Effective Health Care Program

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

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,

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The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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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.

KQ 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?

KQ 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?

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

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.

Figure A. Analytic framework
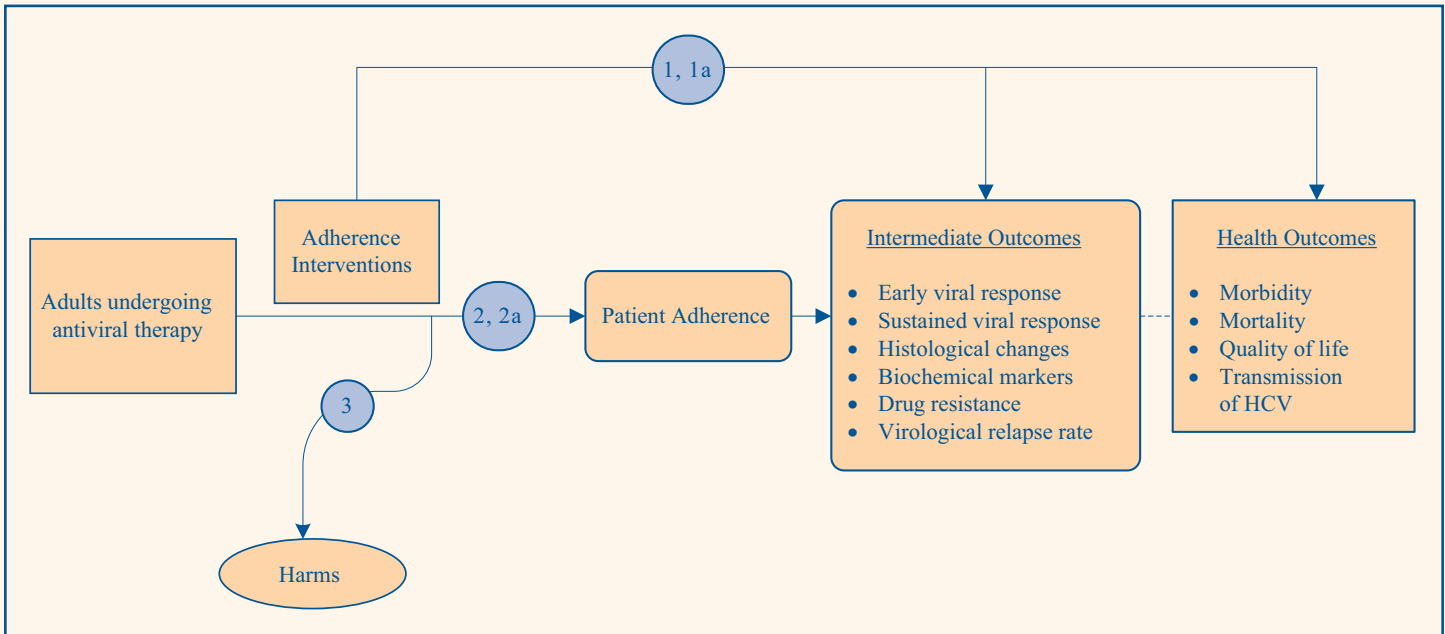
HCV = hepatitis C virus
Note: Numbers in circles refer to Key Questions.

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 Force[20] and the Newcastle-Ottawa Quality Assessment Scale[21] (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
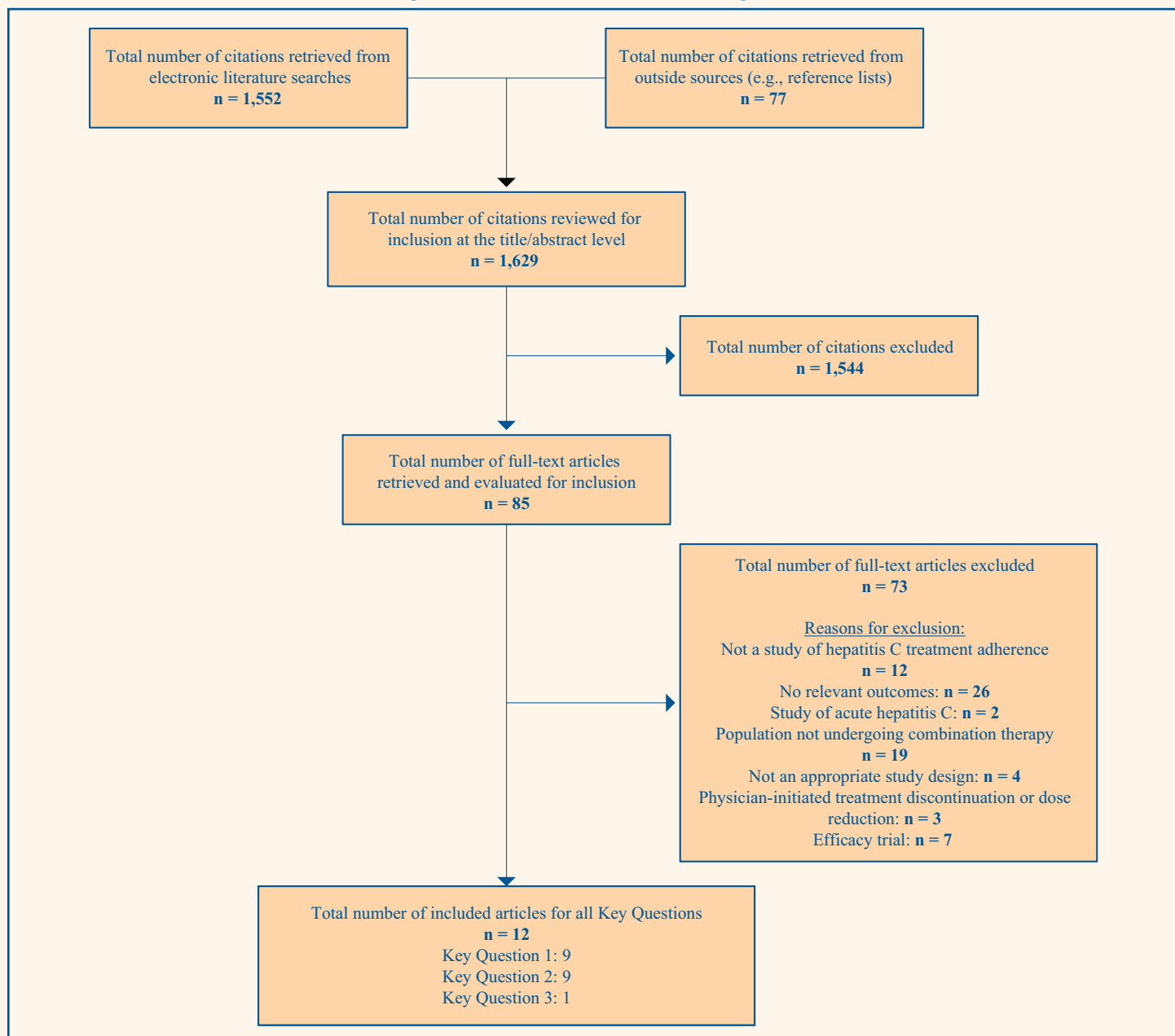
to the U.S. health care setting, as recommended in the AHRQ Methods Guide.[25]

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

Figure B. Literature flow diagram

Total number of citations retrieved from electronic literature searches
n = 1,552

Total number of citations retrieved from outside sources (e.g., reference lists)
n = 77

Total number of citations reviewed for inclusion at the title/abstract level
n = 1,629

Total number of citations excluded
n = 1,544

Total number of full-text articles retrieved and evaluated for inclusion
n = 85

Total number of full-text articles excluded
n = 73

Reasons for exclusion:
Not a study of hepatitis C treatment adherence
n = 12
No relevant outcomes: **n = 26**
Study of acute hepatitis C: **n = 2**
Population not undergoing combination therapy
n = 19
Not an appropriate study design: **n = 4**
Physician-initiated treatment discontinuation or dose reduction: **n = 3**
Efficacy trial: **n = 7**

Total number of included articles for all Key Questions
n = 12
Key Question 1: 9
Key Question 2: 9
Key Question 3: 1

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.

Characteristics of Included Studies

Twelve studies[26-37] met the inclusion criteria for at least one of our Key Questions. Half of these studies were RCTs of fair[36] 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 one[35] 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 colleagues[30] 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 colleagues[28] randomized 48 patients who were enrolled in methadone maintenance programs for at least 3 months to receive supervised (i.e., DOT) pegIFN-α2a (alpha 2a) at methadone clinics once weekly (n=24) compared with self-administration of pegIFN-α2a (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-α2a and ribavirin at methadone clinics once weekly (n=12) or self-administration of HCV therapy (n=9).

Quality of Life

The poor-quality RCT[28] 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 [ORadj], 0.69; 95% confidence interval [CI], 0.37 to 1.30). One poor-quality RCT[28] 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-α2a 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 RCT[37] 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 study[30] 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 study[26] 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 study[29] 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 patients[32] used propensity scoring methods to compare the "Be in Charge" (BIC) program, a patient-support program provided by the manufacturer of pegIFN-α2b (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 RCT[33] 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 study[31] 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–naive 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 study[34] 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 study[27] 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 RCT[35] 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 study[35] 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 crosstrial 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,

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

[a]No 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-related 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-related intervention vs. control	1	High	Unknown	Indirect	Precise	Insufficient
	Adverse event management intervention vs. control	1	High	Unknown	Indirect	Unknown	Insufficient
Key Question 3: 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-related 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

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.

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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