unclear how feasible or effective these interventions would be in real-world settings.

Research Gaps

This review illuminated substantial research gaps for all types of adherence interventions. The included studies were generally small in sample size and of suboptimal quality (e.g., failure to conceal randomization allocation in RCTs and failure to control for the influence of important confounders in observational studies). Studies need to further confirm the effects of adherence interventions on intermediate outcomes, and where possible, investigate the impact of adherence interventions on long-term health outcomes, such as decompensated cirrhosis, hepatocellular carcinoma, and mortality. While reporting these outcomes requires longer followup and may be challenging when conducting studies, the resulting information will improve the applicability of study findings to clinical practice.

The recommended treatment for genotype 1 patients has shifted from the standard combination therapy of pegIFN- α plus ribavirin to triple therapy including protease inhibitors.⁸ Therefore, the available evidence may be of limited value for the treatment of genotype 1 HCV. In particular, the administration of protease inhibitors is complex; adding this agent to the standard combination therapy further complicates treatment. Uncertainty will remain until well-designed and well-conducted studies are available that evaluate the effectiveness of adherence interventions among patients receiving the new treatment regimen.

There is also a strong need for standardizing the definitions of adherence in the context of chronic hepatitis C treatment. The definition of adherence was often ambiguous and varied significantly across studies, which made cross-study comparison difficult. In the eight studies reporting adherence data, at least five different definitions were used. Additionally,

distinguishing between true patient adherence and physician-directed dose reductions was often difficult.

We also did not identify any research that examined comprehensive intervention approaches that targeted multiple levels of influences (e.g., system- and regimen-level components). However, it is likely that the most effective interventions would include a combination of changes made to the systems and settings in which HCV care is received; the packaging and delivery of medications; and the support and education provided to HCV patients, including strategies to help patients manage side effects related to HCV treatment through pharmacological or nonpharmacological methods. Research is needed that evaluates the independent effects of policy, system, provider, regimen, patient, and adverse event management approaches, as well as strategies that target more than one of these factors.

Conclusions

Adherence interventions might improve patient adherence and virological response in patients with chronic hepatitis C, despite the substantial heterogeneity in methodological and clinical characteristics. The strength of evidence is low, however, given the medium to high risk of bias, imprecise effects estimates, and questionable consistency in effects. Little is known about the long-term health outcomes and harms of adherence interventions. More adequately powered and rigorously conducted RCTs are needed to test HCV adherence interventions on both intermediate and health outcomes. Researchers must begin adequately reporting details on their studies' design and conduct.

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Introduction

Condition Definition

Hepatitis C is an infectious liver disease caused by the hepatitis C virus (HCV). Chronic HCV infection is associated with an increased risk of liver complications, such as cirrhosis, liver failure, and hepatocellular carcinoma (HCC).¹

Prevalence and Disease Burden

HCV is the most common chronic blood-borne infectious disease in the United States.^{2,3} The Centers for Disease Control and Prevention estimated that 16,000 Americans were newly infected in 2009, and between 2.7 and 3.9 million community-dwelling persons were living with chronic HCV infection.³ When prevalence estimates specifically include individuals that are not typically part of national surveillance (i.e., those who were incarcerated, homeless, nursing home residents, hospitalized patients, on active military service, or immigrants), this number climbs to 5.2 million.² Additionally, in June 2012, the CDC recommended universal HCV screening of the “baby boomer” population (i.e., individuals born between 1945 and 1965).⁴ Such screening could result in a substantial increase in the number of individuals being infected with HCV.

The prevalence of HCV infection in men is roughly double the rate for women. The prevalence is also highest in non-Hispanic blacks, compared to all other ethnic groups. Individuals born from 1945 through 1965 are five times more likely than other American adults to be infected HCV. Age-related prevalence is highest (4.3%) among individuals who were 40 to 49 years of age from 1999 through 2002.⁵ The prevalence also increases with lower family income and education.⁶ Injection drug users are among those at greatest risk of HCV infection, with an estimated prevalence of 73.4 percent among adults in the United States with a history of injection drug use.⁷ The prevalence of HCV is also estimated to be 4 to 9 times higher among individuals with severe persistent mental illness than in the general population.⁸ In addition, nearly 10 percent of those with chronic HCV infection in the United States are co-infected with HIV. Historically, many of these high-risk groups were considered ineligible for treatment given their previous or hypothesized nonadherence to treatment.^{9,10}

Etiology and Natural History of Hepatitis C Infection

HCV is primarily transmitted through large and repeated percutaneous exposure to infected blood.¹¹ While the most common mode of HCV transmission in the United States is through the use of injection drugs, HCV can also be transmitted through needle-stick injuries and vertical transmission from an infected mother to infant. Less-common modes of transmission include sexual activities with an HCV-infected person and receipt of donated blood or blood products or organs.¹¹

Hepatitis C ribonucleic acid (RNA) can be detected in the blood within 2 weeks after the initial infection with the virus. HCV antibodies can be identified at 8 to 12 weeks after infection.¹² Acute HCV infection can cause symptoms such as jaundice, fatigue, nausea, and vomiting in 15 percent of infected cases.¹³ Fifty-five to 85 percent of patients with acute HCV infection develop chronic HCV infection.¹²

Chronic hepatitis C is defined as failure to clear the HCV within 6 months of acute viral infection.¹ Chronic HCV infection leads to progressive liver fibrosis and 10 to 15 percent of chronic HCV infected patients develop cirrhosis within 20 years.¹⁴ One to 4 percent of those with

established cirrhosis progress to HCC annually.¹ Factors associated with an increased risk of cirrhosis and HCC in those with chronic HCV include: aged 40 years or older, daily alcohol consumption of 50 grams or more, co-infection with hepatitis B virus (HBV), HIV, and male gender.¹⁵

Hepatitis C Virus Genotypes and Detection

HCV is a RNA virus¹⁶ with six major genotypes. In the United States, 75 percent or more of patients are infected with the genotype 1 virus, followed by genotypes 2 (16%) and 3 (8%).^{17,18} Genotyping is among the best predictor of viral response to treatment and is used to determine treatment duration, and more recently the specific treatment, in hepatitis C management.¹²

HCV infection can be detected through an antiHCV serological assay or one of several molecular assays designed to identify HCV RNA.¹² Third-generation serological assays (e.g., enzyme-linked immunosorbent assay [ELISA]) have a sensitivity of 97.2 percent and specificity of over 99 percent in patients with chronic liver disease when appropriately timed.¹⁹ The likelihood of false negatives, however, increases in the presence of immunosuppressive conditions such as HIV.²⁰ Molecular assays, including polymerase chain reaction (PCR) and transcription-mediated amplification (TMA) techniques, are sensitive to HCV RNA levels as low as 10 to 50 IU/mL and have a specificity of 98 to 99 percent.^{21,22} Both of these molecular assay techniques can quantitatively analyze HCV RNA and are often used to diagnose and monitor treatment response.¹²

Treatment of Chronic Hepatitis C Infection

The primary goal of chronic HCV detection and treatment is preventing complications and death from HCV infection. Treatment response is typically defined by surrogate virological measures, such as sustained viral response (SVR) and early viral response (EVR). SVR indicates long-term viral clearance and is defined as the absence of detectable HCV RNA in the serum 24 weeks following the end of therapy.¹² Early viral response is defined as a ≥ 2 log reduction in HCV RNA levels, compared to baseline HCV RNA level, or an undetectable viral load at 12 weeks of therapy. Early viral response is a strong predictor of achieving SVR.¹²

Until early 2011, the standard antiviral therapy for chronic HCV infection was a combination of pegylated interferon-alpha (pegIFN- α) ($\alpha 2a$ or $\alpha 2b$) administered once-weekly by subcutaneous injection in combination with twice-daily oral ribavirin (so-called “dual therapy”). Dual therapy is typically administered for 24 weeks in patients infected with HCV genotype 2 or 3 and is administered for 48 weeks in patients with HCV genotypes 1 or 4.^{12,23} The effects of antiviral dual therapy for HCV have been examined in a large number of randomized trials and systematic reviews, including a recent AHRQ-funded comparative effectiveness review (CER).²⁴⁻³⁰ These studies have consistently shown that the combination of pegIFN- α with ribavirin improves SVR and biochemical response. These studies have also shown this combination may improve histological response, compared to monotherapy or combination therapy with consensus interferon (interferon used before pegIFN- α became available).

In May 2011, the Food and Drug Administration (FDA) approved two novel protease inhibitors (boceprevir and telaprevir) to treat chronic HCV infection. The treatment regimen for these new agents is more complex. According to the American Association for the Study of Liver Diseases (AASLD) Practice Guideline, the protease inhibitors be used in combination with existing antiviral drugs (so-called “triple therapy”) for genotype 1 HCV-infected patients.³¹ The duration of triple therapy treatment varies depending on patient characteristics (e.g., treatment

naïve vs. previously treated; presence vs. absence of cirrhosis), type of protease inhibitor, and is contingent on achieving a satisfactory level of EVR (e.g., 4 and 12 weeks).

Studies have shown that a variety of factors affect treatment response. These factors include viral or disease-related factors, including HCV genotype and disease severity; treatment-related factors such as the dose and duration of treatment and history of prior treatment; and several patient-related factors (i.e., age, ethnicity, and the presence of comorbid conditions).^{9,30-37} HCV genotype is one of the most important factors affecting treatment response. Individuals who are infected with genotype-1 HCV, for example, are the least likely to respond to dual therapy.^{38,39} Medication and medical plan adherence also affects response to treatment in addition to viral, disease, and patient-related factors.

Fully adhering to recommended HCV treatment is particularly challenging given its demands, which include the lengthy treatment duration and the adverse events associated with treatment that are common among many patients. Adverse events include fatigue, depression, flulike symptoms, anemia, dermatologic effects, and gastrointestinal events.^{40,41,41,42} Some of these events can also be severe enough to necessitate clinician-directed dose reductions or discontinuation of treatment.

Because of this, articulating how patient adherence independently impacts treatment response is a very complex matter in HCV. This deliberation must account for differences in clinical recommendations (initially and over the course of treatment) and differences in virus-related, disease-related, and patient-related factors that impact the likelihood of treatment response. As outlined in Table 1, separating the variables that are associated with a lower likelihood of treatment response (as measured by SVR) from those associated with a lower likelihood of patient adherence is conceptually very important. Understanding the different roles these “risk factors” play in treatment response is critical for interpreting the role of confounding in studies of patient adherence interventions (since outcomes are generally measured by SVR), the comparability of study findings, and the applicability to the United States health care setting. Risk factors related to response to treatment and patient nonadherence are discussed below.

Table 1. Variables that may affect viral response and adherence to treatment

	Variable	Response to Treatment (SVR)	Patient Adherence to Treatment
Viral-related	Genotype	↓ with genotype 1 ³⁰	Not a major factor
	Pretreatment Viral Load	↓ with higher viral load	Not a major factor
	Genetic variations	IL28B gene ⁴³	No data suggesting association
Treatment-related	History of Prior Treatment	↓ with prior treatment vs. treatment naïve ³² ↓ with nonresponders vs. relapsers for retreatment	Mixed
	Treatment burden and adverse events management	Not a major factor	↑ with adverse events management ^{9,44} ↓ with higher pill burden and length of treatment ⁴⁵
	Provider Experience & type of facility (high vs. low volume)	Not a major factor	↑ with high volume site and/or provider experience ^{32,46}

Table 1. Variables that may affect viral response and adherence to treatment (continued)

	Variable	Response to Treatment (SVR)	Patient Adherence to Treatment
Patient-related	Demographics	↓with older age and male ³⁰ ↓in African American ^{30,33} ↓in Hispanic ^{33,34}	Not a major factor* ^{34,46}
	Mental Health	Not a major factor ^{9,35}	↓with treatment-related depression when not managed ⁹ Not a major factor when patients receive mental health treatment ^{9,35,47,48}
	Substance Abuse	Not a major factor as long as patients adhere to treatment ^{9,36}	↓with active substance abuse ^{9,36,49} Not a major factor in patients in substance treatment or abstaining ^{48,50-52}
	Comorbid Medical Conditions	↓ with medical comorbidities ^{30,37,53}	Not a major factor† ⁴⁶
	Disease Stage	↓with fibrosis/cirrhosis ³⁰	↓with cirrhosis‡ ⁴⁶
	Socioeconomic status/ social supports	No data suggesting association ⁵⁴	Mixed ^{45,54,55}

SVR = sustained viral response; vs. = versus

*African-Americans may have decreased adherence vs. Caucasians³³.

†Coinfected HIV/HCV in some studies shows higher patient adherence;⁴⁹ however, treating both HIV and HCV at once is associated with an increase in adverse events and a need for clinician-directed reduction in treatment dosages or discontinuation of treatment, especially in women.

‡May be clinician-directed for adverse events of treatment.

Adherence in the Context of Chronic Hepatitis C Treatment

In the medical literature, the terms adherence, compliance, and concordance all generally refer to the extent to which individuals follow their providers' recommended treatment advice.^{45,55-58} Patients often have difficulties adhering to medication regimens, particularly those with chronic diseases. Even within the context of clinical trials, where patients may be closely monitored, adherence rates may average only between 43 to 78 percent.⁵⁹

Adherence to therapy may be particularly challenging for patients undergoing antiviral therapy for Hepatitis C. Adherence, in the context of HCV treatment, includes patient adherence to both the medication regimen and the overall medical plan. *Medication* adherence is defined as the patient's use of antiviral agents according to the prescribed dose, duration, frequency, and timing. In contrast, *medical plan* adherence indicates that patients complete followup visits, laboratory tests, or other medical procedures according to the physician's directions. In this report, we refer to adherence to medication and adherence to the overall medical plan during HCV treatment as patient adherence, or "adherence" more generally.

Adverse events of hepatitis C antiviral therapy may lead physicians to initiate dose reductions or treatment discontinuation.¹² This can complicate the distinctions between patient-led nonadherence that would be amenable to improvement and appropriate clinical care that can result in poorer treatment responses. The most common cause of physician-led treatment change is the presence of laboratory abnormalities (e.g., anemia), for which patients usually do not experience symptoms.¹² Physicians may also advise patients who do not exhibit early viral response to stop therapy.¹² As such, physician-led dose reductions and treatment discontinuation should not be viewed as treatment nonadherence because they do not reflect patient deviation

from an agreed treatment recommendation. Unfortunately, many studies fail to report data on physician-led dose reduction or treatment discontinuation separately from patient-directed treatment reduction or discontinuation.^{45,60,61} Thus, in the HCV literature the reported “adherence” data commonly reflect a mixture of actual patient nonadherence (e.g., missed doses by active decision or simply forgetting) and physician-directed dose reductions or treatment discontinuation data.

Using complex combination drug regimens (dual or triple therapies), with varying lengths of treatment that depend on viral genotype (48 weeks for genotype 1 and 4, and 24 weeks for genotype 2 and 3) also complicates the issue. Measuring adherence to HCV treatment requires considering multiple components, including the type of agents (i.e., pegIFN, ribavirin, and protease inhibitors) and the treatment duration by genotype (24 vs. 48 weeks).

With no current standard for measuring hepatitis C treatment adherence, various adherence measures have been used in the hepatitis C literature. While some studies define adherence as a patient taking 80 percent or more of the total prescribed dose, other studies define patients as adherent if they comply with treatment for 80 percent or more of the prescribed duration.^{39,62,63} Other studies, however, do not use a prespecified threshold.^{64,65} The most commonly used measure of adherence in the HCV literature is the “80/80/80” rule, which is defined as greater than 80 percent adherence to the total number of ribavirin and interferon doses, greater than 80 percent of required dosage of one or both drugs, for greater than 80 percent of the expected duration of therapy.³⁹

Several methods are available to collect hepatitis C treatment adherence data, including DOT, patient self-report, electronic monitoring (e.g. Medication Event Monitoring Systems [MEMS] technology such as MEMS caps[®]), pharmacy refill data, subject diaries, and pill counts.⁴⁵ The strengths and limitations of these methods have been detailed elsewhere.^{45,59}

Risk Factors for Nonadherence to Antiviral Treatment

Understanding the factors that increase a patient’s risk of nonadherence to HCV treatment is a crucial first step in evaluating the success of adherence interventions. Known risk factors for nonadherence to HCV treatment include active substance abuse, nonmanaged treatment related depression, a lack of social support, the patient’s current or previous treatment experience and disease status, provider inexperience or receiving care at a low-volume facility, and poor symptom or side effect management (Table 1).^{32,46,59,66,67} Physicians commonly exclude patients with suspected risk factors for nonadherence from treatment because of the concerns about the emergence of resistant viral strains and possible decreased treatment response, although the appropriateness of this practice has been debated.^{10,45}

A large, retrospective cohort study investigated the risk factors for nonadherence to HCV treatment in a population of genotype 1 HCV infected Veterans Affairs’ patients (n=11,019).⁴⁶ In patients who achieved EVR, the investigators found that cirrhosis, a history of substance abuse, anemia, and a lack of hematopoietic growth factor use were all statistically significant, independent risk factors for early treatment discontinuation prior to completing 12 weeks of treatment. This study also found that lack of growth factor use was a statistically significant risk factor for patient nonadherence during 12 to 24 weeks of treatment, along with depression.⁴⁶ Likewise, separate studies have found that a patient’s treatment history played a significant role in early discontinuation of treatment, with those naïve to treatment being found to have an increased risk of nonadherence.^{32,68}

Association of Adherence With Sustained Viral Response

Studies have shown that fully completing a recommended treatment course improves treatment outcomes in both infectious and chronic diseases.^{59,69-71} As such, clinicians and patients rightly seek to know what is the minimal level of adherence associated with improved treatment response. While some studies have considered this issue for chronic HCV, no study has provided a definitive answer. Several studies have examined the association between adherence and SVR;^{44,72-76} however, it is difficult to quantify this association, in part due to heterogeneous measurement approaches. Definitions of adherence measures, for example, vary across these studies in ways that could impact SVR. One study measured adherence using the commonly cited “80/80/80” rule,⁷² while another study less-stringently defined patients as adherent if they completed 80 percent or more of planned duration.⁷³ A third study identified patients as adherent if they completed the full treatment duration,⁷⁴ while another study defined adherence as completion of 80 percent of recommended dose of pegIFN and 80 percent of the intended duration of ribavirin.⁷⁶ Two other studies^{44,75} did not specify a predefined threshold. Rather, they divided patients according to multiple strata of adherence ($\leq 40\%$, 41-50%, 51-60%, 61-70%, 61-80, 81-90%, 91-100% of treatment completion). The fact that none of the studies examining the relationship between adherence and SVR clearly differentiated between patient- and provider-directed dose reduction or treatment discontinuation further complicates this issue. In two studies,^{73,74} patients categorized as “nonadherent” likely included those who were directed by their physicians to discontinue treatment.

In analyzing the association between adherence and SVR, three studies^{72,74,75} conducted unadjusted analyses, while three others^{38,44,73,76} conducted multivariable regression analyses to control for the influence of other factors. These factors included: baseline viral load, age, body mass index (BMI), genotype, presence of fibrosis, treatment duration, ribavirin dose, and/or race.^{44,73,76} In the two studies that performed unadjusted analyses,^{74,75} more than half of patients with good adherence ($\geq 80\%$) achieved SVR, compared to approximately 10 percent of patients with poor adherence ($< 60\%$). Four studies performing adjusted analyses also found a relationship between higher levels of adherence and a higher probability of patients achieving SVR, but with inconsistent levels of association between SVR and adherence.^{38,44,73,76}

Despite limitations related to measurement and potential confounding, the existing body of literature consistently shows that achieving an increased level of adherence to dual therapy is associated with improved likelihood of SVR. In one study of treatment naïve Asian American HCV patients, the association between adherence and SVR was similar in both unadjusted and adjusted analyses (inclusive of sex, age, BMI, viral load, and genotype) (unadjusted odds ratio [OR] 3.73 vs. adjusted odds ratio [ORadj] 3.49), which suggests that these other factors may not influence this association.⁷⁶ Another study reporting the adjusted association of SVR with different levels of adherence ($\leq 40\%$, 41-50%, 51-60%, 61-70%, 61-80, 81-90%, 91-100%) found that higher adherence levels were associated with improved SVR (trend test $p=0.005$). This result implies that the association may be continuous.⁴⁴ This study also demonstrated that patients with similar levels of adherence with genotype 2 or 3 consistently achieved higher SVR, compared to patients with genotype 1 or genotype 4. This suggests that genotype may be an important modifier of the association between adherence and SVR; thus, it would be prudent to explore the association separately in patients with genotype 1 or 4 and 2 or 3.

Interventions for Improving Adherence

Adherence interventions can be categorized according to the primary risk factor targeted: (1) policy-level interventions, (2) system-level interventions, (3) provider-level intervention, (4) regimen- or therapy-related interventions, (5) patient-level interventions, or (6) interventions designed to help manage adverse events (Table 2). This final category may be particularly relevant to chronic hepatitis C patients receiving antiviral therapy, given the noted treatment side effects. These adherence interventions are often multi-faceted and can be used alone or in combination.

Table 2. Types of interventions for improving patient adherence

Type of Intervention	Examples
Policy-level interventions	Decreasing insurance copay and refill practices Change in prescription formularies
System-level interventions	Increasing convenience of care (e.g., provision at worksite or home) Care coordination Programmed reminder systems Appointment and prescription refill reminders DOTS Augmented pharmacy services
Provider-level interventions	Training regarding communication style and enhancing shared decision-making Training on the use of motivational enhancement techniques
Regimen/Therapy-related interventions	Simplified dosing Dose-dispensing units of medication and medication charts Different medication formulations (e.g., tablet vs. syrup)
Patient-level interventions	Education/instruction for patients (e.g., verbal, written materials) Counseling (about disease, importance of therapy and compliance, empowerment, etc.) Automated telephone, computer-assisted patient monitoring and counseling Special 'reminder' pill packaging Family interventions Self-monitoring Reinforcement or rewards for adherence Lay health mentoring
Adverse event management interventions	Psychological therapy (e.g., CBT) Medications to manage side effects

CBT = cognitive behavioral therapy; DOTS = direct observation treatments; vs. = versus

Interventions designed to increase patient adherence to chronic HCV treatment can include one or more specific components, such as: detailed instructions to patients (e.g., written instructions), increased communication and counseling (e.g., telephone followup, regular counseling programs, medication use training), increasing convenience of medication use (e.g., simplifying drug dosing, tailoring the treatments to daily habits), reminder systems (e.g., devices such as MEMS caps, appointment schedules, medication charts), and reinforcement or incentives for maintaining compliance with treatment (e.g., simplifying clinic visits).^{58,77-82} These interventions can be delivered and/or implemented by various professionals including clinicians, pharmacists, case managers, psychologists, or insurance or other policy makers in the case of policy- or system-level interventions or can be managed by multidisciplinary teams.

Scope and Purpose

No systematically reviewed evidence addresses the impact of HCV treatment-adherence interventions on health outcomes, intermediate outcomes, or adherence itself. A previous

systematic review on screening for hepatitis C completed in 2004 for the U.S. Preventative Services Task Force (USPSTF) included only a limited discussion on treatment adherence and found that 14 to 22 percent of patients receiving the recommended combination therapy of pegIFN- α plus ribavirin discontinued treatment.⁶⁷ Another review descriptively summarized previous studies addressing treatment adherence for HCV antiviral therapy.⁴⁵ Of the nine published guidelines for HCV management, including the AASLD practice guideline, only one discussed treatment adherence, and this discussion was very brief.⁸³

We assessed the comparative effectiveness of treatment adherence interventions for adults receiving standard combination antiviral therapy for chronic HCV infection in this review. The outcomes of interest include all-cause mortality and HCV-specific mortality, liver complications (cirrhosis, liver failure, and liver cancer), quality of life (QOL), transmission of HCV, sustained and early viral response, biochemical response (e.g., alanine transaminase [ALT] level), histological response, and patient adherence.

Key Questions

This report addresses three systematically reviewed key questions that consider the impact of adherence interventions on health outcomes, intermediate outcomes including adherence, and harms related to adherence interventions in the treatment of chronic HCV.

Key Question 1. In adult patients with chronic HCV infection undergoing antiviral therapy, what is the comparative effectiveness of treatment adherence interventions in improving intermediate (e.g., sustained viral response, histological changes, drug resistance, relapse rates, and treatment side effects) and health outcomes (e.g., disease-specific morbidity, mortality, QOL, transmission of HCV)?

- a. Does the comparative effectiveness of treatment adherence interventions differ by patient subgroups?

Key Question 2. What is the comparative effectiveness of treatment adherence interventions in improving treatment adherence (e.g., medication adherence; medical plan adherence)?

- a. Does the comparative effectiveness of treatment adherence interventions in improving treatment adherence differ by patient subgroups?

Key Question 3. What are the harms associated with hepatitis C antiviral treatment adherence interventions?

Methods

The Agency for Healthcare Research and Quality (AHRQ) requested a CER on the effectiveness of Hepatitis C treatment adherence interventions as a part of its Effective Health Care (EHC) Program. The Evidence-based Practice Center (EPC) established a team and a protocol to develop this evidence report.

Topic Development and Refinement

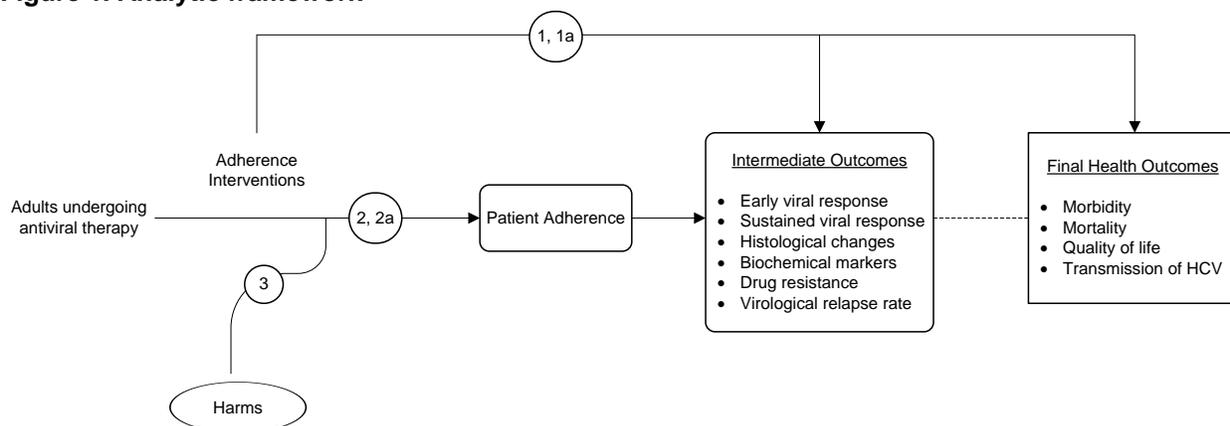
The topic for this report was nominated through a public process. The Scientific Resource Center (SRC) for the AHRQ EHC Program compiled information about this topic to evaluate its priority for CER. EHC Program staff evaluated and discussed this information and it was approved for a full review.

The Oregon EPC drafted a topic refinement document with proposed Key Questions after consulting with five Key Informants. Key Informants included representatives from Hepatitis C patient advocacy groups, gastroenterologists, and infectious disease experts. Key Questions were posted on AHRQ's Web site for public comment in July 2011 for four weeks, and were revised as needed. We then drafted a protocol for the CER and recruited a Technical Expert Panel (TEP) to provide high-level content and methodological expertise throughout the review. The TEP comprised five individuals who specialized in Hepatitis C treatment, treatment adherence, and systematic review methodology. The TEP was established to ensure scientific rigor, reliability, and the methodological soundness of the research. The TEP commented on the review protocol and offered advice on the review process. The final review protocol can be found on AHRQ's EHC Program Web site: http://www.effectivehealthcare.ahrq.gov/ehc/products/326/839/HepatitisC-Adherence_Protocol-amended_20120522.pdf.

Analytic Framework

The analytic framework for evaluating the comparative effectiveness of Hepatitis C treatment adherence interventions is shown in Figure 1. In general, the figure illustrates how Hepatitis C treatment adherence interventions may affect adherence, intermediate outcomes (e.g., early viral response, sustained viral response, drug resistance), and/or ultimate health outcomes (e.g., morbidity, mortality, and QOL). Figure 1 also depicts the possibility of adverse events or harms occurring after exposure to an adherence intervention. We did not systematically review the association between intermediate outcomes and final health outcomes.

Figure 1. Analytic framework



HCV = hepatitis C virus

Note: Numbers in circles refer to Key Questions.

Literature Search Strategy

A research librarian performed comprehensive literature searches in the following databases:

- MEDLINE[®] accessed via Ovid
- PubMed[®]
- Cochrane Central Register of Controlled Trials (CENTRAL)
- PsycInfo
- EMBASE
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)

Appendix A outlines our search strategy for each database. We used these searches to locate relevant studies for all three Key Questions. We restricted searches to the time period of January 2001 to June 20, 2012. We chose 2001 because pegIFN- α received FDA approval in 2001. We supplemented searches of these databases with manual searching of reference lists of relevant review articles and suggestions made by TEP members. We also conducted an ancillary search of the non-English language literature to identify the volume of publications that would have been reviewed if we included non-English-language studies. We also searched ClinicalTrials.gov to identify any trials currently underway that may meet our inclusion criteria once the results are available (Appendix B). Finally, we sent a request to the manufacturer of RibaPak[®] for scientific information that might be relevant to our review.

We downloaded and imported our search results in version 12.0.3 of Reference Manager[®] (Thomson Reuters, New York, NY), a bibliographic management database. We manually removed duplicates. We used Reference Manager to track search results at the levels of title/abstract review and article inclusion/exclusion.

Process for Study Selection

We used a two-step process for study selection. First, two members of the research team independently reviewed each title and abstract (if available) to determine if an article met the broad inclusion/exclusion criteria for study design, population, and intervention (Table 3). We coded each title/abstract as: potentially included, excluded, or background. Next, we retrieved full-text articles for all potentially included studies, including those that were questionable or unclear at the abstract stage. Two reviewers independently assessed each full-text article using a

standard form that detailed the predetermined inclusion and exclusion criteria. We resolved disagreements through discussion.

Table 3. Inclusion and exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Population	Adults undergoing combination HCV antiviral therapy with pegIFN- α 2a or 2b and ribavirin, or Combination therapy with pegIFN, ribavirin, and HCV protease inhibitors	Adults undergoing: HCV monotherapy Long-term HCV maintenance therapy (longer than 52 weeks) Children (<18 years) Patients for whom HCV treatment is contraindicated: Pregnant women Patients with renal failure Hemodialysis patients Transplant recipients
Interventions	Treatment adherence interventions	
Comparator	Other treatment adherence interventions or usual care	
Outcomes	Key Question 1: All-cause mortality HCV-specific mortality QOL Transmission of HCV Liver transplants Liver complications (cirrhosis, liver failure, liver cancer) Change of HCV RNA from baseline Liver function (i.e., change in ALT level from baseline) Histological response (i.e., reduction in fibrosis) Early viral response Sustained viral response HCV relapse rates Key Question 2: Frequency Dosage Treatment length (duration) Timing Key Question 3: Adverse events	Costs
Time period	2001 to present	Studies prior to 2001
Setting	All settings	Not applicable
Study geography	All locations	Not applicable
Publication language	English	All other languages
Study design	RCT of any design (i.e. parallel, cross-over, factorial, cluster) Controlled clinical trial Prospective cohort study Retrospective cohort study Case-control study	Single case studies Cross-sectional studies Case series
Minimum followup	KQ 1–2: 12 weeks postbaseline KQ3: any	
Study quality	Any	

ALT = alanine transaminase; HCV = hepatitis C virus; KQ = Key Question; pegIFN = pegylated interferon; pegIFN- α = pegylated interferon alpha; QOL = quality of life; RCT = randomized controlled trial; RNA = ribonucleic acid; vs. = versus

Data Abstraction and Data Management

We abstracted data from all included studies into a standard evidence table. One investigator abstracted the data and a second checked these data. Discrepancies regarding data abstraction were resolved by rereview, discussion, and comments from others. We collected the following information for each study, where available: author identification; year of publication; study location; study design; recruitment setting and approach; inclusion/exclusion criteria; demographic and health characteristics of the sample including baseline HCV severity (as defined by the individual study [e.g. fibrosis stage, baseline viral load]); description of intervention and control arms (or exposed and nonexposed cohorts); and sample retention. We abstracted the following outcomes: patient adherence, definition and method of adherence measurement, health outcomes (EVR, SVR, histological and biochemical responses), QOL, and adverse events.

Individual Study Quality Assessment

We used predefined criteria developed by the USPSTF⁸⁴ and the Newcastle-Ottawa Quality Assessment Scale⁸⁵ (specific to cohort studies) to assess the internal validity of included studies. Two independent reviewers assigned a quality rating of the internal validity for each study. Disagreements were resolved by discussion and consensus. We assigned a rating of “good,” “fair,” or “poor” to each study using predefined criteria for studies meeting inclusion criteria. For randomized controlled trials (RCTs), specific areas assessed included:

- Adequate randomization, including allocation concealment and whether potential confounders were comparable among groups
- Measurements: equal, reliable, and valid
- Blinding of patients, providers, and outcome assessors
- Adequacy of followup
- Intervention fidelity and compliance with the intervention
- Appropriate analysis (e.g., intention-to-treat)

For cohort studies, specific areas assessed included:

- Selection of the nonexposed cohort
- Ascertainment of exposure
- Demonstration that the outcome of interest was not present at start of study
- Measurements: equal, reliable, and valid (including blinding of outcome assessment)
- Adequacy of followup of cohorts
- Matching or adjustment for potential confounders

We used these items to evaluate the internal validity. Generally, a good-quality study met all major criteria, although it was possible to get a “good” rating if an item was not reported (so could not be assessed) if the remaining methods were judged to be “good.” A fair-quality study did not meet all criteria, but was judged to have no flaws so serious that they invalidated the results. A poor-quality study contained a serious flaw in design, analysis, or execution, such as differential attrition, or some other flaw judged serious enough to cast doubt on the results’ validity. Examples of serious flaws include: very large baseline group differences that were not or could not be adjusted for in the analysis, no information about followup, or insufficient information provided so we could not judge the risk of bias.

Data Synthesis

We summarized all included studies in narrative form as well as in summary tables that present the important features of the study populations, design, intervention, outcomes, and results. We reported odds ratios (ORs) for dichotomous outcomes. When studies did not report effect estimates, but did provide sufficient raw data, we calculated ORs using an approximation method.⁸⁶ Because of the significant clinical and methodological heterogeneity of studies, and poor reporting of results, we did not conduct any pooled analysis. We conducted a qualitative analysis for all Key Questions and stratified the comparisons into four groups based on the primary intervention focus: (1) system-level interventions versus usual care, (2) regimen/therapy-related interventions versus usual care, (3) patient-level interventions versus usual care, and (4) adverse event management interventions versus usual care or placebo. We developed this classification system based on two previous systematic reviews that evaluated the effect of adherence interventions for various disease conditions.^{57,87} There was no literature included that addressed policy-level interventions. We discuss outcomes for each of the four groups separately.

Grading the Strength of Evidence

We graded the strength of the evidence for all outcomes using the standard process of the Evidence-based Practice Centers outlined in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.⁸⁸ Specifically, we assessed the strength of evidence for the subset of major outcomes that are most meaningful for each of the Key Questions. These outcomes included the final health outcomes of QOL, morbidity/mortality, and harms and intermediate outcomes of SVR and EVR, and adherence. The grade of evidence is based on four major domains: (1) risk of bias (low, medium, high), (2) consistency (no inconsistency present, inconsistency present, unknown or not applicable), (3) directness (direct, indirect), and (4) precision (precise, imprecise). The risk of bias domain reflects the degree to which the included studies for a given outcome or comparison were very likely to be adequately protected from the impact of bias in their reported estimates of effect. Low risk of bias suggests a high likelihood that bias is not a major factor. We evaluated risk of bias considering both study design and aggregate quality of the studies. Consistency refers to the degree to which reported effect sizes from included studies appear to have the same direction and magnitude of effect. When only a single study was included, consistency could not be judged. Directness relates to whether the evidence links the interventions directly to health outcomes. Precision refers to the degree of certainty surrounding an effect estimate with respect to a given outcome. We assigned an overall strength of evidence grade based on the ratings for these four individual domains for each key outcome and for each comparison of interest. The overall strength of evidence was rated using four basic grades (as described in the AHRQ Methods Guide): high, moderate, low, or insufficient (Table 4).⁸⁸ We rated the evidence as insufficient when no studies were available for an outcome or comparison of interest or the evidence was limited to small trials that are methodologically flawed and/or highly heterogeneous. Ratings were assigned based on our judgment of the likelihood that the evidence reflected the true effect for the major comparisons of interest.

Table 4. Strength of evidence grades and definitions

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence is unavailable or does not permit a conclusion.

Applicability

To assess applicability, we used data abstracted on the population studied, the intervention and comparator, the outcomes measured, settings (including cultural context), and timing of assessments to identify specific issues that may limit the applicability of individual studies or the body of evidence to the U.S. health care settings, as recommended in the AHRQ Methods Guide.⁸⁹ We used these data to evaluate applicability, paying particular attention to study eligibility criteria, inclusion/exclusion criteria, baseline demographic factors, and the intervention characteristics (e.g., setting).

Review Process

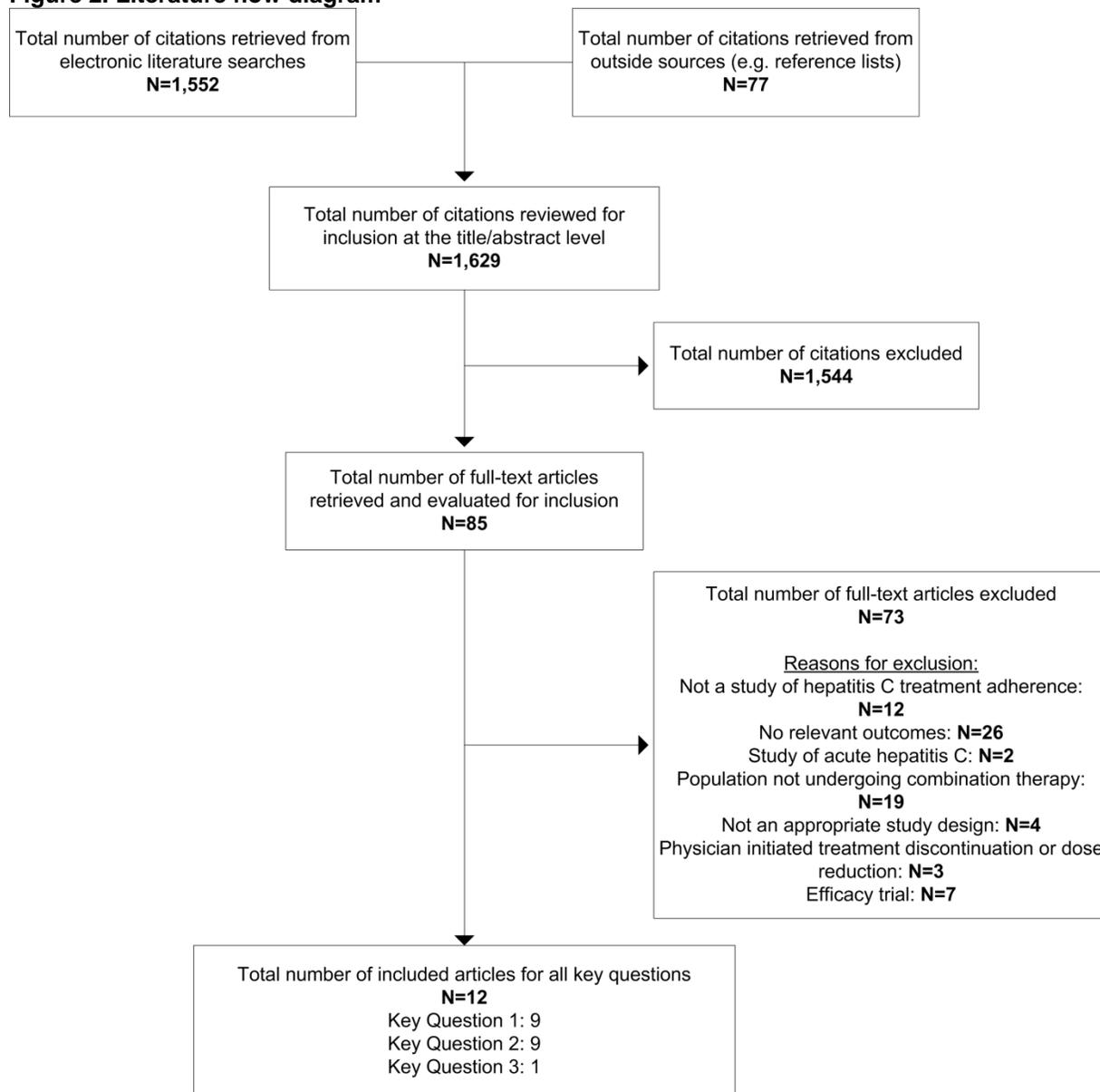
A full draft report was reviewed by experts and posted for public commentary from July 11, 2012 through August 8, 2012. Comments received from either invited peer reviewers or through the public comment Web site were compiled and addressed in a disposition of comments table. The disposition of comments will be posted three months after the final report is posted on the EHC Web site.

Results

Literature Search

Our search of English-language publications yielded 1,629 citations. From this body of literature, we provisionally included 85 articles for full-text review based on abstracts and titles (Figure 2). After screening full text articles against our inclusion/exclusion criteria (Table 3), we excluded 73 for various reasons, such as having no relevant outcomes (k=26), including a population not undergoing combination therapy of pegIFN- α plus ribavirin (k=19), or not evaluating hepatitis C treatment adherence (k=12). While we also searched for non-English publications and identified 99 potentially relevant studies, evaluating the non-English studies was not within the scope of this review. The full list of English-language excluded studies (including reasons for exclusion) is provided in Appendix C.

Figure 2. Literature flow diagram



Characteristics of Included Studies

Twelve studies^{61,64,65,90-98} met the inclusion criteria for at least one of our Key Questions (Table 5). About half of these studies were RCTs of fair⁹⁷ or poor quality.^{61,64,94,96,98} The remaining studies were cohort studies rated as good,^{91,93} fair,^{65,90} or poor quality^{92,95} (see Appendix D and E for individual study quality ratings for the RCT and cohort studies, respectively). Most of these studies were conducted in United States clinic-based settings, although two were conducted in hospital-based settings in Italy and two were multi-site studies conducted in France. Six primarily poor-quality studies had sample sizes less than 50,^{64,92,95-98} while three primarily poor-to-fair-quality studies enrolled 100 to 250 patients.^{61,65,90,91,93} Only two studies measured patient-important health outcomes,^{61,64} while the remaining studies

measured intermediate disease management outcomes (e.g., EVR, SVR) and/or treatment adherence.

We included studies that evaluated a variety of adherence approaches (Table 5), including one fair- and two poor-quality studies examining interventions targeting system-level factors,^{64,65,98} one fair-quality study targeting regimen- or therapy-related factors,⁹⁰ two good- and two poor-quality studies addressing patient-level factors,⁹¹⁻⁹⁴ and three fair- and one poor-quality studies accessing the direct management of adverse events.^{61,95-97} We did not include any studies that included interventions targeting policy- or provider-level factors. All of the trials, except one,⁹⁶ compared an adherence intervention with usual care. This single trial was conducted by Morasco and colleagues⁹⁶ comparing the use of citalopram to placebo in decreasing therapy-induced depression. None of the studies defined what “usual care” consisted of in the study’s respective setting. All of the included cohort studies compared the presence (or absence) of exposure to the specific intervention being investigated among study participants that were intended to otherwise be comparable. In all of these instances, the usual care condition represented a minimal standard of adequate medical care, and thus all studies are comparative effectiveness. Even though there were three-to-four studies comparing intervention approaches within one intervention category (e.g., system-level or adverse event management interventions), none of these within-category studies tested the same adherence interventions. Thus, the body of evidence is generally limited to single studies of different intervention types and is further limited by the noncomparability of enrolled study populations, as described next.

Table 5. Included adherence interventions and comparisons

Intervention Category	Description/Examples	Comparator	Number of Included Trials
System-level interventions	Designed to change the delivery or coordination of care. Examples include: increasing the convenience of care and augmented pharmacy services.	Usual care	3 ^{64,65,98}
Regimen/Therapy-related interventions	Designed to change the complexity of the treatment regimen or therapy. Example includes simplified dosing.	Usual care	1 ⁹⁰
Patient-level interventions	Designed to influence patient behaviors/beliefs. Examples include: provision of educational materials, telephone support, counseling.	Usual care	4 ⁹¹⁻⁹⁴
Adverse event management interventions	Designed to prevent or manage adverse events related to treatment and/or pre-existing comorbidities. Examples include: use of Epoetin alpha to manage anemia, use of antidepressants to prevent/manage depression, and CBT to manage depression.	Usual care/placebo	4 ^{61,95-97}

CBT = cognitive behavioral therapy

Study participants varied widely across studies in important ways that may impact the probability of treatment response (i.e., SVR) and/or affect treatment adherence, which were the main outcomes available from these studies (Table 6). Response to dual therapy (the only therapy examined in these adherence studies) is primarily affected by the genotype of the HCV infection and by previous treatment history (Table 1). Most studies included several HCV genotypes (with varying probabilities of response to dual therapy)^{64,65,92,94-98} or did not report HCV genotypes.⁹³ Three studies limited their study participants to a single genotype (e.g., genotype 1)^{61,90} or to genotypes 2 or 3, which are similarly responsive to treatment.⁹¹ Two of the larger studies targeted those naive to treatment, who are most likely to respond to treatment^{65,91}

and many did not report this important participant characteristic.^{61,92,93,96,98} Other characteristics that may affect likelihood of treatment adherence were similarly variable across studies (Table 7).

Table 6. Study characteristics

Study, Year Quality	Study Design & Aim	Country Study Setting	Sample Size (N)	Intervention Category & Description	HCV Genotype, %	Naïve to Treatment, %	Substance Abuse*, %	Outcomes Measured
Alam, 2010 ⁹⁰ Fair	Prospective cohort To examine whether improved adherence to HCV therapy was associated with prescribed RibaPak vs. traditional ribavirin.	US Multiple clinic sites	Total: 503 E: 346 NE: 157	<i>Regimen-related intervention</i> Patients were prescribed RibaPak doses of ribavirin (400-600 mg). At each visit, site personnel counted the number of pills brought in by the patient and asked them about the number of doses taken.	Genotype 1: 100	96.2*	NR	Adherence
Bertino, 2010 ⁶¹ Poor	RCT To investigate whether epoetin alpha administration improves treatment adherence & leads to a higher percentage of EVR/SVR.	Italy Hospital hepatology units	Total: 134 IG1: 67 IG2: 67	<i>Adverse event management intervention</i> Patients were prescribed pegIFN-α2A and WBR dosage (1,000-1,200 mg/day) + epoetin (10,000 IU 2x a wk).	Genotype 1b: 100*	NR	Current alcohol or drug use: 0	EVR SVR QOL Harms
Bonkovsky, 2008 ⁶⁴ Poor	RCT To assess the safety & efficacy of HCV treatment in injection drug users enrolled in methadone maintenance programs.	US Methadone clinics	Total: 48 IG: 24 CG: 24	<i>System-level intervention</i> Patients came to methadone clinic once a wk during the 24- or 48-wk treatment period for their injections & once a wk during the 24-wk treatment free period.	Genotype 1 IG: 54.0 CG:67.0	100	History of IV drug use: 100* Current IV drug use: 0	SVR QOL

Table 6. Study characteristics (continued)

Study, Year Quality	Study Design & Aim	Country Study Setting	Sample Size (N)	Intervention Category & Description	HCV Genotype, %	Naïve to Treatment, %	Substance Abuse*, %	Outcomes Measured
Bruce 2012 ⁹⁸ Poor	RCT To examine HCV adherence among patients receiving modified DOT for HCV treatment integrated with methadone maintenance treatment.	US Clinic providing treatment for substance use disorders including methadone maintenance	Total: 21 IG: 12 CG: 9	<i>System-level intervention</i> Patients received modified DOT of ribavirin once daily and pegIFN-α2a once weekly in addition to nurse-administered methadone.	Genotype 1, 4 IG: 66.7 CG: 66.7 Genotype 2, 3 IG: 33.3 CG: 33.3	NR	History of opioid use: 100 Current opioid use: 33 Current other alcohol or drug use: NR	EVR SVR
Cacoub, 2008 ⁹¹ Good	Prospective cohort To evaluate the impact of therapeutic education on adherence to treatment & SVR.	France Teaching hospitals, nonteaching hospitals, & private practice offices highly involved in the management of Hep C	Total: 674 E: 370 NE: 304	<i>Patient-level intervention</i> Therapeutic education by a third party (health care professionals other than the prescribing physician) during individual sessions. Provided at the discretion of the physician-no instruction given about how the education should be provided.	Genotype 2 IG: 32.0 CG: 28.0 Genotype 3 IG: 68.0 CG: 72.0	IG: 82 CG: 80	History of substance abuse: 49.3% Current drug use: 4.2%	SVR Adherence

Table 6. Study characteristics (continued)

Study, Year Quality	Study Design & Aim	Country Study Setting	Sample Size (N)	Intervention Category & Description	HCV Genotype, %	Naïve to Treatment, %	Substance Abuse*, %	Outcomes Measured
Cohen, 2009 ⁶⁵ Fair	Retrospective cohort To compare specialty care to standard retail pharmacies in HCV treatment outcomes & completion.	US Academic medical center, hepatology section	Total: 197 E: 95 NE: 102	<i>System-level intervention</i> Patients treated at a specialty pharmacy (specialty pharmacies provided insurance benefit coordination, access to knowledgeable pharmacists, patient education services, 24-hr phone service, improved access to medications, & facilitation of communication with physicians).	Genotype 1 IG: 62.0 CG: 65.0 Genotype 2 IG: 21.0 CG: 19.0 Genotype 3 IG: 15.0 CG: 16.0 Genotype 4 IG: 2.0 CG: 1.0	IG: 67 CG: 59	NR	SVR Adherence
Curcio, 2010 ⁹² Poor	Prospective cohort To propose a multidisciplinary method for the management of HCV among drug using patients in hopes to improve adherence.	Italy Hospital with a drug addiction center, an infectious disease unit, and mental health service	Total: 48 E: 16 NE: 32‡	<i>Patient-level intervention</i> TTTC patients received regular counseling on the risks of HCV infection & were given psychological support to help modify behavior & deal with treatment side effects from addiction specialist physicians, psychologists, infectious disease specialists, and case managers.	Genotype 1¶ IG: 50.0 CG: 21.9 Genotype 3¶ IG: 50.0 CG: 15.6 Genotype 4¶ IG: 0 CG: 3.1 Unknown IG: 0 CG: 59.4	NR	History of substance abuse: 100 Current alcohol or drug use: 0	SVR Adherence

Table 6. Study characteristics (continued)

Study, Year Quality	Study Design & Aim	Country Study Setting	Sample Size (N)	Intervention Category & Description	HCV Genotype, %	Naïve to Treatment, %	Substance Abuse*, %	Outcomes Measured
Hussein, 2010 ⁹³ Good	Retrospective cohort To apply propensity score matching in a real-world evaluation of a program that aims to improve patient adherence to HCV treatment.	US NR	Total: 1,560 E: 780 NE: 780†	<i>Patient-level intervention</i> Patients on pegIFN-α2b enrolled in the BIC program, a comprehensive patient support program that encourages adherence by providing personalized nursing support by telephone (available 24/7), mailed HCV education materials, and motivational letters throughout therapy.	NR	NR	NR	Adherence
Larrey, 2011 ⁹⁴ Poor	RCT To determine the effects of systematic consultation by a nurse on patient adherence & the efficacy of HCV therapy.	France 10 medical centers	Total: 250 IG: 123 CG: 127	<i>Patient-level intervention</i> Patients received medical consultations by the investigating physician and were evaluated by a nurse during scheduled treatment visits. The nurse's goals were to evaluate the patient's understanding of the disease & side effects of treatment, and to improve adherence to treatment.	Genotype 1 IG: 57.0 CG: 53.0 Genotype 2/3 IG: 36.0 CG: 38.0	IG: 57 CG: 64	NR	EVR SVR Adherence
Liu, 2010 ⁹⁵ Poor	Retrospective cohort To examine the influence of antidepressant treatment on HCV treatment adherence.	US Patients were treated at Mayo Clinic, Rochester	Total: 100§ E: 25 NE: 17	<i>Adverse event management intervention</i> Patients on HCV treatment who experienced depression and took antidepressants.	Genotype 1: 65.0 Other: 35.0	83*	History of substance abuse: 45* No current alcohol use (current drug use NR)	SVR

Table 6. Study characteristics (continued)

Study, Year Quality	Study Design & Aim	Country Study Setting	Sample Size (N)	Intervention Category & Description	HCV Genotype, %	Naïve to Treatment, %	Substance Abuse*, %	Outcomes Measured
Morasco, 2010 ⁹⁶ Poor	RCT To determine if the use of the antidepressant citalopram prevents the development of major depression in HCV patients undergoing antiviral therapy and in turn improves patient adherence to treatment.	US VA medical centers (Portland, OR; Seattle, WA)	Total: 39 IG: 19 CG: 20	<i>Adverse event management intervention</i> Patients received 20 mg of citalopram each day (dose increased if depression worsened) starting 2 wks before the initiation of HCV treatment and continuing throughout the course of treatment (medication was self-administered). They were followed up at regularly scheduled appointments.	Genotype 1 IG: 63.2 CG: 45.0 Genotype 2/3 IG: 36.8 CG: 55.0	NR	NR	EVR SVR Adherence Harms

Table 6. Study characteristics (continued)

Study, Year Quality	Study Design & Aim	Country Study Setting	Sample Size (N)	Intervention Category & Description	HCV Genotype, %	Naïve to Treatment, %	Substance Abuse*, %	Outcomes Measured
Ramsey, 2011 ⁹⁷ Fair	RCT To determine the efficacy of a cognitive-behavioral therapy intervention to prevent depression among methadone maintenance treatment patients undergoing HCV treatment.	US Primary care clinic	Total: 29 IG: 14 CG: 15	<i>Adverse event management intervention</i> Patients received eight 50 min sessions of cognitive behavior therapy. The therapy included training in skills that were relevant to dealing with depression, including mood monitoring, pleasant activities, constructive thinking, social skills, & assertiveness. Also, some HCV specific elements were added.	Genotype 1 IG: 50.0 CG: 33.4 Genotype 2 IG: 14.3 CG: 13.3 Genotype 3 IG: 35.7 CG: 40.0 Genotype 4 IG: 0 CG: 13.3	100	History of IV drug abuse: 100 No current IV drug use	Adherence

BIC = Be in Charge; CG = control group; DOT = directly observed therapy; E = exposed group; EVR = early viral response; HCV = hepatitis C virus; Hr = hour; IG = intervention group; IU = international units; mg = milligram; IV = intravenous; NE = nonexposed group; NR = not reported; OR = Oregon; PegIFN = pegylated interferon; QOL = quality of life; RCT = randomized controlled trial; SVR = sustained viral response; TTTC = Together to Take Care; US = United States; VA = Veterans affairs; WA = Washington; WBR = weight-based reduction; Wk = week(s)

*Entire cohort.

†Controls pair matched 2:1 with treatment group.

‡Matched controls.

§Other groups included those with no depression/ antidepressant use (n=35) and those on antidepressants prior to the start of therapy (n=23).

|| Percentages as reported in study.

¶ Value calculated.

Table 7. Additional study characteristics

Study, Year Quality	Sample Size (N)	Inclusion Criteria	Exclusion Criteria	% Female	Race/Ethnicity*, %	Comorbidities, %
Alam, 2010 ⁹⁰ Fair	Total: 503	≥ 18 years; diagnosed with chronic HCV; prescribed RibaPak or 200 mg ribavirin in conjunction with a weekly pegIFN injection	Known hypersensitivity to ribavirin; currently prescribed Consensus Interferon or any nonpegIFN; HIV, HBV or HDV coinfection or autoimmune hepatitis; pregnant or lactating women; men whose female partners were pregnant; individuals with haemoglobinopathies	E: 47.1 NE: 45.2	Caucasian: 70.6‡ African American: 14.1‡ Asian: 7.6‡ Other: 7.8‡	NR
Bertino, 2010 ⁶¹ Poor	Total: 134	≥ 18 years of age; elevated ALT levels over the previous 6 months; antiHCV antibody positivity; detectable HCV RNA, HCV genotype 1b; liver histology of CH; BL Hb >13 (men) & >12 (women); serum creatinine ≤1.5 mg/dl; HOMA-IR < 2.5	HBV infection, HBV-HCV coinfection, HIV infection, HCV genotype other than 1b, overall Ishak score ≥13, decompensated cirrhosis; sig atherosclerotic heart disease; starting Hb <13 (men) & <12 (women); alcohol or drug abuse; history of hematological disorders or neoplastic disease, Wilson's disease, and hemochromatosis	49.5*	Caucasian: 100	NR
Bonkovsky, 2008 ⁶⁴ Poor	Total: 48	Men & women ≥ 18 years old; chronically infected with HCV genotypes 1,2, or 3; serum HCV RNA concentration > 600 IU/mL 30 days prior to first treatment; enrolled in methadone maintenance programs with documented for ≥ 3 months prior to study enrollment; agreed to abstain from alcohol & drug use throughout the study	Treated previously for HCV; pregnant women; neutrophil count <1,500/mm ³ ; hemoglobin concentration <12 g/dL in women or <13 g/dL in men; a white blood cell count >11 x 10 ⁹ /L; platelet count <75,000/mm ³ ; or BL increased risk of anemia; coinfecting with HIV or any other cause of liver disease; significant comorbid med condition; history of severe psychiatric disease	IG: 17.0 CG: 33.0	Caucasian: 79.2‡	NR

Table 7. Additional study characteristics (continued)

Study, Year Quality	Sample Size (N)	Inclusion Criteria	Exclusion Criteria	% Female	Race/Ethnicity*, %	Comorbidities, %
Bruce 2012 ⁹⁸ Poor	Total: 21	Prescribed methadone and were opioid negative by urine toxicology in the past 30 days, aged \geq 18 years, underwent documented HIV testing, competent to provide informed consent, and detectable HCV RNA and genotype testing. Those with genotype 1 and 4 with fibrosis score > 1 using Metavir staging	NR	IG: 58.3 CG:33.3	Caucasian: 76.2‡ African American: 9.5‡ Hispanic: 14.3‡	<i>HIV/AIDS</i> IG: 25 CG: 33.3 <i>Depressive Disorders</i> IG: 66.7 CG: 55.6 <i>Anxiety Disorders</i> IG: 66.7 CG: 33.3
Cacoub, 2008 ⁹¹ Good	Total: 674	Aged \geq 18 years with chronic HCV (genotype 2/3) with initiation of bitherapy with pegIFN- α 2b & ribavirin scheduled	NR	E: 38.0 NE: 44.0	NR	<i>Depression</i> IG: 31.0 CG: 22.0† <i>Psychiatric Disorder</i> IG: 27.0 CG: 20.0† <i>Chronic Disease</i> IG: 24 .0 CG: 22 .0
Cohen, 2009 ⁶⁵ Fair	Total: 197	HCV patients treated at single academic institution.	HBV or HIV coinfection, transplant recipients, patients receiving experimental treatment protocols, patients lacking sufficient chart data	E: 47.0 NE: 39.0	Caucasian: 68.0‡ African American: 18.8‡ Hispanic : 9.1‡ Other: 4.1‡	NR

Table 7. Additional study characteristics (continued)

Study, Year Quality	Sample Size (N)	Inclusion Criteria	Exclusion Criteria	% Female	Race/Ethnicity*, %	Comorbidities, %
Curcio, 2010 ⁹² Poor	Total: 48	Patients with HCV-RNA positivity and a toxicologically stabilization phase (complete abstinence from the use of opiates, cocaine, and alcohol); history of drug use, but currently in addiction therapy	Repeated use of opiates, cocaine, and alcohol; chronic diseases; thyroiditis; cardiomyopathy; psychiatric diseases; autoimmune diseases; anemia; advanced cirrhosis	E: 6.0 NE: 9.0	Caucasian: 100	IG: 2.0 CG: 12.0 ¶
Hussein, 2010 ⁹³ Good	Total: 1,560	HCV patients starting pegIFN- α 2b treatment after Jan. 1, 2004; 18 years or older; successfully linked to their medical/pharm/hospital claims by NDCHealth	Patients who couldn't be observed for at least 12 weeks after treatment initiation in the NDCHealth database	E: 53.7 NE: 53.5	NR	<i>HIV/AIDS</i> IG: 19.2 CG: 20.5 <i>Dementia/ insomnia</i> IG: 6.5 CG: 7.7 <i>Any chronic illness</i> IG: 13.5 CG: 12.8
Larrey, 2011 ⁹⁴ Poor	Total: 250	Adult patients (≥ 18 years) with documented genotype 1 HCV & an indication for treatment with pegIFN-ribavirin treatment	HIV or HBV coinfection; serious psychiatric illness; clinical thyroid disorder; severe cardiac or coronary insufficiency; severe hematological disorders; renal insufficiency; uncontrolled epilepsy; severe retinopathy; progressive autoimmune disease; uncontrolled neoplasia; pregnant or breast feeding females	IG: 36.0 CG: 39.0	NR	NR

Table 7. Additional study characteristics (continued)

Study, Year Quality	Sample Size (N)	Inclusion Criteria	Exclusion Criteria	% Female	Race/Ethnicity*, %	Comorbidities, %
Liu, 2010 ⁹⁵ Poor	Total: 100* #	Clinical diagnosis with chronic HCV; treatment of HCV with pegIFN with intention to cure; verification of completed treatment course	Use of IFN other than pegIFN; active use of alcohol during treatment; incomplete data available on treatment course for any reason	28.0*	NR	Depression: 33* Anxiety/other mood disorder: 12.0* Insomnia: 4.0* Unknown**: 4.0* Hep B: 4.0*
Morasco, 2010 ⁹⁶ Poor	Total: 39	Infected with HCV; ≥ 18 years old; eligible for antiviral therapy; agreed to undergo IFN-alpha/ribavirin treatment.	Ongoing depression or active psychotic symptoms during the previous 3 months; substance abuse in the previous 6 months; medical comorbidities that could interfere with treatment; current antidepressant use	IG: 5.3 CG: 10.0	Caucasian: 84.6‡	History of major depression: IG: 10.5 CG: 15.0

Table 7. Additional study characteristics (continued)

Study, Year Quality	Sample Size (N)	Inclusion Criteria	Exclusion Criteria	% Female	Race/Ethnicity*, %	Comorbidities, %
Ramsey, 2011 ⁹⁷ Fair	Total: 29	≥ 18 years old; HCV antibody positive & detectable HCV RNA in serum; no medical contraindications to treatment; evidence of chronic hepatitis; drinking less than "at-risk" levels during the past month (≤14 drinks per week and no more than 4 drinks on 1 occasion for men, ≤7 drinks per week and no more than 3 drinks on 1 occasion for women); English speaking; enrolled in methadone maintenance for at least 6 months; no current (past month) depressive episode; not currently taking antidepressants; not currently suicidal or psychotic; no previous treatment for HCV; no intention to relocate from study area for the next 6 months	NR	IG: 0 CG: 26.7	Caucasian: 89.7‡ American Indian/Alaskan native: 3.0 Hispanic: 17.0 Other: 7.0	Participants were monoinfected with HCV; no comorbidities were present

AIDS = acquired immune deficiency syndrome; ALT = alanine transaminase; BL = baseline; CG = control group; CH = chronic hepatitis; DL = deciliter; E = exposed group; G = grams; Hb = hemoglobin; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; Hep; hepatitis; HOMA-IR = homeostasis model assessment–insulin resistance; IFN = interferon; IG = intervention group; IU = international units; L = liter; Med = medical; Mg = milligram; NE = nonexposed group; NR = not reported; PegIFN = pegylated interferon; RNA = ribonucleic acid

*Entire study cohort.

†Statistically significant (p< 0.05).

‡Value calculated.

|| HIV.

¶Details of comorbid infections not reported.

#Other groups included those with no depression/ antidepressant use (n=35) and those on antidepressants prior to the start of therapy (n=23).

**No diagnosis of depression/mental disorder, but were taking psychiatric medications.

Results of Included Studies

We discuss the results of the four different types of comparisons separately: system-level interventions compared with usual care (Table 8), regimen-related interventions compared with usual care (Table 9), patient-level interventions compared with usual care (Table 10), and adverse event management interventions compared with usual care or placebo (Table 11) (see end of Chapter for all results tables). Studies reported highly variable outcomes (Table 6). In addition, the definition each study used for adherence and the specific methods for measuring adherence varied. We did not include reports that clearly reflected discontinuation or dose reductions initiated by a physician. In terms of health outcomes, no studies reported morbidity, mortality, or HCV transmission. Only two studies^{61,64} reported quality-of-life outcomes. Additionally, only two studies reported harms related to the adherence intervention.^{61,96} We present the results of Key Questions 1 (intermediate and health outcomes) and 2 (adherence) together due to the paucity of data for all outcomes.

Key Question 1 (Intermediate and Health Outcomes) and Key Question 2 (Treatment Adherence)

Key Question 1. In adult patients with chronic HCV infection undergoing antiviral therapy, what is the comparative effectiveness of treatment adherence interventions in improving intermediate (e.g. sustained viral response, histological changes, drug resistance, relapse rates, and treatment side effects) and health outcomes (e.g., disease-specific morbidity, mortality, QOL, transmission of HCV)?

Key Question 2. What is the comparative effectiveness of treatment adherence interventions in improving treatment adherence (e.g., medication adherence, medical plan adherence)?

System-Level Interventions Versus Usual Care

Key Points

- Three, small fair- or poor-quality studies compared the effectiveness of system-level HCV treatment adherence interventions versus usual care, and none of these reported on important health outcomes (e.g., morbidity, mortality, or the transmission of HCV). (Strength of evidence = insufficient)
- One poor-quality trial evaluated how a system-level treatment adherence intervention affected health-related QOL. Hepatitis-specific limitations and distress improved over time in the intervention group, but not in the control group. Data were insufficient to draw conclusions, however, due to high risk of bias and no statistical test of group differences. (Strength of evidence = insufficient)
- Three studies examined the effectiveness of system-level treatment adherence interventions compared with usual care on SVR, adherence, or both. System-level interventions had an imprecise impact on SVR. In two studies, more methadone-maintenance patients receiving DOT achieved SVR compared with controls, while fewer patients receiving care at a specialty pharmacy, achieved SVR than those receiving usual pharmacy care. However, no results were statistically significant. Findings were further

limited by moderate-to-high study-level risk-of-bias and the fact that we could not compare interventions across studies. (Strength of evidence = insufficient)

- One fair-quality cohort study reported no benefit of specialty pharmacy care compared to usual pharmacy care for patient self-discontinuation of treatment. (Strength of evidence = insufficient)

Two poor-quality RCT^{64,98} and one fair-quality retrospective cohort study⁶⁵ evaluated the effectiveness of a system-level intervention on QOL, SVR, EVR, and/or adherence, compared to usual care (Table 8).

A fair-quality retrospective cohort study by Cohen and coauthors⁶⁵ compared the effects of patients' use of specialty care pharmacies with patients' use of standard retail pharmacies on SVR and adherence. Data were collected from the medical charts at a single academic institution. Pharmacies self-designated as either a specialty or standard retail pharmacy. Patients were placed into the study arm according to where they filled their prescriptions. This study included 197 patients: 95 in the specialty pharmacy group and 102 in the standard pharmacy comparison group. Sixty-three percent of all patients were naïve to prior HCV therapy and the majority of patients (63%) were genotype 1. While no significant differences existed between groups in terms of HCV genotype, there were significant differences in terms of ethnicity—more Caucasian than African American patients used standard retail pharmacies and more African American patients than Caucasians used specialty pharmacies. All but three patients (all in the standard pharmacy comparison group and receiving pegIFN monotherapy) received pegIFN plus ribavirin. This study's major threats to validity include the reliability and validity of the designation of pharmacy type (pharmacy self-reported) and the fact that the analysis did not adjust for potential confounders in the analysis of adherence outcomes.

A poor-quality RCT by Bonkovsky and colleagues⁶⁴ included 48 patients enrolled in methadone maintenance programs for at least 3 months prior to study inclusion. All patients agreed to abstain from illicit drugs and alcohol throughout the study period. Patients were excluded if they had any significant medical comorbidity or a history of severe psychiatric disease. Most participants (83% of the intervention group [IG] and 67% of the control group [CG]) were male and 79 percent of the combined sample was Caucasian. Sixty percent of enrolled patients were genotype 1 (54% in the IG, compared to 67% in the CG, statistical differences not presented) and all were naïve to HCV treatment. Genotype 1 patients were treated with pegIFN- α 2a (alpha 2a) (180 μ g/week) and ribavirin (1,000/1,200 mg/day) for 48 weeks. Patients with genotypes 2 and 3 were treated with pegIFN- α 2a (180 μ g/week) and ribavirin (800 mg/day) for 24 weeks. Patients were randomized to receive supervised (i.e., DOT) pegIFN- α 2a at methadone clinics once weekly (n=24) compared to self-administration of pegIFN- α 2a (n=24). Self-administration patients received their first injection at the study site and subsequent injections were self-administered. Ribavirin was self-administered in both groups. The majority of patients in both groups also received methadone on nearly all of the study treatment days. This study followed patients for 24 weeks after treatment. Seventy-seven percent of patients completed their full length of therapy and group differences were not statistically significant. In addition to completion rates, the study assessed SVR and health-related QOL using a validated, self-administered survey that measured physical, psychological, and general health, and hepatitis-specific QOL domains (i.e., the Hepatitis QOL Questionnaire). The hepatitis-specific domains measured limitations and health distress due to hepatitis C. This study included an unadjusted analysis on the intent-to-treat population to assess the effect of the DOT intervention compared to self-administration on SVR. The authors also report change in QOL

measures over time. This study had several quality concerns, including the lack of reporting on the method of randomization and whether or not group assignment was concealed. In addition, patients were not blinded to their condition, which could have influenced self-reported responses, including QOL measures.

Another small, poor-quality RCT⁹⁸ similarly randomized patients receiving methadone maintenance to either modified DOT (n = 12) or self-administered therapy (n = 9). All patients initiating HCV therapy received pegIFN- α 2a (180 μ g/week) and weight-based ribavirin. Subjects randomized to the intervention group received their methadone as part of their HCV therapy whereas control group participants received their methadone elsewhere. The major risk of bias of this trial is the high attrition in the control group (data were unavailable in 5 out of 9 patients). Whereas all participants in the DOT group patients started HCV treatment, only 44.4 percent (4/9) of patients in the self-administered group started HCV therapy. Data on EVR and SVR from this study are reported as being preliminary; it appears that more patients will be enrolled in this study.

Quality of Life

Only one poor-quality RCT⁶⁴ reported quality-of-life outcomes. There was an improvement in hepatitis-specific limitations mean score from baseline in the supervised DOT treatment group (84.2 at the end of followup vs. 74.5 at baseline), whereas these self-reported limitations became worse in the self-administered control group (mean score of 68.9 at followup vs. 76.8 at baseline). Similarly, the mean score on self-reported health distress was improved at followup in the intervention group from baseline (81.6 vs. 63.8). There was a very small change in the self-administered treatment group (67.3 vs. 69.8). The study did not report statistical tests of changes over time or of differences between groups.

Sustained Viral Response

All three studies reported the adherence intervention's effect on SVR with imprecise, nondefinitive results. In the cohort study,⁶⁵ 48 percent (46/95) of patients using specialty pharmacies achieved a SVR, compared with 56 percent (56/102) of those using a standard retail pharmacy. This difference was not statistically significant in unadjusted or adjusted analysis that accounted for age, sex, ethnicity, genotype, and prior treatment (ORadj 0.69, 95% confidence interval [CI], 0.37 to 1.30). One poor-quality RCT⁶⁴ reported a higher achievement of SVR in 54 percent (13/24) of patients enrolled in the supervised DOT treatment, compared with 33 percent (8/24) using self-administered treatment (unadjusted OR 2.36, 95% CI, 0.73 to 7.60). Among patients with genotype 1, the SVR rate did not differ between groups. However, among patients with genotypes 2 or 3, SVR was achieved in 91 percent (10/11) of patients in the DOT group as opposed to 25 percent (2/8) of patients in the self-administration group. The other RCT found that 6 out of 12 patients (50%) receiving modified DOT of pegIFN- α 2a and ribavirin versus 1 of 9 patients (11%) randomized to the self-administration group achieved a SVR. Five patients in the control group did not initiate HCV treatment.⁹⁸

Early Viral Response

Only one poor-quality RCT⁹⁸ reported data on EVR. In this study, 10 out of 12 patients (83%) in the modified DOT group versus 3 out of 9 patients (33%) in the control group achieved early viral response.

Adherence

Both RCTs reported no adherence data.^{64,98} In the cohort study⁶⁵ ten patients included in the specialty pharmacy group self-discontinued treatment, compared with 4 in the control group (calculated OR 0.35, 95% CI, 0.11 to 1.15). Physician-directed reasons for discontinuation of therapy included nonresponse or breakthrough.

Regimen-Related Interventions Versus Usual Care

Key Points

- No studies evaluated the effect of regimen-related interventions on health outcomes or the intermediate outcomes of SVR or EVR. (Strength of evidence = insufficient)
- A single fair-quality cohort study that compared packaging to reduce pill burden for ribavirin (RibaPak) with regular ribavirin reported the intervention effects on adherence, which the study measured three ways (duration of treatment, proportion of prescribed doses taken, and proportion taking at least 80% of prescribed doses). This study reported improved adherence in the reduced-pill-burden intervention on all three measures at 24 weeks and on two of three measures at 12 weeks. (Strength of evidence = low)

One fair-quality prospective cohort study,⁹⁰ addressed the effect of regimen-related interventions on adherence (Table 9). No other outcomes were reported for this study. The “Accurate Dosing in Hepatitis C: Examining the RibaPak Experience” or ADHERE study was a 24-week, United States study at 33 sites in adults with HCV. The primary aim of the study was to evaluate the treatment adherence of patients who were prescribed RibaPak, available in 400 mg and 600 mg ribavirin tablets (i.e., reduced pill burden), compared with patients prescribed 200 mg ribavirin tablets. All patients were concurrently receiving weekly pegIFN injections. Patients were identified by their treating physician. Five-hundred and three patients were enrolled at a ratio of 3:1 (RibaPak vs. regular ribavirin); all patients were genotype 1 (personal communication, I. Alam, May 30, 2012). Participants in both groups were similar in terms of age, gender, race, BMI, and baseline viral load. The analysis did not adjust for other potential confounders, however, such as previous HCV treatment, mental health status, or substance abuse history. Data were collected at 4 weeks, 12 weeks, and 24 weeks from the start of treatment with each followup time point specific to the 4 weeks prior to the assessment.

Adherence

Adherence was assessed in three ways: (1) the proportion of patients remaining on treatment at each followup, (2) the proportion of prescribed doses taken among those remaining on treatment, and (3) the proportion of patients who took at least 80 percent of their prescribed dose. The proportion of prescribed doses taken was measured objectively based on pill counts at each visit. Left over pills were counted by site personnel and were compared with the number of pills that should have been left over based on the prescribed daily dose and the number of days in the treatment period.

A greater proportion of RibaPak patients than patients taking traditional ribavirin remained on treatment at both 12 weeks (86.4% compared with 77.7%, $p = 0.01$) and 24 weeks (71.4% compared with 62.4%, $p = 0.045$). There was no significant difference between the groups in the mean number of doses missed at 12 weeks. At 24-weeks, there was a statistically significantly greater mean number of missed doses among the traditional ribavirin patients (1.12 missed doses) than the RibaPak patients (0.36 missed doses) ($p = 0.01$). At both 12 and 24 weeks,

patients using RibaPak were statistically significantly more likely to have taken at least 80 percent of their prescribed medication than those using traditional ribavirin (12 weeks: 94% vs. 84%, OR 2.28, 95% CI, 1.54 to 3.38; 24 weeks: 98% vs. 89%, OR 1.90, 95% CI, 1.30 to 2.78) (data reported in Table 9).

Patient-Level Interventions Versus Usual Care

Key Points

- No patient-level adherence intervention studies reported health outcomes. (Strength of evidence = insufficient)
- Three studies (one good-quality cohort, one poor-quality cohort, and one poor-quality RCT) comparing patient-level adherence interventions with usual care all tended toward increased proportions achieving SVR among patients receiving enhanced patient education and support, although no differences were statistically significant. (Strength of evidence = low)
- Four studies (two good-quality cohort studies, one poor-quality RCT, and one poor-quality cohort study) comparing patient-level adherence interventions with usual care all tended toward better adherence at the end of treatment among patients receiving the adherence interventions. (Strength of evidence = moderate)

Three cohort studies (two good-quality,^{91,93} one poor-quality⁹²) and one poor-quality RCT⁹⁴ compared the effect of a patient-level intervention with usual care among adults with HCV on SVR and adherence (Table 10).

One good-quality prospective cohort study⁹¹ in France included 674 HCV patients infected with genotype 2 or 3. Patients undergoing HCV dual therapy with pegIFN- α 2b and ribavirin were compared according to whether they received therapeutic education from a third party (health care professionals other than the prescribing physician) (n=370) or no therapeutic education (usual care) (n=304). Therapeutic education was provided at the discretion of the treating physician and included the distribution of education materials during individual sessions. Patients were considered to have adhered to pegIFN if they received three of four injections during the past 4 weeks, and to have adhered to ribavirin if they had taken at least 22 (200 mg) capsules over the past week. Patients were considered to have adhered to the full therapy if they had adhered to both drugs for at least 20 of the 24 weeks of treatment. Patients receiving therapeutic education had statistically significantly higher rates of depression, psychiatric disorder, drug use, and significant liver fibrosis. In order to account for these baseline differences, adjusted analyses were conducted to evaluate the association between exposure to therapeutic education and adherence and SVR. Twelve variables were used for the adjusted analyses, including sex, weight, BMI, educational level, history of depression, psychiatric disorders, alcohol consumption, drug abuse, duration of HCV infection, previous antiHCV treatment, HCV genotype, and pegIFN dose prescribed at treatment initiation.

One good-quality retrospective cohort study⁹³ used propensity scoring methods to compare the “Be in Charge” (BIC) program, a patient-support program provided by the manufacturer of pegIFN- α 2b (alpha 2b), with usual care. The BIC program was designed to improve patient adherence. Patients prescribed pegIFN- α 2b plus ribavirin could join the program at any point during the course of their HCV therapy. Those enrolled in the program received personalized nursing support by telephone and/or mailed educational materials and motivational letters throughout therapy. The patients chose what level of intervention intensity they wished to

receive, which ranged from 24 hour/7 days a week (24/7) access to a registered nurse to 24/7 access plus regular outbound telephone calls, motivational letters and other requested mailings. The study applied propensity scores based on observed covariates believed to be associated with the likelihood of enrolling in the BIC program such as age, sex, use of other HCV medications used in the 6 months prior to pegIFN initiation, and history of several comorbid conditions to match patients in the intervention group with those not enrolled in the intervention at a ratio of 1:1. A total of 1,560 patients (780 in each group) were included in the analyses. This study did not report data on HCV genotype or history of prior HCV treatment. Adherence data, which was defined as proportion of patients who filled all doses of the prescribed pegIFN- α based on pharmacy claims data, were collected at 12 weeks, 24 weeks, and 48 weeks. Of the 1,560 included patients, data at 48 weeks were available in only 666 patients (the main quality concern with this study). This study reported no other outcomes.

The poor-quality RCT⁹⁴ took place in France. Two-hundred fifty patients were randomized to either therapeutic education by a nurse (n=123) or conventional clinical followup with the investigating physician (i.e., usual care) (n=121). The method of randomization was not reported including whether allocation was concealed. The intervention included regular consultation with a nurse who evaluated the patients' understanding of the disease and side effects of treatment and aimed to increase adherence. Nurse consultation took place in addition to medical consultation with the physician at the beginning of treatment and weeks 4, 8, 12, 24, and 36 (among those completing 48 weeks of treatment). Just over half (54.9%) were genotype 1-infected patients and the majority (59.8%) were treatment naïve. Groups were similar at baseline on a number of characteristics including age, sex, BMI, genotype, and treatment history. All patients received pegIFN- α 2a (180 μ g/week) and twice-daily ribavirin weight-based dosing (<75 kilograms [kg], 1000 mg/day; >75 kg, 1200 mg/day), for 24 or 48 weeks depending on genotype, viral load, and previous treatment. Reported outcomes included adherence to treatment and SVR. It was unclear whether the measurements, particularly around treatment completion and patient adherence were equal between groups or valid measures. In addition, patients were not blinded to their condition, a factor that could have influenced reporting. Analysis was conducted on an intent-to-treat analysis.

Finally, one poor-quality prospective cohort study,⁹² conducted in Italy, evaluated the “Together To Take Care” (TTTC) program, a multidisciplinary educational intervention in which patients who had a history of substance abuse received counseling on the risks of HCV infection and psychological support to help them modify their behavior. A case manager was assigned to each patient to coordinate treatment and counseling regarding the disease itself, addiction, and mental health. This study included a total of 48 patients: 16 patients in addiction therapy who received the TTTC intervention and 32 control group patients also in addiction therapy, who were consecutively pair matched 2:1 for age, sex, and time of HCV infection at enrollment. Though control patients were pair matched, patients in the TTTC intervention group were generally older at the time of infection than control participants (32.5 years compared to 28 years, respectively), although the authors report this as “presumptive”). Baseline data for both groups are presented at the individual patient level, making it difficult to make direct comparisons. It appears that the majority of patients in the intervention group were genotype 1 or 3, while several of the participants in the control group were reported to have “nondetermined” genotypes. It is not clear what proportion of patients in each group had received prior treatment for HCV. Control group patients were being treated with dual therapy for HCV at other health centers, but receiving treatment for drug addiction at the same center as the intervention group

patients. While control group patients received care at the same drug addiction center, they did not receive the same “progressive and constant monitoring” that treatment group patients did via their case manager; however, there is some risk that control group patients may have also received enhanced education or psychological support from operators at the drug addiction center.

Sustained Viral Response

Three studies^{91,92,94} reported data on SVR. All three of these studies consistently showed that patients enrolled in interventions targeted patient-level factors (e.g., therapeutic education) achieved a higher level of SVR than usual care. The difference was statistically significant in the poor-quality RCT evaluating a nurse-led therapeutic education intervention compared to usual care (38.2% vs. 24.8%; unadjusted OR 1.88, 95% CI, 1.08 to 3.25),⁹⁴ but not in the prospective observational study of therapeutic education (77% vs. 70%; ORadj 1.54, 95% CI, 0.99 to 2.40),⁹¹ or the multidisciplinary patient-support program (68.7% vs. 45.8%; OR 2.6, 95% CI, 0.69 to 9.81).⁹²

Early Viral Response

Of the four studies included in this group, only the RCT reported data on EVR. This study reported that patients enrolled in the nurse education intervention were more likely to achieve EVR (72.8% vs. 57.6%; $p < 0.01$).⁹⁴

Adherence

All four studies reported data on adherence. Two studies reported data at 12 weeks, 24 weeks, and 48 weeks.^{93,94} All studies consistently showed that patient-level interventions improved adherence, despite variability in study designs, study quality, adherence definitions, and analytical techniques (Table 10). Patients in the intervention groups generally had approximately 50-percent higher odds of adhering to therapy or continuing with treatment at 24-48 weeks compared with control groups. One poor-quality study⁹² showed a statistically significant OR of 4.38 when comparing the intervention group with the usual care. Although the level of adherence decreased over time in all studies, data from studies reporting multiple time-points of followup suggested that the effect size (or difference between patient-level adherence interventions compared to usual care) tended to increase over time (e.g., 48 weeks vs. 24 weeks). In the good-quality prospective cohort study by Cacoub and colleagues, for example,⁹¹ 66 percent of patients receiving therapeutic education were adherent to both drugs at 12 weeks, compared to 63 percent of patients in the control group. This difference was nonsignificant. At 24 weeks, however, the difference was statistically significant: 61 percent of the exposed were considered adherent to both drugs, compared to 47 percent of the nonexposed group (ORadj 1.58, 95% CI, 1.02 to 2.46). In the Hussein study,⁹³ the proportion of patients who refilled the maximum number of pegIFN- α 2b decreased from 72 percent in the intervention group at 12 weeks to 22 percent at 48 weeks. This proportion fell from 64 percent in the control group at 12 weeks to 13 percent at 48 weeks. The odds of having refilled their injections among BIC enrollees was 1.77 (95% CI, 1.20 to 2.62) at 48 weeks compared to controls.

Adverse Event Management Interventions Versus Usual Care/Placebo

Key Points

- There were no studies of the effects of adverse event management interventions on health outcomes besides QOL. (Strength of evidence = insufficient)
- One small, fair-quality RCT found greater improvements in QOL (as measured by increased energy and activity) in dual-therapy–treated, genotype 1 HCV patients with anemia who received epoetin, an agent to reduce anemia, compared with those whose anemia was managed by a reduction in ribavirin. Patients receiving epoetin showed a significant increase in hemoglobin serum levels over the course of treatment whereas those just receiving a reduction in ribavirin did not. Improvement in SVR was also reported in the epoetin-treated group, compared with the ribavirin reduction group. (Strength of evidence = insufficient)
- Two studies of depression prevention (citalopram, an antidepressant) or management (antidepressants for documented symptoms) to improve adherence in dual-therapy-treated HCV patients did not provide clear evidence about the effect on SVR due to reporting or risk-of-bias limitations. The study of prophylactic citalopram found greater EVR at 12 weeks, particularly in genotype-1 patients. (Strength of evidence = insufficient)
- One study comparing prophylactic citalopram with placebo and one study comparing cognitive behavioral therapy (CBT) with usual care showed no statistical difference between groups in terms of treatment completion or adherence. The CBT intervention participants were less likely to be adherent to their pegIFN- α therapy than control participants, although the difference was not significant. (Strength of evidence = insufficient)

Three small, fair- and poor-quality RCTs^{61,96,97} and one poor-quality retrospective cohort study⁹⁵ assessed the effect of interventions to prevent or manage adverse events (e.g., anemia, depression) related to HCV treatment on health outcomes (i.e., QOL) or intermediate outcomes (i.e., SVR, EVR, and/or adherence) (Table 11).

The first, a fair-quality RCT,⁹⁷ randomized 29 HCV-treatment-naïve patients with multiple genotypes to receive either eight 50-minute individual sessions of CBT in addition to standard HCV dual therapy or usual care. All patients were enrolled in methadone maintenance treatment program for at least six months. The authors report that the sample was recruited from an urban hospital-based primary care clinic among those seeking antiviral treatment. Of the original 117 patients deemed to be provisionally eligible, 88 were excluded (primarily for antidepressant use). No statistically significant differences existed between groups at baseline for a number of demographic variables, illicit drug use, and depression scores. The distribution of patients according to genotype did not appear to differ significantly (e.g., seven patients were genotype 1 in the CBT group, compared to 5 in the control group). The CBT included training in skills for depression management, such as mood monitoring, pleasant activities, constructive thinking, social skills, and assertiveness. This trial also included specific counseling regarding the unique needs of patients on antiviral medication for HCV, such as regular mood ratings to track depressive symptoms and addressing strategies for coping with drug cravings. This trial excluded patients taking antidepressant medication. Adherence was defined as receiving at least 24 pegIFN injections over 24 or 48 weeks of treatment. Data were abstracted from medical charts.

Five (18%) patients were lost to followup in this study. The analysis of adherence was conducted on an intent-to-treat basis.

In the second, a poor-quality RCT,⁶¹ 134 HCV-infected, genotype-1 patients treated with dual therapy who were experiencing a therapy-induced reduction in hemoglobin (Hb) levels (i.e., anemia) were randomized to receive epoetin alpha (epoetin) (group 1, n = 67) or to receive a reduction of ribavirin (800-1,000 mg/day) (group 2, n = 67) for 48 weeks. In this study, 214 patients were enrolled and started HCV dual therapy with the standard doses of subcutaneous pegIFN- α 2a plus weight-based doses of ribavirin. This study only randomized patients who experienced a Hb reduction of greater than 2 g/dL at week 12 to the two groups. At week 12, no significant statistical difference was found between the groups concerning total bilirubin, platelets count, Hb, ferritin, and albumin serum levels. This study presented no other baseline comparisons by group. The study analyzed data on SVR 6 months after the end of treatment (week 72) based on an intent-to-treat basis. No patient-related adherence data were reported. QOL was assessed using the Linear Analogue Self-Assessment (LASA) scale at baseline and 36 weeks. This was an open-label trial with no blinding of patients or providers. While the authors state that randomization was performed using a computer program, it is unclear if the method was valid and whether or not the allocation was concealed. As previously stated, this randomization occurred *after* the assessment of EVR.

The third, a poor-quality RCT,⁹⁶ evaluated the efficacy of taking citalopram in preventing the development of pegIFN- α -induced depression and improving treatment completion among HCV patients. Thirty-nine patients with HCV genotypes 1, 2, or 3 were randomized to receive prophylactic citalopram (20-mg tablets) (n = 19) or placebo pills (n = 20), which were dispensed to participants blindly. Participants who experienced increasing depression scores (according to the Beck Depression Inventory-II) were given a dose increase of 20 mg/day of citalopram or up to three additional placebo tablets. Participants with moderate-to-severe depression or suicidal thoughts were placed into a rescue arm of the study. While this study reported that participants were excluded if they had ongoing depression or active psychotic symptoms during the prior 3 months or current antidepressant use, a mean score for baseline current depression severity (indicating current depression) was presented for the full sample. No significant baseline differences existed between groups on any demographic or medical-related variables. After 24 weeks, blinding for treatment assignment was broken and all patients who continued therapy for 48 weeks (genotype 1) were offered citalopram for the duration of their treatment. While this study was originally powered to detect significant differences among groups for the development of pegIFN-induced depression, small sample sizes and the low rate of depression among both groups limited the ability to detect differences between groups. This study defined adherence as the completion of the recommended course of treatment. Unadjusted analysis was conducted to assess the association of citalopram use with adherence and SVR.

The poor-quality retrospective cohort study⁹⁵ examined the effect of the use of antidepressants among those experiencing or not experiencing depressive symptoms during HCV therapy. Patients were categorized as having depression if there was at least one mention of depressive symptoms in their medical chart during the course of their HCV therapy, regardless of any followup treatment. This study compared four treatment groups: (1) no depressive symptoms experienced; (2) depressive symptoms experienced, but no antidepressant treatment received; (3) pre-existing and/or prophylactic antidepressant use before therapy; and (4) on-demand therapy for depressive symptoms. For the purpose of our review, we only compared two relevant strategies—on-demand psychiatric therapy (group 4, n = 25) compared with no antidepressant

treatment in the presence of depressive symptoms (group 2, n = 17). This study made no comparisons by group according to important patient characteristics and none of the analyses were adjusted for potential confounders, which presents a major risk of bias in this study. In addition, although the percent of patients who completed treatment was presented by group, this outcome reflected physician-directed discontinuations in treatment *not* patient-directed lack of adherence.

Quality of Life

One study⁶¹ applied the LASA scale to assess the change in QOL from baseline in patients using epoetin compared with those receiving a reduction in ribavirin. The LASA scale includes scores for energy- and activity-related QOL. At 36 weeks, improvements were apparent in both scores from baseline in group 1 patients using epoetin (energy score change, 18 ± 17.3 ; activity score change, 20 ± 18.5) and in group 2 patients (with weight-based reduction in ribavirin (energy score change, 12.2 ± 21.6 ; activity score change, 7 ± 18.7). These changes were statistically significantly larger in the epoetin group ($p < 0.05$ for energy score, and $p < 0.01$ for activity score) than the ribavirin-reduction comparison group (Appendix F).

Sustained Viral Response

Three studies^{61,95,96} reported SVR. Of these, one RCT⁹⁶ did not report sufficient data to allow calculation of effect estimates. In the comparative effectiveness trial that compared epoetin with a reduction of ribavirin dosing, patients on epoetin were statistically significantly more likely to achieve SVR (59.7% vs. 34.4%; OR 2.83, 95% CI, 1.40 to 5.72).⁶¹ While the use of antidepressants appeared to reduce SVR compared with usual care (36% vs. 53%; OR 0.5, 95% CI, 0.14 to 1.75),⁹⁵ this result was based on a poor retrospective study.

Early Viral Response

One study⁹⁶ reported EVR for genotype 1 and genotypes 2/3. In both patient genotype cohorts, a higher proportion of patients on citalopram than patients receiving a placebo achieved EVR (75% vs. 44.4% in genotype 1; 85.7% vs. 81.8% in genotypes 2/3). These differences, however, were not statistically significant.

Adherence

Two studies^{96,97} reported adherence outcomes. In study by Morasco and colleagues,⁹⁶ 84.2 percent of patients receiving citalopram completed their recommended course of treatment, compared with 75.0 percent of patients receiving placebo, although this difference was not statistically significant (OR 2.13, 95% CI, 0.34 to 13.24). The reasons patients did not finish recommended treatment did not differ between the two groups and included medical factors (n = 3) and noncompliance (n = 1). In the RCT by Ramsey and colleagues,⁹⁷ 50 percent of the CBT-intervention group were considered to be adherent (i.e., received at least 24 pegIFN- α injections over the course of their therapy), compared with 80 percent of the control group. Again, this was not a statistically significant difference (ORadj, 0.19 95% CI, 0.03 to 1.15).

Does the Comparative Effectiveness of Treatment Adherence Interventions Differ by Patient Subgroups?

None of the included studies assessed whether the comparative effectiveness of adherence interventions on adherence differed by patient subgroups.

Key Question 3. Harms

Key Question 3. What are the harms associated with hepatitis C antiviral treatment adherence interventions?

Only two poor-quality RCTs^{61,96} reported information on harms related to an adherence intervention. Both studies evaluated the use of medications (i.e., epoetin and citalopram) to prevent or manage the side effects related to antiviral treatment. Although neither study found adverse events associated with the use of epoetin or citalopram, both studies were quite small and short-term. In addition, the relatively small trial (n = 29) comparing the effect of CBT with usual care found that more participants in the usual care control group than in the intervention group received at least 24 pegIFN- α injections at 24 weeks (i.e., were considered adherent). This effect was also not statistically significant.

Table 8. Outcomes of system-level interventions

Study, Year Quality	Study Design	Comparison	Group	Sample Size (N)	EVR*, n (%)	SVR†, n (%)	Odds Ratio (95% CI)	Adherence Definition & Measurement Method	Time Point	Adherence Outcome, n (%)	OR (95% CI)
Cohen, 2009 ⁶⁵ Fair	Retro-spective cohort	Specialty care vs. standard retail pharmacies	E	95	NR	46 (48)	0.69 (0.37 to 1.30)§	Patients who did not self-discontinue treatment‡ Chart review	Complete treatment (24 or 48 weeks)	85 (89)	0.35 (0.11 to 1.15) [¶]
			NE	102		57 (56)				98 (96)	
Bonkovsky, 2008 ⁶⁴ Poor	RCT	Supervised treatment vs. self-administered treatment in methadone users	IG	24	NR	13 (54) [¶]	2.36 (0.73 to 7.60) [¶]	NA	NA	NA	NA
			CG	24		8 (33) [¶]					
Bruce 2012 ⁹⁸ Poor	RCT	Supervised treatment vs. self-administered treatment in methadone users	IG	12	10 (83)	6 (50)	8.0 (0.75-85.31) [¶]	NA	NA	NA	NA
			CG	9	3 (33)	1 (11)					

CG = control group; CI = confidence interval; E = exposed group; EVR = early viral response; HCV = hepatitis C virus; IG = intervention group; NA = not applicable; NE = nonexposed group; OR = odds ratio; RCT = randomized controlled trial; SVR = sustained viral response; Vs = versus

*EVR is traditionally defined as an undetectable viral load at 12 weeks of treatment.

†SVR is traditionally defined as an undetectable viral load 24 weeks after treatment is completed.

|| Physician directed discontinuation of treatment.

‡Other reasons for treatment discontinuation include: nonresponder (32) and breakthrough (4).

§Based on a multivariate analysis.

[¶]Value calculated.

Table 9. Outcomes of regimen-related interventions

Study, Year Quality	Study Design	Comparison	Group	Sample Size (N)	Adherence Definition & Measurement Method	Time Point	Adherence Outcome, n (%)	OR (95% CI)
Alam, 2010 ⁹⁰ Fair	Prospective cohort	RibaPak vs. traditional ribavirin	E	346	Those who took at least 80% of their doses during the 4 wks prior to the 12- or 24-week followup	12 weeks	251 (94)*	2.18 (1.47 to 3.23)§
						24 weeks	209 (98)†	1.90 (1.30 to 2.78)§
			NE	157		12 weeks	86 (84)*	
						24 weeks	70 (89)†	

CI = confidence interval; E = exposed group; NE = nonexposed group; OR = Odds ratio; Vs = versus; wks = weeks

*p<0.05.

†p<0.01.

§Value calculated.

Table 10. Outcomes of patient-level interventions

Study, Year Quality	Study Design	Comparison	Group	Sample Size (N)	EVR*, n (%)	SVR†, n (%)	Odds Ratio (95% CI)	Adherence Definition & Measurement Method	Time Point	Adherence Outcome, n (%)	OR (95% CI)		
Cacoub, 2008 ⁹¹ Good	Prospective cohort	Therapeutic education vs. usual care	E	370	NR	230 (77)‡	1.54 (0.99 to 2.40)	Adhered to the 2 treatment drugs for at least 20 wks.	12 weeks	164 (66)	1.04 (0.69 to 1.56)		
				24 weeks		126 (61)§			1.58 (1.02 to 2.46)				
			NE	304		171 (70)‡		Self-reported via patient questionnaire	12 weeks	137 (63)			
									24 weeks	83 (47)§			
Hussein 2010 ⁹³ Good	Retrospective cohort	Patient support program vs. usual care	E	780	NR	NR	NA	Number of pegIFN injections dispensed & the proportion of patients for whom an average of at least 1 injection per week was dispensed during followup	12 weeks	562 (72) ^{§¶}	1.45 (1.17 to 1.80)#		
				24 weeks					332 (52) ^{§¶}	1.47 (1.19 to 1.80)#			
				48 weeks					73 (22) ^{§¶}	1.77 (1.20 to 2.62)#			
			NE	780					171 (70)‡	Health claims data	12 weeks	499 (64) ^{§¶}	
											24 weeks	262 (41) ^{§¶}	
											48 weeks	43 (13) ^{§¶}	
Larrey, 2011 ⁹⁴ Poor	RCT	Nurse education vs. usual care	IG	123	86 (72.8)§	47 (38.2)§	1.88 (1.08 to 3.25) ¶	Non-patient directed discontinuation ††	Complete treatment**	113 (92)	1.48 (0.63 to 3.47)		
			CG	121	64 (57.6)§	30 (24.8)§				NR		107 (88)	

Table 10. Outcomes of patient-level interventions (continued)

Study, Year Quality	Study Design	Comparison	Group	Sample Size (N)	EVR*, n (%)	SVR†, n (%)	Odds Ratio (95% CI)	Adherence Definition & Measurement Method	Time Point	Adherence Outcome, n (%)	OR (95% CI)
Curcio, 2010 ⁹² Poor	Prospective cohort	Multidisciplinary education vs. usual care	E	16	NR	11 (68.7)	2.6 (0.69 to 9.81)	"Completed therapy", no other details given	Complete treatment**	12 (75)	4.38 (1.16 to 16.64)‡
			NE	32		11 (45.8)		Clinical interviews & nurse administered doses	Complete treatment**	13 (41)	

CI = confidence interval; CG = control group; E = exposed group; EVR = early viral response; IG = intervention group; NA = not applicable; NE = nonexposed group; NR = not reported; OR = Odds ratio; RCT = randomized controlled trial; SVR = sustained viral response; Vs = versus; Wks = week(s)

*EVR is traditionally defined as an undetectable viral load at 12 weeks of treatment.

† SVR is traditionally defined as an undetectable viral load 24 weeks after treatment is completed.

‡p<0.05.

§p<0.01.

|| Based on a multivariate analysis.

¶ Value calculated.

#Value calculated based on adjusted data from propensity score matching.

**24 or 48 weeks.

†† Other reasons for discontinuation include: side effects (22), associated disease (9), no virologic response (14), alcohol abuse (5), lost to followup (5), other (6).

Table 11. Outcomes of adverse event management interventions

Study, Year Quality	Study Design	Comparison	Group	Sample Size (N)	EVR*, n (%)	SVR†, n (%)	OR (95% CI)	Adherence Definition & Measurement Method	Time Point	Adherence Outcome, n (%)	OR (95% CI)
Ramsey, 2011 ⁹⁷ Fair	RCT	Cognitive-behavioral therapy to prevent depression vs. usual care	IG	14	NR	NR	NR¶	Having received 24 pegIFN injections at 24 weeks of treatment Chart review	Complete treatment (24 or 48 weeks)	7 (50.0)	0.19 (0.03 to 1.15)
Bertino, 2010 ⁶¹ Poor	RCT	HCV Patients on epoetin vs. usual care	IG1	67	NR	40 (59.7)‡	2.83 (1.40 to 5.72)	NA§	NA	NR	NR
			IG2	67		23 (34.4)‡					
Morasco, 2010 ⁹⁶ Poor	RCT	HCV Patients on citalopram vs. placebo	IG	19	Genotype 1: NR (75) Genotype 2/3: NR (85.7)	Genotype 1: NR (41.7) Genotype 2/3: NR (28.6)	NR¶	Completion of the recommended course of treatment NR	Complete treatment (24 or 48 weeks)	16 (84.2)	2.13 (0.34 to 13.24)¶
			CG	20	Genotype 1: NR (44.4) Genotype 2/3: NR (81.8)	Genotype 1: NR (33.3) Genotype 2/3: NR (63.6)				15 (75.0)	
			CG	15						12 (80.0)	

Table 11. Outcomes of adverse event management interventions (continued)

Study, Year Quality	Study Design	Comparison	Group	Sample Size (N)	EVR*, n (%)	SVR†, n (%)	OR (95% CI)	Adherence Definition & Measurement Method	Time Point	Adherence Outcome, n (%)	OR (95% CI)
Liu, 2010 ⁹⁵ Poor	Retro-spective cohort	Depressive HCV patients & took antidepressants vs. patients who took no antidepressants	E	25	NR	9 (36)	0.5 (0.14 to 1.75)	NA§	NA§	NA§	NA§
			NE	17		9 (53)					

CG = control group; CI = confidence interval; E = exposed group; EVR = early viral response; HCV = hepatitis C virus; IG = intervention group; NA = not applicable;

NE = nonexposed group; NR = not reported; OR = odds ratio; PegIFN = pegylated interferon; RCT = randomized controlled trial; SVR = sustained viral response; Vs = versus

*EVR is traditionally defined as an undetectable viral load at 12 weeks of treatment.

†SVR is traditionally defined as an undetectable viral load 24 weeks after treatment is completed.

‡p<0.01.

§Physician-directed discontinuation of treatment.

|| Value calculated.

¶ Insufficient data for calculating.

Summary and Discussion

Overview of Main Findings

We identified 12 studies—including 6 RCTs and 6 cohort studies—that addressed the comparative effectiveness of adherence interventions on health outcomes, intermediate markers, and patient adherence in hepatitis-C patients treated with the standard dual combination viral therapy. This existing body of literature, however, had substantial methodological and clinical heterogeneity.

The six included RCTs were rated as primarily poor quality, and all included small sample sizes (21-250). While two good-quality cohort studies^{91,93} included a relatively large number of patients (674 and 1560) and reported effect estimates that adjusted for the influence of potential risk factors, the remaining cohort studies had serious methodological limitations and generally had small sample sizes. We also found important variations in patient populations in all of the included studies, such as including patients with differing genotypes, history of substance abuse, and history of antiviral treatment. These factors may represent potentially important risk factors for treatment response and/or adherence (see Table 1). Patient populations also differed in racial and ethnicity distribution, as well as patient comorbidities.

How these studies evaluated adherence interventions was another source of heterogeneity. While studies are grouped into four general categories, studies within a single category often investigated interventions that differed in their components and intensity. Interventions for managing adverse events, for example, included medications addressing different conditions (e.g. epoetin for preventing anemia vs. antidepressants for depression), the use of antidepressants to prevent or to manage depression once it occurred, and CBT to prevent depression. Similarly, the three system-level interventions had different approaches. One intervention evaluated the effect of specialty compared with standard pharmacy services and the other two evaluated direct observation treatments on QOL or intermediate outcomes. The most consistent grouping was the four patient-level interventions that enhanced patient education and/or support in order to improve adherence. Despite this, we were not able to identify the most successful intervention components given the lack of detailed descriptions, differences in intervention providers (e.g., nurses vs. physicians vs. psychologists), and differences in approaches in the various interventions.

The included studies rarely reported health outcomes, which hampered our ability to directly interpret the evidence. In addition, we were unable to pool the intermediate outcomes due to differing definitions and measurement methods for adherence. Although the completion of HCV treatment is a commonly used definition, studies used different thresholds for defining treatment completion. We encountered additional issues in cross-trial comparisons for these studies, including studies that may target the completion of different antiviral agents (i.e., ribavirin vs. pegIFN- α vs. both) or fail to clarify which antiviral agents they measured. The methods of measuring adherence included self-reported questionnaire, one-on-one interviews, pill counts, treatment administration records, or chart reviews. Several studies did not report this information. While SVR was commonly reported, this outcome was generally not comparable across studies due to diverse patient populations (with different likelihood of responding to treatment) across the body of evidence.

Outcomes of Adherence Interventions

There is a paucity of evidence assessing the effect of adherence interventions on health outcomes, particularly hepatitis C complications and mortality. Only two small poor-quality studies^{61,64} reported data on QOL. Both studies suggested a tendency toward improved QOL in the adherence intervention groups compared with usual care, despite the interventions' reflecting completely different approaches in very different patient populations: the use of epoetin to manage treatment-associated anemia in 67 patients⁶¹ and the use of DOT in methadone maintenance clinic attendees.⁶⁴ We cannot eliminate the possibility that these positive findings are affected by publication, reporting, or other biases. Nonetheless, the fact that the few studies that reported any health outcomes tended towards benefit and also did not indicate a decrement in intermediate measures of adherence and treatment response (i.e., SVR) should be encouraging to patients, clinicians, and researchers as this would be consistent with overall potential health benefit.

The association of adherence interventions with viral response, particularly SVR, was the most commonly investigated outcome in the available literature. In general, adherence interventions tended to result in greater proportions of patients achieving SVR (and EVR where reported), but few studies showed statistically significant differences between groups. When considered by intervention type, the evidence for increased SVR was most consistent for patient-level adherence interventions. Whether viewed by intervention type or considered as a whole, however, the available evidence is very weak in suggesting a clear improvement in SVR through adherence interventions.

Almost all included studies that measured adherence showed that interventions tended to improve adherence, despite the varying quality, interventions, definitions, and measurements. Additionally, the magnitude of the association remained consistent (or increased) over time (12 vs. 24 vs. 48 weeks) in those studies reporting adherence data in multiple followup time points.^{90,91,93} The two fair-quality studies – one evaluating the effect of specialized pharmacy care⁶⁵ and the other evaluating the effect of CBT⁹⁷ – that showed no impact on adherence (and suggested a possible increase in nonadherence) after the interventions were imprecise in their estimates and relatively small. The existing body of literature offers little data about the harms associated with adherence interventions.

Strength of Evidence

We present the strength of the evidence for *health outcomes* for all studies by intervention group in Table 12. The strength of the evidence for *intermediate outcomes* for all studies by intervention group is presented in Table 13. We summarize this information by outcome and intervention group in narrative below.

Health Outcomes

Overall, we found insufficient evidence to determine the effect of adherence interventions on health outcomes. No studies reported morbidity, all-cause mortality, or HCV-specific mortality. In addition, no studies reported on HCV transmission. One poor-quality RCT and one poor-quality cohort study provided evidence for quality-of-life improvements that resulted from patient adherence interventions, but it was insufficient due to risk of bias, imprecision, and lack of a sufficient number of studies.

Two poor-quality RCTs with a high risk of bias provided insufficient evidence for harms related to adherence interventions. Both of these studies tested the effect of medications (e.g., epoetin and citalopram) to help manage side effects related to HCV treatment. Both studies reported that no patients showed adverse events related to the use of these medications, but provided no additional details.

Intermediate Outcomes

The strength of evidence is insufficient-to-low for SVR achievement through adherence interventions that manage adverse events, provide patient education and support, or directly oversee HCV therapy in patients at high risk for nonadherence (methadone maintenance clinic patients). This rating is due to medium-to-high risk of bias, imprecision, and lack of sufficient numbers of comparable studies.

We also found insufficient evidence on how interventions affected EVR based on three RCTs with high risk of bias. One study presented inadequate data, which precluded determination of estimates of overall consistency and precision.

We deemed the strength of evidence to be insufficient (based on one fair- and two poor-quality RCTs) or low (based on five primarily fair-to-good quality cohort studies) for improved adherence as a result of various types of interventions. In general, the cohort studies found that adherence interventions had a consistent benefit on patient adherence.

System-Level Interventions Versus Usual Care

We found insufficient evidence regarding the impact of system-level interventions on QOL, SVR, EVR, or adherence. No evidence exists regarding mortality and morbidity.

Regimen-Related Interventions Versus Usual Care

We found insufficient evidence on the association between regimen-related interventions and patient adherence. We found no evidence about other outcomes.

Patient-Level Interventions Versus Usual Care

We judged the strength of evidence for the association between patient-level interventions and the achievement of SVR to be low. We made this valuation based on a medium risk of bias across three studies with consistent effects, despite imprecise estimates and the fact that these outcomes were indirect.

The studies provided generally consistent and precise effect estimates related to patient adherence. We judged the strength of evidence to be moderate given the relatively few studies (four) with overall medium risk of bias and the indirectness of the outcome. More research in this area may affect this estimate and our confidence in the effect estimate. Only one study examined the effect of a patient-level intervention on EVR. As a result, we found the strength of evidence to be insufficient. There was no evidence regarding health outcomes, including harms related to patient-level adherence interventions.

Adverse Event Management Interventions Versus Usual Care/Placebo

The strength of evidence on QOL was found to be insufficient, based on a relatively small poor-quality RCT. The evidence on harms was also insufficient given the high risk of bias and the lack of detail provided. Similarly, we judged the evidence on SVR, EVR, and adherence to be insufficient due to high risk of bias, the inconsistency and imprecision of the effects, and the

indirectness of the outcomes. Again, no evidence addressed the effects of the intervention on mortality or morbidity.

Table 12. Strength of evidence for health outcomes

Outcome	Group	Number of Studies	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence
Key Question 1: Quality of life	All interventions vs. control	2 RCTs	High	Unknown	Direct	Imprecise	Insufficient
	System-level interventions vs. control	1	High	Unknown	Direct	Imprecise	Insufficient
	Regimen-related intervention vs. control	0	--	--	--	--	Insufficient
	Patient-related intervention vs. control	0	--	--	--	--	Insufficient
	Adverse event management intervention vs. control	1	High	Unknown	Direct	Imprecise	Insufficient
Key Question 1: Mortality & Morbidity	All interventions vs. control	0	--	--	--	--	Insufficient
	System-level interventions vs. control	0	--	--	--	--	Insufficient
	Regimen-related intervention vs. control	0	--	--	--	--	Insufficient
	Patient-related intervention vs. control	0	--	--	--	--	Insufficient
	Adverse event management intervention vs. control	0	--	--	--	--	Insufficient
Key Question 3: Harms	All interventions vs. control	2 RCTs	High	Unknown	Unknown†	Unknown†	Insufficient
	System-level interventions vs. control	0	--	--	--	--	Insufficient
	Regimen-related intervention vs. control	0	--	--	--	--	Insufficient
	Patient-related intervention vs. control	0	--	--	--	--	Insufficient
	Adverse event management intervention vs. control	2	High	Unknown†	Unknown†	Unknown†	Insufficient

DOT = directly observed therapy; QOL = quality of life; RCT = randomized controlled trial; vs. = versus

†No reported adverse events related to intervention without further detail. Thus, the consistency, directness, and precision of the outcomes are unknown.

Table 13. Strength of evidence for intermediate outcomes

Outcome	Group	Number of Studies	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence
Key Question 1: SVR	All interventions vs. control	5 RCTs	High	Consistent	Indirect	Imprecise	Low
		4 Cohort	Medium	Inconsistent	Indirect	Imprecise	Insufficient
	System-level interventions vs. control	3	High	Inconsistent	Indirect	Imprecise	Insufficient
	Regimen-related intervention vs. control	0	--	--	--	--	Insufficient
	Patient-level intervention vs. control	3	Medium	Consistent	Indirect	Imprecise	Low
	Adverse event management intervention vs. control	3	High	Inconsistent	Indirect	Imprecise	Insufficient
Key Question 1: EVR	All interventions vs. control	3 RCTs	High	Unknown	Indirect	Unknown	Insufficient
	System-level interventions vs. control	1	High	Unknown	Indirect	Unknown	Insufficient
	Regimen-related intervention vs. control	0	--	--	--	--	Insufficient
	Patient-level intervention vs. control	1	High	Unknown	Indirect	Precise	Insufficient
	Adverse event management intervention vs. control	1	High	Unknown	Indirect	Unknown	Insufficient
Key Question 2: Adherence	All interventions vs. control	3 RCTs	High	Inconsistent	Indirect	Imprecise	Insufficient
		5 Cohort	Medium	Consistent	Indirect	Precise	Low
	System-level interventions vs. control	1	Medium	Unknown	Indirect	Imprecise	Insufficient
	Regimen-related intervention vs. control	1	Medium	Unknown	Indirect	Precise	Low
	Patient-level intervention vs. control	4	Medium	Consistent	Indirect	Precise	Moderate
Adverse event management intervention vs. control	2	Medium	Inconsistent	Indirect	Imprecise	Insufficient	

EVR = early viral response; RCT = randomized controlled trial; SVR = sustained viral response; vs. = versus

Findings in Relationship to What Is Already Known

To our knowledge, there are no published systematic reviews that specifically examine the effectiveness or comparative effectiveness of adherence interventions for antiviral therapy of hepatitis C. However, AHRQ recently published a systematic review that examined the comparative effectiveness of adherence interventions in patients with chronic diseases with self-administered medication.⁸⁷ This review has important differences with our study. For example, it excluded patients with infectious conditions and conditions for which medications are administered in hospitals or health care offices, while these are the target population of our study. Similar to our study, the published review identified significant heterogeneity in the methods for measuring adherence, types and characterization of adherence interventions, as well as suggested low strength of evidence for a number of adherence interventions. In summary, our study provides supplementary and useful evidence in relation to the published AHRQ review. In particular, our study addressed a disease condition that was not assessed in the published review. Both studies identified similar patterns of evidence and research gaps.

Applicability of the Evidence to the United States Health Care System

The findings from included studies have generally good applicability to HCV patients in the United States receiving standard (dual) combination therapy of pegIFN- α and ribavirin. However, given the recent recommendation for adding protease inhibitors to the existing combination therapy for patients with genotype 1 HCV, which represents the preponderance of HCV infections in the United States,¹⁷ the available evidence is unlikely to be directly applicable to the present patients with genotype 1 HCV.³¹ In general, patient adherence to medication regimens often decreases as the complexity of the treatment regimen increases. It is plausible that the addition of a third agent administered multiple times per day is likely to further impact patients' ability and likelihood of complying to treatment. In June 2012, the CDC called for universal HCV screening of the "baby boomer" population (i.e., individuals born between 1945 and 1965).⁴ Such screening could result in a rapid increase in the number of individuals being treated for HCV and subsequently struggling with adherence.

Seven of the 12 included studies were conducted in the United States. The remaining trials were conducted in France (k=2) or Italy (k=2). Two studies enrolled patients from a primary care setting,^{96,97} two from specialized hepatology units,^{61,65} three from addiction management centers,^{64,92,98} and four from multiple clinics.^{90,91,94,95} The other trial did not specify study setting. These studies included both academic and nonacademic centers.

Most studies had wide inclusion criteria, although a number of studies excluded those presumed to be less responsive to therapy (i.e., with coexisting infections or previous history of HCV treatment) or those at risk for poor adherence (i.e., with psychological illnesses or current or previous substance abuse). Patients coinfecting with HBV, HIV, and/or hepatitis D virus (HDV) were excluded in five studies,^{61,64,65,90,94} those with ongoing depression were excluded in two,^{94,96} and patients having a history of and/or active substance use were excluded in two studies.^{95,96} Across all studies, there were a larger proportion of males than females and the majority of patients were Caucasian. Patients with HCV genotypes 1 or 4 were the primarily studied population, and the majority of patients had genotype 1 HCV in seven of the 12 included studies. Four studies^{64,92,97,98} exclusively enrolled patients currently abstinent from drugs and

other substances, but seeking treatment for drug abuse in methadone maintenance or other addiction centers. These data, although limited, suggest that patients at risk for poorer adherence may be appropriate candidates for HCV therapy coupled with effective adherence interventions. Generally, patients included in those studies were representative of the prevalent HCV population in the United States.

Patients in the included studies exclusively used standard doses of combination antiviral therapy of pegIFN- α and ribavirin. The intended duration of treatment in all studies was 48 weeks for patients with genotypes 1 or 4, and 24 weeks for those with genotype 2 or 3. Again, although the antiviral therapy was consistent with the current recommendations for patients with genotypes 2, 3, or 4, the currently recommended treatment for patients genotype 1 has shifted from the standard combination therapy to the triple therapy, in which a protease inhibitor is added to the combination of pegIFN- α plus ribavirin.¹²

A wide variety of adherence interventions were investigated in the included studies. These interventions included simplifying dosing, the use of medications or counseling for managing adverse events, patient education and support by various parties to motivate antiviral medication use or help manage adverse events, and provision of care within specialized care delivery systems (e.g., specialized pharmacies, methadone clinics). We found no studies that directly compared the effectiveness of one type of intervention with that of another type of intervention. In addition, very little detail was given in the majority of the studies regarding the specific intervention components, messages, frequency, and duration. Thus, it is unclear how feasible or effective these interventions would be in real-world settings.

Limitations

Potential Limitations of Our Approach

Our approach has a number of potential limitations. Our systematic review methodology may not be the ideal method to synthesize findings across studies that are predominately poor quality, with a high level of heterogeneity. Additionally, there are likely major limitations in determining the effect of treatment adherence interventions on both intermediate and final health outcomes because of multiple confounding factors that also affect response to treatment (e.g., age, genotype, BMI, viral load). Because we are limited to the data that are presented in the primary studies, we were unable to adjust for many of these potential confounders. We discuss other limitations of the literature below.

We also excluded studies with length of followup shorter than 12 weeks. Although these short-term results may be of interest, such studies can only provide evidence on rapid virological response and possibly EVR, both of which were judged as much less important intermediate outcomes than SVR.

We did not include non-English language studies, and thus may be missed some relevant data. Our search found only 99 citations for potentially relevant studies that were published in languages other than English. The majority of these studies were written in Spanish, French, and German. More importantly, the vast majority of non-English studies may be less applicable to the United States health care system. Therefore, their findings may be of very limited value to the context of our review.

In this systematic review, we included four studies that clearly described adverse event management as a mechanism to help improve patient adherence outcomes and/or reported adherence outcomes (e.g., treatment-related depression). We understand that managing adverse

events is largely a part of the clinical management of antiviral therapy for chronic HCV patients and not solely an issue regarding patient adherence. However, these types of interventions—which often aim to reduce symptomatic adverse events—can improve patients’ use of medications, and represent an important approach to enhancing patient adherence to treatment. Additionally, achieving improved adherence was clearly stated as an aim in those studies.

Limitations of the Literature

There are several major limitations of the available literature. First, the studies are limited to relatively small sample sizes and are of suboptimal quality. Four of the six RCTs had sample sizes smaller than 50, and the other two included 134 and 250 patients, respectively. One RCT was of fair quality, and the other five were considered poor. The quality of cohort studies varied. In the only two good-quality studies,^{91,93} a relatively large number of patients (674 and 1560) were included. Other cohort studies were generally small and had important methodological limitations, including the fact that almost all failed to adjust for the influence of potentially important confounding factors. Additionally, the subpopulations varied substantially in terms of their risk for nonadherence and nonresponse to treatment across studies, which hamper our ability to pool data or results across studies.

Second, inadequate reporting of details about study design and conduct was prevalent across all studies. This resulted in substantial difficulties collecting data and determining the quality and applicability of study findings. For example, limited information was available about the intensity and length of interventions and the parties that carried out interventions. Collectively, these issues represent particularly important potential limitations because most interventions were behavior-based, and lack of implementation details makes it challenging to judge the fidelity, comparability, and applicability of study findings. In another example, many cohort studies, particularly retrospective studies, failed to detail the sources of data, the approaches to acquiring and measuring data, and strategies for controlling the influence of bias. Data on loss to followup were also inadequately reported. There was a significant and disproportionate loss to followup between intervention and control groups in four studies,^{64,93,97,98} which impedes our ability to interpret the true effect of interventions.

Third, there were several serious variations and ambiguities in the definition of adherence used across studies. For example, two studies^{65,92} defined adherence as “completion of treatment.” However, it was unclear which agent or agents (pegIFN- α vs. ribavirin vs. both) this referred to, whether it allowed for any missed doses over the course of treatment, and to what extent it reflected patient- versus physician-initiated changes in treatment. In the eight studies reporting adherence data, at least five different definitions were used (Tables 8–11). The widely varying definitions and measurement of adherence used by study investigators created a major obstacle in our ability to compare findings across studies; this also hampers the ability of clinicians, patients, and policy-makers in using the evidence for practice and decision making.

Many studies failed to distinguish between physician-initiated reductions in dosage or therapy duration and patient-directed nonadherence. Physician-initiated dose-modification or even discontinuation generally represents individualized patient care, which should not be considered as nonadherence. Patient-directed dose-reduction and discontinuation may be due to toxic effects, and many other reasons (e.g., patients not remembering dosing schedule, having difficulties in using pegIFN).⁹⁹ Although debate continues about the inclusion of physician-directed treatment discontinuation or modification in defining “nonadherence,”⁴⁵ for this review we decided that patient-directed nonadherence was the primary focus. Thus, we excluded many

studies that did not present patient- and physician-directed treatment discontinuation separately in their analyses.

Populations varied substantially in terms of their risks for nonresponse to treatment (e.g., what genotypes, previous treatment history, or ages were represented) and their risks for potential nonadherence (i.e., current or past drug users). Within studies, these potentially important factors were not generally assessed for baseline comparability or controlled for in analyses. This was particularly true in prospective and retrospective cohort studies. Of the five cohort studies, only two adequately adjusted for the influence of confounding factors.^{91,93} Other studies either failed to adjust for or inadequately controlled for the influence of other important factors.

Another important limitation in this literature is the fact that all identified studies relied on intermediate outcomes. Likewise, none reported long-term health outcomes besides two that reported on QOL. The goal of adherence interventions is to improve treatment response, typically SVR, and ultimately improve hepatitis C complications, such as cirrhosis and HCC. However, no evidence has examined whether interventions for adherence improve those final long-term health outcomes. Additionally, available evidence assessing the comparative effectiveness of interventions for intermediate outcomes such as SVR is very weak.

Finally, while treatment standards for HCV have been rapidly evolving, available studies have only included patients receiving dual therapy through a standard combination of pegIFN- α and ribavirin. Further research is needed to determine how patient adherence may change with the addition of a third antiviral agent into the standard treatment regimen, and how adherence interventions should be designed to incorporate the new class of drugs. Prior reviews examining treatment adherence have found that patient adherence decrease as treatment regimens become more complex.⁵⁹ However, it is unclear how adherence may change in patients undergoing antiviral therapy for chronic HCV infection with the new therapy regimen. New studies are needed to address the effectiveness of adherence interventions in patients with this new regimen.

Implications for Clinical and Policy Decisionmaking

Available evidence does not provide a clear direction for clinical practice to improve adherence in hepatitis C treatment. The included studies suggest that adherence interventions tended towards improved adherence and/or SVR. In particular, three fair or good cohort studies with moderate sample sizes suggested that patient education and support program as patient-level interventions, as well as special drug packing (i.e. RibaPak) to reduce pill load improved patient adherence. While these findings look promising for clinical practice, the studies included various patient populations and used diverse interventions, and their impact on SVR and health outcomes are uncertain. Thus, we believe that readers should exercise caution when applying the evidence to practice.

Moreover, it continues to be uncertain which specific interventions are effective and what degree of improvement could be expected in current practice, particularly considering the recent updated recommendation for triple therapy in genotype-1 patients. Additionally, the research on the resources and methods for implementing adherence interventions was not within the scope of this systematic review. However, these are important considerations for those who consider implementing adherence interventions in practice,

In general, the available evidence on guiding efforts to improve adherence to recommended treatments of patients with chronic hepatitis C remains very limited. We did not find compelling evidence to suggest that adherence interventions were essential to increase adherence, surrogate

and health outcomes. Nonetheless, general principles such as patient education and support and reducing pill burden that have been shown to increase patient adherence to treatment may be considered, since existing epidemiological studies suggest a consistency in the association between a higher level of adherence and an improved SVR.^{44,73,76}

Evidence Gaps

Substantial gaps exist for all types of adherence interventions. Across all trials, no trials investigated the impact of adherence interventions on long-term health outcomes, such as decompensated cirrhosis, HCC, and mortality. Nearly all studies included genotype-1 HCV patients that received the standard combination antiviral therapy. Therefore, the results may not be applicable to current clinical practice.

For system-level interventions, evidence was inconsistent regarding SVR and substantial uncertainty remains regarding adherence. While it appears that dose simplification is an effective regimen-related strategy to improve adherence, the evidence on SVR is lacking. While generally low, the evidence of patient-related interventions suggested a trend of improvement in SVR and adherence. The evidence for adverse events management is conflicting, although studies with fair-quality RCTs suggest a trend of improvement in SVR.

We identified no studies that evaluated the effect of an intervention that targeted two or more levels of influence (e.g., system-level changes plus patient counseling). It is likely that the most effective interventions would include a combination of changes made to the systems and settings in which HCV care is received, the packaging and delivery of medications and the support and education provided to HCV patients, including strategies to help patients manage side effects related to HCV treatment through medications or behavioral interventions. There is a need in the HCV literature to design and test such comprehensive approaches. Likewise, we identified no studies that evaluated the use of patient reminder systems to improve adherence. This type of intervention has been shown to improve medication adherence related to several other medical conditions.¹⁰⁰

Future Research

Future research should use more rigorous methods in the design and conduct of hepatitis C adherence intervention studies. Although various designs can assess the comparative effectiveness of adherence interventions, RCTs remain the optimal approach for hypothesis testing.¹⁰¹ While cohort studies may be used, they are susceptible to selection bias and are less able to account for unknown prognostic factors than RCTs,¹⁰² despite the use of novel approaches such as propensity scoring.¹⁰³ Future studies should have sufficient power for testing hypotheses, and ideally include longer followup periods to capture long-term health outcomes. As noted earlier, the quality and design of the available literature was a serious limitation in our review.

Studies should also strive to use direct health-related outcomes such as HCV-morbidity, mortality, and QOL, in addition to the surrogate outcomes that are most often reported in the current literature. However, we acknowledge that these outcomes will require longer followup and may be challenging. While longer-term outcome data, such as cirrhosis and HCC, are less readily available in RCTs, it is possible to use cohort studies that rely on patient registries to address this issue. In the meantime, better designed and conducted studies should confirm the relationship between adherence to treatment and SVR, including the effect of adherence interventions on SVR.

The recommended treatment for genotype-1 patients has shifted from the standard combination therapy of pegIFN- α plus ribavirin to triple therapy including protease inhibitors.¹² As such, the available evidence is of very limited value to the treatment of genotype 1 HCV. Although the available literature base may provide indirect evidence regarding interventions for this population, it is unclear how adding new antiviral agent will affect patient adherence. In particular, the administration of the protease inhibitor is complex, and adding this agent to the standard combination therapy will further complicate the treatment. Studies that clearly delineate the risk factors affecting the adherence in this specific group of patients are thus warranted, and adequately powered RCTs testing adherence interventions that address the identified risk factors for the nonadherence to the new treatment regimen are needed.

There is also a strong need for standardizing the definitions of adherence in the context of chronic hepatitis C treatment. Multiple components—including treatment duration, dosing, timing, and intensity—are used in the varying definitions of adherence that we found, and treatment adherence can be associated with one or more antiviral agents in hepatitis C treatment. The multiplicity of domains and components may result in many variants in the definitions about adherence to hepatitis C treatment. In particular, future research should consider using consistent terms and clearly defining the terms in their studies. Emerging systems for defining adherence may help hepatitis C adherence interventions researchers appropriately use and interpret their research.¹⁰⁴ The “80/80/80” criterion is often used in hepatitis C literature but has two major limitations. First, this definition will no longer be applicable to the triple antiviral therapy for genotype 1 HCV patients. Second, there seems a continuous relationship between the level of adherence and the treatment response⁴⁴ so defining adherence vs. nonadherence based on an arbitrary threshold may thus be suboptimal.

Future studies should clearly distinguish physician-initiated dose-reduction or discontinuation from patient nonadherence to treatment. Although physician initiated dose-reduction or discontinuation seems related to adherence, this treatment change is typically due to vital adverse events associated with antiviral therapy, and is based on the treatment protocol. The nature of this change differs from patient nonadherence, in which patients fail to match agreed treatment plan probably because of difficulties in remembering taking medications or following the complex treatments, unwillingness to continue the treatment, and reduced QOL.

In our exploration of risk factors associated with treatment response, we have found a number of potentially important factors associated with treatment response and patient nonadherence (Table 1). Future studies, particularly observational studies, should consider the issue about patient comparability in exposure and nonexposure groups. Efforts are needed to adequately adjust for the influence of those factors.

Finally, as noted earlier, many of the studies we found were of poor quality, with inadequate reporting of study design and intervention details. Future studies should include clearer and more detailed reporting of study design and conduct. Studies need to provide sufficient information about how adherence interventions are undertaken, including the parties of undertaking intervention, such details of interventions such as intervention components, intensity, and duration. Studies should also describe methodological characteristics in more details. RCTs should report details on patient selection, allocation, and followup. In the results, the data on loss to followup should be clearly reported. Cohort studies should provide detail on collected variables, sources of data, accuracy of measurements, and approaches that are used to minimize bias. In addition, studies should be more explicit and clear in defining and measuring adherence. Ideally, study reports should include a section to describe the definition and measurement of

adherence. Due to space limitations in most peer-reviewed journals, authors and journal editors should be encouraged to publish these details as appendices, supplementary material, or as separate design-specific papers, at the very least published online.

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100. Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. *Ann Intern Med*. 2012 Jun 5;156(11):817-284. W. PMID: 22393036.
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104. Vrijens B, De GS, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012 May;73(5):691-705. PMID: 22486599.

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106. Klein MB, Cooper C, Brouillette MJ, et al. CTN-194 (PICCO): design of a trial of citalopram for the prevention of depression and its consequences in HIV-hepatitis C co-infected individuals initiating pegylated interferon/ribavirin therapy. *Contemporary Clinical Trials*. 2008 Jul;29(4):617-30.
107. Litwin AH, Berg KM, Li X, et al. Rationale and design of a randomized controlled trial of directly observed hepatitis C treatment delivered in methadone clinics. *BMC Infect Dis*. 2011 Nov 12;11:315.
108. North CS. Psychoeducation for Hepatitis and Alcohol Behaviors. 2008.
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109. Shun SS. Effects of Activity and Education Program on Patients With Chronic Hepatitis C Infection. 2012.
<http://clinicaltrials.gov/ct2/show/NCT01572233>
110. Sulkowski M. Management of Hepatitis C in HIV Infected Injection Drug Users (IDUs). 2011.
<http://clinicaltrials.gov/ct2/show/NCT01448915>
111. Weiss JJ, Ferrando SJ. Armodafinil for Patients Starting Hepatitis C Virus Treatment. 2011.
<http://clinicaltrials.gov/ct2/show/NCT01470651>

Abbreviations and Acronyms

AASLD	American Association for the Study of Liver Diseases
ALT	alanine transaminase
AHRQ	Agency for Healthcare Research and Quality
BIC	Be In Charge
BMI	body mass index
CBT	cognitive behavioral therapy
CDC	Centers for Disease Control and Prevention
CENTRAL	Cochrane Central Register of Controlled Trials
CER	comparative effectiveness review
CHIP	Children's Health Insurance Program
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DOTS	direct observation treatments
EHC	Effective Health Care
ELISA	enzyme-linked immunosorbent assay
EPC	Evidence-based Practice Center
EVR	early viral response
FDA	Food and Drug Administration
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
Kg	kilograms
LASA	linear analogue self-assessment
MEMS	Medication Event Monitoring System
OR	odds ratio
ORadj	adjusted odds ratio
PCR	polymerase chain reaction
pegIFN	pegylated interferon
pegIFN- α	pegylated interferon alpha
QOL	quality of life
RCT	randomized controlled trial
RNA	ribonucleic acid
SRC	Scientific Resource Center
SVR	sustained viral response
TEP	technical expert panel
TMA	transcription-mediated amplification
TTTC	Together to Take Care
USPSTF	U.S. Preventative Services Task Force
vs.	versus
Wks	weeks

Appendix A. Original Search Strategy

Key:

/ = subject heading (including MeSH, Emtree, etc.)

MH = subject heading

ti = word in title

ab = word in abstract

adj# = adjacent within x number of words

\$ = truncation

* = truncation

pt = publication type

sb = subset

kw = keyword

Databases searched:

MEDLINE

PubMed (publisher-supplied references only)

Cochrane Central Register of Controlled Trials (CENTRAL)

PsycINFO

Cumulative Index to Nursing and Allied Health (CINAHL)

Embase

MEDLINE via Ovid [search date: 12/2/2011]

Database(s): Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2011, Ovid MEDLINE(R) Daily Update November 16, 2011, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 01, 2011

#	Searches	Results
1	Hepatitis C/	19947
2	Hepatitis C, chronic/	12822
3	Hepacivirus/	15764
4	hepatitis c.ti,ab.	37596
5	hcv.ti.	5683
6	1 or 2 or 3 or 4 or 5	45172
7	"Patient Acceptance of Health Care"/	18940
8	Patient Dropouts/	3594
9	Patient Compliance/	27211
10	Medication Adherence/	3080
11	Patient Participation/	10918
12	Patient Satisfaction/	43563
13	Patient Preference/	981

14 Treatment Refusal/	6511
15 "Retention (Psychology)"/	3782
16 ((adhere\$ or nonadhere\$) adj6 (treatment\$ or medication\$ or therapy\$ or therapies or regimen)).ti,ab.	12806
17 ((compliance or comply\$ or complies or complied) adj6 (treatment\$ or medication\$ or therapy\$ or therapies or regimen)).ti,ab.	9662
18 ((compliance or comply\$ or complies or complied) adj3 patient\$).ti,ab.	7688
19 (noncomplan\$ adj6 (treatment\$ or medication\$ or therapy\$ or therapies or regimen)).ti,ab.	946
20 (noncomplan\$ adj3 patient\$).ti,ab.	751
21 (persistence adj6 (treatment\$ or medication\$ or therapy\$ or therapies or regimen)).ti,ab.	1628
22 (concordance adj6 (treatment\$ or medication\$ or therapy\$ or therapies or regimen)).ti,ab.	399
23 patient cooperation.ti,ab.	312
24 (refusal adj3 (treatment\$ or medication\$ or therapy\$ or therapies or regimen)).ti,ab.	449
25 (withdrawal adj3 (treatment\$ or medication\$ or therapy\$ or therapies or regimen)).ti,ab.	3890
26 (discontinua\$ adj3 (treatment\$ or medication\$ or therapy\$ or therapies or regimen)).ti,ab.	12505
27 ((dropout\$ or drop\$ out\$) adj3 patient\$).ti,ab.	1428
28 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	144127
29 6 and 28	1469
30 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/	142687
31 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.	403700
32 control groups/ or double-blind method/ or single-blind method/	80471
33 random\$.ti,ab.	440638
34 placebo\$.ti,ab.	90664
35 clinical trial\$.ti,ab.	133471
36 controlled trial\$.ti,ab.	73483
37 case-control studies/	126566
38 retrospective studies/	304625
39 cohort studies/	111550
40 longitudinal studies/	50064
41 follow-up studies/	262459

42 prospective studies/	227185
43 cohort.ti,ab.	155175
44 longitudinal.ti,ab.	80303
45 follow up.ti,ab.	366017
46 followup.ti,ab.	10035
47 prospective\$.ti,ab.	275033
48 retrospective\$.ti,ab.	241307
49 comparison group\$.ti,ab.	7362
50 control group\$.ti,ab.	169872
51 observational.ti,ab.	48908
52 nonrandom\$.ti,ab.	8674
53 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52	1959137
54 29 and 53	886
55 limit 54 to yr="2001 -Current"	769
56 remove duplicates from 55	766
57 limit 56 to english language	700
58 56 not 57	66

PubMed [search date: 12/2/2011]

#1 "hepatitis c" AND publisher[sb] AND (adhere*[tiab] OR compliance[tiab] OR nonadhere*[tiab] OR noncomplian*[tiab] OR refusal[tiab] OR dropout*[tiab]) Limits: Publication Date from 2001 to 2013 25

#2 "hepatitis c" AND publisher[sb] AND (adhere*[tiab] OR compliance[tiab] OR nonadhere*[tiab] OR noncomplian*[tiab] OR refusal[tiab] OR dropout*[tiab]) Limits: English, Publication Date from 2001 to 2013 24

#3 #14 NOT #15 1

Embase via Ovid [search date: 11/28/2011]

Database(s): Embase 1996 to 2011 Week 46 via Ovid

#	Searches	Results
1	hepatitis C/	49960
2	Hepatitis C virus/	30192
3	1 or 2	61667

4 patient attitude/	32594
5 patient compliance/	65391
6 patient participation/	10418
7 patient preference/	947
8 patient satisfaction/	61564
9 refusal to participate/	586
10 treatment refusal/	6852
11 or/4-10	165624
12 3 and 11	1271
13 randomized controlled trial/	244592
14 clinical trial/ or clinical study/	686750
15 controlled clinical trial/	166321
16 meta analysis/	53262
17 randomization/	45268
18 double blind procedure/	75164
19 single blind procedure/	13023
20 placebo/	140037
21 "systematic review"/	45174
22 case control study/	50896
23 population based case control study/	3688
24 retrospective study/	208153
25 cohort analysis/	99458
26 longitudinal study/	39417
27 follow up/	463440
28 prospective study/	152369
29 control group/	27599
30 observational study/	24075
31 or/13-30	1592663
32 12 and 31	645
33 limit 32 to yr="2001 -Current"	637

34 limit 33 to english language 596

35 33 not 34

41

PsycINFO via APA PsycNET [search date: 11/29/2011]

((KEYWORDS:adhere* OR ab:adhere*) OR (KEYWORDS:nonadhere* OR ab:nonadhere*) OR (KEYWORDS:compliance OR ab:compliance) OR (KEYWORDS:noncompliant* OR ab:noncompliant*)) OR ((IndexTermsFilt:("Client Attitudes" OR "Client Participation" OR "Client Satisfaction" OR "Treatment Barriers" OR "Treatment Compliance" OR "Treatment Dropouts" OR "Treatment Refusal"))

AND

(KEYWORDS:"hepatitis c") OR (ab:"hepatitis c")

AND

[2001 TO 2011]:PublicationYear = 114

english:Language= 109

non-english = 5

CINAHL via EBSCOhost [search date: 11/29/2011]

S1 ((MH "Hepatitis C, Chronic") OR (MH "Hepatitis C")) OR TX "hepatitis c"

S2 ((MH "Medication Compliance") OR (MH "Patient Compliance")) OR ((MH "Patient Dropouts") OR (MH "Patient Satisfaction")) OR (MH "Treatment Refusal")

S3 TX (adhere* OR nonadhere*) OR TX (compliance OR noncompliant*)

S4 S2 or S3

S5 S1 and S4

S6 (MH "Case Control Studies") OR (MH "Matched Case Control") OR (MH "Population-Based Case Control") OR (MH "Prospective Studies") OR (MH "Concurrent Prospective Studies") OR (MH "Nonconcurrent Prospective Studies")

S7 (MH "Correlational Studies") OR TX cohort OR TX observational

S8 (MH "Randomized Controlled Trials") OR (MH "Clinical Trials") OR (MH "Random Assignment") OR (MH "Single-Blind Studies") OR (MH "Double-Blind Studies") OR (MH "Triple-Blind Studies") OR TX clinical n1 trial* OR TX controlled n1 trial* OR PT Clinical trial OR PT randomized controlled trial

S9 S6 or S7 or S8

S10 S5 and S9 Limiters - Published Date from: 20010101-20111231 = 80

Cochrane Central Register of Controlled Trails via Wiley, issue 4 of 4, Oct. 2011 [search date: 12/2/2011]

#1	"hepatitis c":ti,ab,kw, from 2001 to 2011 in Clinical Trials	1779
#2	adhere*:ti,ab,kw OR nonadhere*:ti,ab,kw OR compliance:ti,ab,kw OR noncompliant*:ti,ab,kw, from 2001 to 2011 in Clinical Trials	9853
#3	"patient acceptance":ti,ab,kw OR refusal:ti,ab,kw OR dropout*:ti,ab,kw, from 2001 to 2011 in Clinical Trials	2606
#4	(#2 OR #3), from 2001 to 2011	11922
#5	(#1 AND #4), from 2001 to 2011	112

Appendix B. Studies Pending Assessment

Table B-1. Studies pending assessment

Study Reference	Design	Aim	Location	Number of Participants	Intervention Description	Relevant Outcomes	2012 Status
Bruce 2008 ¹⁰⁵	RCT	Investigate whether integrating HCV treatment into methadone and buprenorphine improves HCV outcomes	US	125	Integrated substance abuse and HCV treatment with DOT	1. HCV viral load 2. Adherence 3. Drug treatment outcomes	Protocol
Klein 2008 ¹⁰⁶	RCT	Investigate whether antidepressant prophylaxis can increase successful completion of HCV therapy	Canada	NR	Administration of citalopram to prevent neuro-psychiatric symptoms	1. Proportion of prescribed pegIFN and ribavirin doses taken per month 2. Development of depression	Protocol
Litwin 2011 ¹⁰⁷	RCT	Investigate whether enhanced DOT (PEG/RBV-DOT) is associated with increased adherence and SVR compared to standard DOT (PEG-DOT)	US	80	Provide adults with directly observed daily ribavirin plus provider-administered weekly IFN	1. Self-reported and pill count adherence 2. End to treatment response or SVR	Protocol; Currently recruiting
North 2008 ¹⁰⁸	RCT	Investigate whether family-responsive psychoeducation can increase eligibility and adherence to HCV treatment	US	400	PsychoEducation Response to Families (PERF)	1. Treatment readiness and adherence to HCV treatment 2. Quality of life	Protocol
Shun 2012 ¹⁰⁹	RCT	Investigate whether exercise can improve health related fitness, quality of life and adherence to HCV therapy	Taiwan	300	Personalized Physical Activity and Psych-Education (PPAPE) Program	1. Health related physical fitness 2. Quality of life 3. Adherence	Protocol; Currently recruiting
Sulkowski 2011 ¹¹⁰	RCT	Determine extent of HCV disease and treatment in IDU;	US	800	Contingent Voucher Incentive (CVI) provided based on	1. Treatment eligibility 2. Liver disease	Protocol; Currently recruiting

		evaluate if behavioral reinforcement interventions increase adherence			clinic visits and HCV treatment adherence	3. staging 4. Treatment incentives 5. Liver stiffness 6. BMI 7. Serum markers	
Weiss 2011 ¹¹¹	RCT	Investigate whether patients undergoing HCV treatment receiving Armodafinil have fewer missed doses, dose reductions, treatment discontinuation.	US	130	Administration of Armodafinil (FDA approved stimulant)	7. Adherence to medications 8. Fatigue Severity Scale (FSS)	Currently recruiting

DOT = directly observed treatment; FDA = Food and Drug Administration; HCV = hepatitis C virus; IDU = intravenous drug users; IFN = interferon; PEG = pegylated; RBV = ribavirin; RCT = randomized controlled trial; SVR = sustained viral response; US = United States

Appendix C. Excluded Studies

1. Alavian SM, Aalaei-Andabili SH. Education by a Nurse Increases the Adherence to Therapy in Chronic Hepatitis C Patients. *Clin Gastroenterol Hepatol* 2012;10(2):203. **KQ1E5, KQ3E5, KQ4E5.**
2. Arase Y, Suzuki F, Suzuki Y, et al. Side effects of combination therapy of peginterferon and ribavirin for chronic hepatitis-C. *Internal Medicine* 2007;46(22):1827-32. PMID: 18025763. **KQ2E1.**
3. Baran RW, Bhor M, Dietz B, et al. Poor adherence to treatment with pegylated interferon/ribavirin in patients with chronic hepatitis C infection is associated with detrimental health outcomes. *Hepatology*. 60th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2009 Boston, MA; 2009. p. 653A. PMID: 70074157. **KQ2E2.**
4. Brau N, Bini EJ, Currie S, et al. Black patients with chronic hepatitis C have a lower sustained viral response rate than non-Blacks with genotype 1, but the same with genotypes 2/3, and this is not explained by more frequent dose reductions of interferon and ribavirin*. *Journal of Viral Hepatitis* 2006 Apr;13(4):242-49. PMID: 16611190. **KQ2E4a.**
5. Chainuvati S, Khalid SK, Kancir S, et al. Comparison of hepatitis C treatment patterns in patients with and without psychiatric and/or substance use disorders. *Journal of Viral Hepatitis* 2006 Apr;13(4):235-41. PMID: 16611189. **KQ2E4a.**
6. Chen T-M, Huang P-T, Wen C-F, et al. Reappraisal of the importance of mutations in the NS5A-PKR-binding domain of hepatitis C-1b virus in the era of optimally individualized therapy. *Journal of Viral Hepatitis* 2011;18(2):119-28. PMID: 20236237. **KQ2E8.**
7. Chun DS. An assessment of support group participation on depression and adherence in veterans with hepatitis C. 63 ed. US: ProQuest Information & Learning; 2002. **KQ3E4a.**
8. Costiniuk CT, Mills E, Cooper CL. Evaluation of oral cannabinoid-containing medications for the management of interferon and ribavirin-induced anorexia, nausea and weight loss in patients treated for chronic hepatitis C virus. *Canadian Journal of Gastroenterology* 2008;22(4):376-80. PMID: 18414712. **KQ3E4a, KQ4E4a.**
9. De Careaga BO. Predictive factors for response to treatment of chronic hepatitis C. *Annals of Hepatology* 2006;5(Suppl 1):S24-S28. **KQ2E1.**
10. Delgado JS, Baumfeld Y, Novack V, et al. Efficacy of combined pegylated interferon and ribavirin therapy in Jewish patients of Israel suffering from chronic hepatitis C. *Hepatology Int* 2011 May 8 PMID: 21553307. **KQ2E8.**
11. Dore GJ, Hellard M, Matthews GV, et al. Effective treatment of injecting drug users with recently acquired hepatitis C virus infection. *Gastroenterology* 2010 Jan;138(1):123-35. PMID: 19782085. **KQ2E4.**
12. Ebner N, Wanner C, Winklbaaur B, 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. *Addiction Biology* 2009 Apr;14(2):227-37. PMID: 19291011. **KQ1E1, KQ2E1, KQ3E1, KQ4E1.**
13. El Makhzangy H, Esmat G, Said M, et al. Response to pegylated interferon alfa-2a and ribavirin in chronic hepatitis C genotype 4. *J Med Virol* 2009 Sep;81(9):1576-83. PMID: 19626613. **KQ2E8.**
14. Evon DM, Esserman DA, Ramcharran D, et al. Social support and clinical outcomes during antiviral therapy for chronic hepatitis C. *Journal of Psychosomatic Research* 2011 Nov;71(5):349-56. PMID: 21999979. **KQ2E2.**
15. Falasca K, Ucciferri C, Mancino P, et al. Use of epoetin beta during combination therapy of infection with hepatitis c virus with ribavirin improves a sustained viral response. *J Med Virol* 2010 Jan;82(1):49-56. PMID: 19950239. **KQ1E1, KQ3E1.**

16. Fumaz CR, Munoz-Moreno JA, Ballesteros AL, et al. Influence of the type of pegylated interferon on the onset of depressive and neuropsychiatric symptoms in HIV-HCV coinfecting patients. *AIDS Care* 2007 Jan;19(1):138-45. PMID: 17129869. **KQ2E2.**
17. Gardenier D, Wisnivesky J, McGinn LK, et al. Hepatitis C treatment completion in individuals with psychiatric comorbidity and depression. *Gastroenterol Nurs* 2011 Mar;34(2):102-06. PMID: 21455042. **KQ3E1.**
18. Gazdag G, Horvath G, Szabo O, et al. Difficulties with interferon treatment in former intravenous drug users. *Brazilian Journal of Infectious Diseases* 2011 Apr;15(2):163-66. PMID: 21503405. **KQ2E2.**
19. Gleason OC, Yates WR, Isbell MD, et al. An open-label trial of citalopram for major depression in patients with hepatitis C. *J Clin Psychiatry* 2002 Mar;63(3):194-98. PMID: 11926717. **KQ3E1.**
20. Gonzalez SA. Consensus interferon: tailored therapy and the impact of adherence. *Digestive Diseases & Sciences* 2011 Mar;56(3):631-34. PMID: 21259073. **KQ1E4, KQ2E4, KQ3E4, KQ4E4.**
21. Grebely J, Matthews GV, Hellard M, et al. Adherence to treatment for recently acquired hepatitis C virus (HCV) infection among injecting drug users. *Journal of Hepatology* 2011;55(1):76-85. PMID: 21145855. **KQ2E4.**
22. Huang JF, Yu ML, Huang CF, et al. The efficacy and safety of pegylated interferon plus ribavirin combination therapy in chronic hepatitis c patients with hepatocellular carcinoma post curative therapies - a multicenter prospective trial. *Journal of Hepatology* 2011 Feb;54(2):219-26. PMID: 21056500. **KQ2E8.**
23. Huckans MS, Loftis JM, Blackwell AD, et al. Interferon alpha therapy for hepatitis C: treatment completion and response rates among patients with substance use disorders. *Substance Abuse Treatment, Prevention, & Policy* 2007;2:4. PMID: 17222348. **KQ2E4a.**
24. Jeong SW, Kim JD, Woo HY, et al. Impact of adherence to peginterferon-ribavirin combination therapy in chronic hepatitis C patients on achieving a sustained virologic response. *Korean Journal of Hepatology* 2009 Sep;15(3):338-49. PMID: 19783883. **KQ2E7.**
25. Kawaguchi Y, Mizuta T, Takahashi K, et al. High-dose vitamins E and C supplementation prevents ribavirin-induced hemolytic anemia in patients with chronic hepatitis C. *Hepatology Research* 2007 May;37(5):317-24. PMID: 17441803. **KQ1E4a, KQ2E4a, KQ3E4a, KQ4E4a.**
26. Kevans D, Farrell G, Hopkins S, et al. Haematological support during peg-interferon therapy for HCV-infected haemophiliacs improves virological outcomes. *Haemophilia* 2007 Sep;13(5):593-98. PMID: 17880449. **KQ2E1.**
27. Kogure T, Ueno Y, Fukushima K, et al. Pegylated interferon plus ribavirin for genotype 1b chronic hepatitis C in Japan. *World Journal of Gastroenterology* 2008;14(47):7225-30. PMID: 19084938. **KQ2E8.**
28. Krook AL, Stokka D, Heger B, et al. Hepatitis C treatment of opioid dependants receiving maintenance treatment: results of a Norwegian pilot study. *Eur Addict Res* 2007;13(4):216-21. PMID: 17851243. **KQ1E1, KQ4E1.**
29. Larrey D, Salse A, Pageaux GP, et al. Effects of systematic nurse-provided therapeutic education on adherence and efficiency of PEG-interferon-ALPHA2A (PEGASYS®)ribavirin treatment in chronic hepatitis C (PEGOBS protocol). *Journal of Hepatology* 2008;48(Suppl 1):S300. **KQ1E2, KQ3E2, KQ4E2.**
30. Larrey D, Salse A, Ribard D, et al. Education by a Nurse Increases Response of Patients With Chronic Hepatitis C to Therapy With Peginterferon-alpha2a and Ribavirin. *Clinical Gastroenterology and Hepatology* 2011;9(9):781-85. PMID: 21683161. **KQ4E2.**
31. Lebray P, Nalpas B, Vallet-Pichard A, et al. The impact of haematopoietic growth factors on the management and efficacy of antiviral treatment in patients with hepatitis C virus. *Antiviral Therapy* 2005;10(6):769-76. PMID: 16218177. **KQ1E7, KQ3E7.**
32. Mak C, Heft SM, Amkraut H, et al. Compliance as an explanatory variable in Hepatitis-C. *Drug Information Journal* 2001;35(4):1351-61. **KQ2E1.**

33. Malaguarnera M, Vacante M, Bertino G, et al. The supplementation of acetyl-L-carnitine decreases fatigue and increases quality of life in patients with hepatitis C treated with pegylated interferon-alpha 2b plus ribavirin. *Journal of Interferon and Cytokine Research* 2011;31(9):653-59. PMID: 21923249. **KQ1E2.**
34. Mangia A, Dalgard O, Minerva N, et al. Ribavirin dosage in patients with HCV genotypes 2 and 3 who completed short therapy with peg-interferon alpha-2b and ribavirin. *Alimentary Pharmacology & Therapeutics* 2010 Jun;31(12):1346-53. PMID: 20222909. **KQ2E1.**
35. Manolakopoulos S, Deutsch MJ, Anagnostou O, et al. Substitution treatment or active intravenous drug use should not be contraindications for antiviral treatment in drug users with chronic hepatitis C. *Liver International* 2010;30(10):1454-60. **KQ1E4a, KQ2E4a.**
36. Marino EL, Alvarez-Rubio L, Miro S, et al. Pharmacist intervention in treatment of patients with genotype 1 chronic hepatitis C. *Journal of Managed Care Pharmacy* 2009 Mar;15(2):147-50. PMID: 19236128. **KQ1E2, KQ3E2, KQ4E2.**
37. McHutchison JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology* 2002 Oct;123(4):1061-69. PMID: 12360468. **KQ1E2, KQ2E2.**
38. Missiha S, Heathcote J, Arenovich T, et al. Impact of asian race on response to combination therapy with peginterferon alfa-2a and ribavirin in chronic hepatitis C. *American Journal of Gastroenterology* 2007 Oct;102(10):2181-88. PMID: 17640318. **KQ2E4a.**
39. Morasco BJ, Rifai MA, Loftis JM, et al. A randomized trial of paroxetine to prevent interferon-alpha-induced depression in patients with hepatitis C.[Erratum appears in *J Affect Disord*. 2009 Feb;113(1-2):201]. *Journal of Affective Disorders* 2007 Nov;103(1-3):83-90. PMID: 17292481. **KQ1E4a, KQ3E4a, KQ4E2.**
40. Nudo CG, Wong P, Hilzenrat N, et al. Elderly patients are at greater risk of cytopenia during antiviral therapy for hepatitis C. *Canadian Journal of Gastroenterology* 2006 Sep;20(9):589-92. PMID: 17001400. **KQ3E4a.**
41. Raptopoulou-Gigi M, Tsantoulas D, Vafiadi I, et al. The effect of adherence to therapy on sustained response in daily or three times a week interferon alpha-2b plus ribavirin treatment of naive and nonresponder chronic hepatitis C patients. *Journal of Viral Hepatitis* 2005;12(1):91-95. PMID: 15655054. **KQ2E4a.**
42. Ridruejo E, Adrover R, Cocozzella D, et al. Efficacy, tolerability and safety in the treatment of chronic hepatitis C with combination of PEG-Interferon - Ribavirin in daily practice. *Annals of Hepatology* 2010 Jan;9(1):46-51. PMID: 20308722. **KQ2E8.**
43. Robaeys G, Van VH, Mathei C, et al. Similar compliance and effect of treatment in chronic hepatitis C resulting from intravenous drug use in comparison with other infection causes. *European Journal of Gastroenterology & Hepatology* 2006 Feb;18(2):159-66. PMID: 16394797. **KQ2E4a.**
44. Rodis JL, Kibbe P. Evaluation of medication adherence and quality of life in patients with hepatitis C virus receiving combination therapy. *Gastroenterol Nurs* 2010 Sep;33(5):368-73. PMID: 20890160. **KQ3E2.**
45. Saab S. Academic perspectives on hepatitis C treatment adherence. *Gastroenterology and Hepatology* 2009;5(3 Suppl 9):6-7. **KQ4E5.**
46. Saito H, Tada S, Ebinuma H, et al. Role of erythrocytes as a reservoir for ribavirin and relationship with adverse reactions in the early phase of interferon combination therapy for chronic hepatitis C virus infections. *Journal of Clinical Microbiology* 2006 Oct;44(10):3562-68. PMID: 17021083. **KQ2E4a.**
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Excluded Codes:

E1: Study relevance: not a study of Hepatitis C Treatment Adherence

E2: No relevant outcomes

E3: Duration of follow-up

E4: Population

E4a: Population not undergoing combination therapy

E4b: >5% of population age <18

E5: Study design

E6: Precedes search period (2001)

E7: Physician initiated tx discontinuation or dose reduction

E8: Efficacy trial

Appendix D. Quality of Included Randomized Controlled Trials

Table D-1. Quality of included randomized controlled trials

Study, Year	Valid Random Assignment?	Allocation Concealed ?	Groups Similar at Baseline?	Measurements: Equal, Reliable, Valid	Blinding of Patients	Blinding of Outcome Assessors	Completeness of Followup	Intervention Fidelity?	Adequate Compliance to Intervention ?	ITT Analysis	Overall Quality
Bertino 2010 ⁶¹	NR	NR	NR	Likely	No	NR	Week 72 Total: 134/134 = 100% IG: 100% CG: 100%	NR	NR	ITT	Poor
Bonkovsky 2008 ⁶⁴	NR	NR	Yes	Likely	No	NR	Total (28/48=58%) IG: 16/42=63% CG: 12/24=50%	NR	NR	ITT	Poor
Bruce 2012 ⁹⁸	Uncertain	NR	Unclear	Likely	No	No	Total (16/21=76.2%) IG: 100% CG: 4/9=44.4%	Likely	NR	Completers only	Poor
Larrey, 2011 ⁹⁴	NR	NR	Yes	NR	No	NR	Total (244/250=97.6%) IG: 123/123=100% CG: 121/127=95.3%	Likely	NR	ITT	Poor
Morasco, 2010 ⁹⁶	Uncertain	NR	Yes	NR	Yes	NR	NR	Likely	NR	NR	Poor
Ramsay, 2011 ⁹⁷	Yes	Yes	No	Likely	NR	NR	Total 82.5% at 48 weeks for DNA data IG: 10/14=71% CG: 14/15=93%	Likely	IG completed mean of 5.93 (out of 8) sessions; 9 of 14 participants completed 6 or more sessions	ITT	Fair

CG = control group; IG = intervention group; ITT = intention to treat; NR = not reported

Appendix E. Quality of Included Cohort Studies

Table E-1. Quality of included cohort studies

Study, Year	Study Type	Selection of the Nonexposed Cohort	Method of Ascertaining Exposure	Measurements: Equal, Reliable, Valid	Blinding of Outcome Assessors	Completeness of Followup	Adjustment/Matching for Potential Confounders	Overall Quality
Alam, 2010 ⁹⁰	Prospective cohort study	Appropriate	Patient registry data	Likely	NR	24 weeks Total: 450/503=89.5% E: 311/346=89.9% NE: 139/157=88.5%	Unadjusted	Fair
Cacoub, 2008 ⁹¹	Prospective cohort study	Appropriate	Patient self-report of therapeutic education by a third party including distribution of support documents	Likely	NR	Total (646/674=96%) Loss to followup not presented by exposure	Adjusted for all important factors that could be obtained	Good
Cohen, 2009 ⁶⁵	Retrospective cohort study	Appropriate	Patient charts; Pharmacy reports of being a "specialty" versus "standard" pharmacy added to patient chart	Likely	NR	NR (all patients included in analyses)	Adjusted for a limited number of important factors in SVR analyses, but not in adherence analyses	Fair
Curcio, 2010 ⁹²	Prospective cohort study	Inappropriate	Exposure is the TTTC group (adequate exposure)	Uncertain	Uncertain	Total (100/100=100%)	Inadequate matching	Poor
Hussein, 2010 ⁹³	Retrospective cohort study	Appropriate	Enrollment in BIC program recorded in claims database	Likely	NR	Retrospective cohort - but missing data at 24 and 48 weeks 24 weeks: E: 638/780=81.8%	Used propensity score matching technique, included several factors in generating propensity score	Good

Study, Year	Study Type	Selection of the Nonexposed Cohort	Method of Ascertaining Exposure	Measurements: Equal, Reliable, Valid	Blinding of Outcome Assessors	Completeness of Followup	Adjustment/Matching for Potential Confounders	Overall Quality
						NE: 7014/8572=81.8%		
Hussein, 2010, cont.						48 weeks: E: 333/780=42.7% NE: 4071/8572=47.5%		
Liu, 2010 ⁹⁵	Retrospective cohort study	Appropriate	Chart review of antidepressant use	Likely	NR	Total (100/100=100%)	Unadjusted	Poor

BIC = Be in Charge; E = exposed group; NE = nonexposed group; NR = not reported; SVR = sustained viral response; TTTC = Together to Take Care

Appendix F. Quality of Life Outcomes

Table F-1. Quality of life outcomes

Study, Year Quality	Study Design	Comparison	Group	Sample Size (N)	Quality of Life Measure	Followup	Quality of Life Score, Mean (SD)	P-value for Difference Between Groups at Followup
Bertino, 2010 ⁶¹ Fair	RCT	HCV Patients on epoetin vs. usual care	IG	67	Energy Score Change*	36 weeks	18 ± 17.3	Energy Score Change: p<0.05 Activity Score Change: p<0.01
					Activity Score Change*		20 ± 18.5	
			CG	67	Energy Score Change*		12.2 ± 21.6	
					Activity Score Change*		7 ± 18.7	
Bonkovsky, 2008 ⁶⁴ Poor	RCT	Supervised treatment vs. self-administered treatment in methadone clinic users	IG	24	Hepatitis specific limitations	Baseline	74.5 (6.0)	NR
						End of Treatment	59.1 (7.4)	
						End of Followup (72 weeks)	84.2 (5.6)	
					Hepatitis specific health distress	Baseline	63.8 (5.5)	
						End of Treatment	58.7 (8.2)	
						End of Followup (72 weeks)	81.6 (6.0)	
			CG	24	Hepatitis specific limitations	Baseline	76.8 (6.1)	
						End of Treatment	40.0 (8.7)	
					Hepatitis specific health distress	End of Followup (72 weeks)	68.9 (9.6)	
						Baseline	69.8 (5.7)	
End of Treatment	50.4 (7.4)							

Study, Year Quality	Study Design	Comparison	Group	Sample Size (N)	Quality of Life Measure	Followup	Quality of Life Score, Mean (SD)	P-value for Difference Between Groups at Followup
Bonkovsky 2008, cont.						End of Followup (72 weeks)	67.3 (7.3)	

*Linear Analogue Self-Assessment (LASA) Scale

CG = control group; HCV = hepatitis C virus; IG = intervention group; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; Vs = versus