

Factors associated with hepatitis C treatment adherence: an integrative review

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Abstract *This integrative review examined factors associated with hepatitis C treatment adherence. The articles included were published in English, Spanish and Portuguese in the Lilacs, Medline, PsycINFO, Web of Science, Scopus and CINAHL databases, between 2000 and 2019. Initially, 540 publications were found and, after applying the study inclusion criteria, 22 articles were selected. Percentage non-adherence to treatment ranged from 12% to 32%. The variables identified as facilitating adherence were: receiving treatment for psychiatric disorders identified during treatment; knowing about medications and disease; receiving less complex treatment with greater likelihood of cure; fewer adverse events; social support; doctor-patient communication; and/or being in relationships. Barriers to adherence identified were: presence of depressive symptoms and other mental disorders; abuse of alcohol and psychoactive substances; education; age; ethnicity; unemployment; not having a steady partner; stigma; distance from health services; and the complexity and adverse effects of treatment. This review identified gaps in research on adherence.*

Key words *Treatment adherence; Hepatitis C, Review*

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Introduction

The development of an effective therapy using direct-acting antiviral agents to cure infection by the hepatitis C virus has made it even more important to assure adherence to treatment¹. Prevalence of hepatitis C worldwide is approximately 1%, affecting more than 71 million individuals² and accounting for 400,000 deaths annually as a result of its two main complications: hepatic cirrhosis and hepatocellular carcinoma³.

Treatment of hepatitis C with second-generation direct-acting antiviral agents, including sofosbuvir, simeprevir, ledipasvir/sofosbuvir, velpatasvir/sofosbuvir, ombitasvir/paritraprevir/ritonavir and glecaprevir/pibrentasvir with or without ribavirin (RBV), began to be available in 2014, replacing the existing treatment for hepatitis C, which involved using pegylated interferon (PEG-IFN) in association with ribavirin (PEG-IFN+RBV) in a variety of regimes depending on the virus genotype⁴⁻⁶.

In Brazil, treatment with direct-acting antiviral agents has been available in the national health system (*Sistema Único de Saúde*, SUS) since 2015. In many countries and regions, however, the high cost of the medicines is a barrier to access, which is also conditional on certain criteria^{5,6}.

The regime for this new treatment consists in one or two tablets by mouth in contrast to the previous treatment, which involved the patient needing weekly subcutaneous injections of pegylated interferon, as well as taking tablets of ribavirin. In addition to the changes in medications and their administration, the current treatment period is shorter – 8 to 24 weeks, as compared with 72 weeks in previous regimes – and there is less likelihood of adverse events.

With this new treatment, the sustained virological response (SVR) rate, which means that infection by the hepatitis C virus is cured, is 90-95%^{4,7}. Buti and Esteban⁸ and Campos Fernández de Sevilla *et al.*¹ note that the treatment's efficacy can vary with several factors, such as the virus genotype, the severity of the disease and adherence to the treatment. Studies of these new medications suggest that high levels of adherence are necessary in order to achieve sustained virological response and reduce the development of drug resistance, which would prejudice possible future treatments^{9,10}.

It is thus important to bear in mind that treatment adherence is a dynamic, multi-factor process¹¹ which needs to be examined, evaluated and understood, so as to be stimulated in hep-

atitis C treatment with direct-acting antiviral agents.

There is a great deal of diversity in the study of treatment adherence, because of a lack of uniformity in the literature as to the concept, the terminology used and the different measurements used to evaluate adherence^{11,12}. This lack of standardisation has prevented comparisons between research findings and limited the implementation of effective procedures and measures to increase adherence to health-related behaviours^{11,12}.

In this study, adherence was defined as “the extent to which a person's behaviour – taking medication following the recommended diet and/or implementing lifestyle changes – corresponds to the recommendations made by a health professional”¹¹(p.3).

The complexity of this phenomenon stems from the fact that adherence behaviour results from the interaction of factors of different kinds, which can be grouped as: a) individual factors; b) socioeconomic factors; c) factors connected with health services and health personnel; d) factors connected with the disease; and e) factors connected with the treatment itself^{11,13-15}.

In the clinical context, as well as in the research context, there are discussions and divergences as to the best way to assess adherence, given that no method can be considered to be the gold standard^{14,16}. The main methods are known as direct and indirect methods. Self-reporting, pill counts, pharmacy records and patient records, electronic devices and the patient diary are considered to be indirect measurements for assessing treatment adherence. The direct measurements are: detecting the medication in the blood and therapeutic serum level^{11,13-16}. One option for refining assessment of adherence has been to use combined methods^{14,15}.

In addition to different forms of monitoring, quantitative studies apply different standards in considering someone to be adhering or not to treatment^{13,16}. Qualitative studies on this issue are also important and will be included in this review, because they permit greater understanding of adherence-related phenomena from the patient's standpoint, considering social, cultural, psychological, health service- and treatment-related factors and those relating to the relationship between patient and health personnel¹⁶.

There is insufficient systematised knowledge on factors that favour hepatitis C treatment adherence behaviour, understanding such behaviour is inherently complex and it is fundamental to the success of treatment with direct-acting antiviral

agents. Accordingly, it is important to locate and examine studies designed to identify variables associated with hepatitis C treatment adherence. This is crucial, because of the severity of the disease, the complexity and cost of treatment, the requirement of complete adherence in order to obtain SVR and the personal and social impact of the disease and its treatment, which make it a public health problem.

In view of the foregoing, the objectives of this integrative review were to identify, describe and analyse factors associated with adherence to hepatitis C treatment in studies published from January 2000 to October 2019.

Method

To achieve these objectives, an integrative review was conducted^{17,18}, so that studies with different methodological designs (observational studies, cross-sectional studies and qualitative design studies) could be included in the analysis, thus making it possible to identify and analyse the multiple factors that can be associated with treatment adherence behaviour.

An integrative review requires six steps: (1) selecting the topic and developing the research question; (2) establishing the criteria for including studies from the literature; (3) specifying the information to be extracted from the studies selected; (4) evaluating the studies; (5) interpreting the results; and (6) presenting the review^{17,18}.

The guiding question for this integrative review was: “What factors are associated with adherence to hepatitis C treatment?”. In order to conduct this review, the Health Sciences Descriptors (*Descritores em Ciências da Saúde*, DeCS) and Medical Subject Headings (MeSH) were used. Unindexed keywords were also used with a view to encompassing more publications in the search based on three groups of keywords combined using the Boolean method OR and AND: (“hepatitis C” [MeSH Terms] OR “hep C” [Title/Abstract] OR HCV [Title/Abstract] OR “hepatitis c, chronic” [MeSH Terms]) AND Adherence [Title/Abstract] OR “medication adherence” [MeSH Terms] OR “treatment adherence” [All Fields] OR “treatment compliance” [All Fields] OR non-adherence [Title/Abstract] OR nonadherent [Title/Abstract] OR Compliance [Title/Abstract] OR “patient compliance” [MeSH Terms] OR non-compliance [Title/Abstract] OR noncompliant [Title/Abstract]) AND (“psychological factor” [TIAB] OR “psychological predictor” [TIAB] OR

“psychological influence” [TIAB] OR “facilitators” [TIAB] OR “psychological barriers” [TIAB] OR “psychosocial factors” [All Fields] OR “psychosocial barriers” [All Fields] OR “psychosocial influence” [All Fields] OR “socioeconomic factors” [MeSH Terms] OR barriers [All Fields])).

The data search was performed in October 2019 and articles were selected from the electronic data bases Medical Literature Analysis and Retrieval System (Medline), Latin American and Caribbean Health Sciences Literature (Lilacs), PsycINFO, Web of Science, Scopus and Cumulative Index to Nursing and Allied Health Literature (CINAHL).

The inclusion criteria used in this study accepted articles on the subject of hepatitis C treatment adherence in adult patients, published between January 2000 and October 2019, in Portuguese, English or Spanish. The criteria excluded theses, articles arising from reviews, intervention studies and duplicate articles. Publications indexed in more than one database were extracted from the base in which they were first identified, thus eliminating duplicate occurrences.

In order to specify the information to be extracted from the studies selected, the authors developed a data collection instrument, with which they systematised the articles by year of publication, authorship, journal, design, sample size, country of origin of the article, study objective, treatment medication type, method used to assess adherence and significant findings.

The first stage of this study (locating the references) was performed by the first reviewer by reading the titles of the articles encountered in the data bases. In the second stage, the article abstracts were read. In the third and final stage, the articles were read in full to confirm that they met all the study criteria. In the second and third stages, the articles were read and analysed by two researchers independently, so as to avoid selection bias. Disagreements were discussed and evaluated jointly.

The studies were grouped by five factors that could be associated with adherence behaviour^{11,12}: *Individual factors* - lifestyle changes, psychological symptoms, abuse of alcohol and other substances and the presence of psychiatric disorders; *Socioeconomic factors* - age, sex, ethnicity, level of schooling, employment status, marital status, housing conditions, social support and stigma; *Factors relating to the health service and health personnel* - relationship and communication between patient and health professional, limitations of the health service, access to services and medications; *Factors relating to the disease* -

genotype, symptomatology, comorbidity; *Factors relating to the treatment* - number of tablets to be taken daily, treatment type, prior treatments and adverse events.

The factors associated with hepatitis C treatment adherence were analysed in detail and critically, exploring the relations among the issues and seeking explanations for the differing or conflicting findings in different studies. The articles were classified by level of evidence, following the proposal of Melnyk and Fineout-Overholt¹⁹.

Results and discussion

The database search found 540 articles and, in the first stage, from reading the titles, 80 articles were selected for their abstracts to be read. Articles on other subjects were excluded. After reading and discussing the abstracts together, the two reviewers excluded any articles that did not assess factors associated with adherence, intervention studies and review articles. From that procedure, 48 studies were selected to be read in full. Once read in full by both reviewers, 24 more studies were excluded for not investigating factors associated with adherence (16) and another (8) for being intervention studies (Figure 1).

As shown in Chart 1, the study corpus consisted of 22 articles, with the following characteristics: they were written in English, published from 2001 to 2019, about studies conducted in the United States (54%), Australia (18%) and on the European continent (in Spain, Germany and France) (18%), as well as one study in Pakistan (5%) and another in Brazil (5%). The fact that only one study in South America was found seems to indicate that studies of factors associated with adherence to hepatitis C treatment are rare in Latin American countries.

The articles were encountered in 18 journals, as shown in Chart 2. The journals *European Journal of Gastroenterology & Hepatology*, *Digestive Diseases and Sciences* and *Journal of Clinical Gastroenterology* accounted for the largest portion (32%) of the articles included in this review.

As regards the studies' distribution over time, 46% had been published in the previous five years, three in 2019, two in 2018, two in 2017 and three in 2015; another three dated from 2013, four from 2011 and one each from 2014, 2010, 2008, 2007 and 2001. From the studies' publication dates, it can be seen that research into factors associated with treatment adherence are relatively recent in the literature.

In their methodological design, seven (32%) of the studies were qualitative and 15 (68%) were quantitative, the latter being predominantly observational cohort-type studies (87%) – three retrospective cohorts – and two cross-sectional studies (13%). Sample size varied in the quantitative studies, ranging from 71 to 5706 participants, and five were multicentre studies¹³⁻¹⁷.

Evaluation of findings as regards treatment adherence in the studies selected

The criterion used to assess adherence, in most of the studies included in this review, was doses taken as a percentage of doses prescribed. Percentage non-adherence to treatment, on the criteria established in the studies analysed here, ranged from 12% to 32%.

Self-reporting was used in 23% of the studies²⁰⁻²⁴, 14% used pharmacy records²⁵⁻²⁷, 14% combined methods²⁸⁻³⁰, 9% electronic monitoring^{31,32}, 4% used nursing records of weekly administration of PEG-IFN injections³³, 4% used patient record data (attendance to start treatment, attendance at medical referral, absence of relapse in use of injected drugs or alcohol and absence of treatment dropout)³⁴, 9% used the treatment conclusion annotation in the patient record^{35,36} and 23% (the qualitative studies)³⁷⁻⁴¹ did not measure adherence objectively.

The criteria used for satisfactory adherence also differed, ranging from 80% to 100% of appropriate use of prescribed medication. Accordingly, the studies' use of different standards, and forms of monitoring, for adherence made it difficult to compare their findings.

It can thus be concluded that the standards applied in order to evaluate adherence and the ways it is measured need to be improved. To date, there is no method that can be considered the "gold standard" for assessing adherence behaviour^{14,15}. Self-reporting is still the method most used, because it is quick, inexpensive, flexible and easy to apply, but its limitations must be noted: as it is subjective, it may lend itself to patients' overestimating adherence^{12,15}.

Adherence and treatment-related factors

Thirteen studies (59%) evaluated adherence to treatment with interferon in association with ribavirin, another five (23%) evaluated adherence to direct-acting antiviral agents and one study (4%) evaluated adherence among patients in treatment with interferon in association with

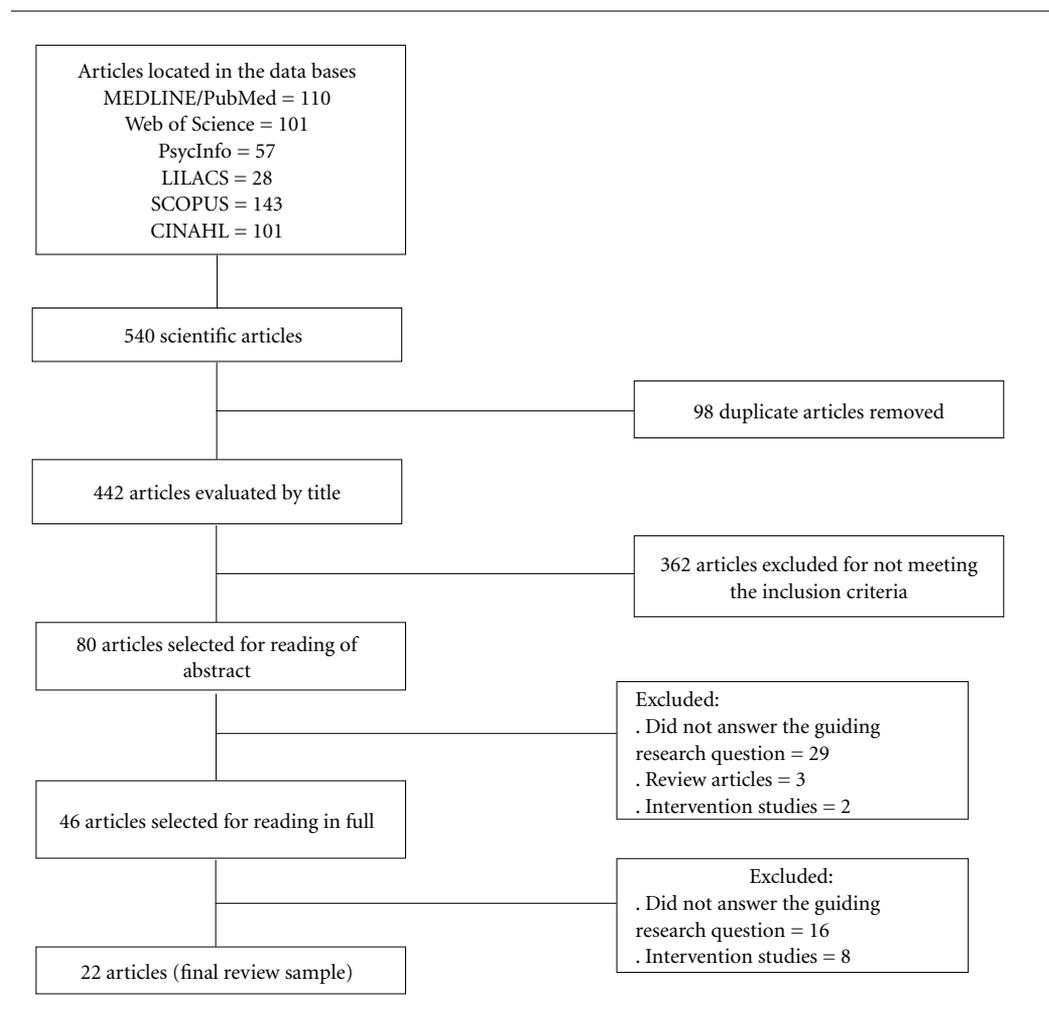


Figure 1. Flow diagram of the selection process for articles reviewed.

Source: Authors.

ribavirin or patients participating in a phase II clinical trial to assess the combination of direct-acting antivirals with ribavirin and interferon. Three (13%) did not specify the treatment given.

The studies that evaluated factors associated with adherence to the treatment regime with interferon and ribavirin noted that the complexity of the treatment, the weekly injections and oral ingestion of large numbers of tablets at different times, which called for changes of routine and were long-duration treatments, were con-

sidered variables that constituted barriers to adherence³⁷⁻³⁹. Lesser adherence to treatment with PEG-IFN+RBV was also associated with the adverse events – extreme fatigue, nausea, irritability, hair loss, skin eruptions and insomnia – caused by using those medications^{30,38,39}. Also, the knowledge that this complex, difficult treatment might possibly be completed without achieving the hoped-for outcome was also considered a barrier to adherence³⁷. Another study showed that being in treatment for the first time was associated with greater adherence ($p=0.02$)²⁰.

Chart 1. Characteristics of selected studies of factors associated with hepatitis C treatment adherence.

Year	Authors	Design	N	Country	Objective	Treatment type	Measurement used to assess adherence	Findings
2001	Kraus et al. ³⁴	Cohort	74	Germany	To investigate psychiatric symptoms, interpersonal problems, different manners of contracting hepatitis C and sociodemographic factors as variables possibly associated with adherence	Interferon (IFN)-a-2b with or without Ribavirin	Attending to start treatment; attending follow-up; maintaining abstinence and not dropping out of treatment	Predictors of non-adherence: phobic anxiety (p=0.04); depression (p=0.01); hostility (p<0.01); intrusiveness (p=0.01).
2007	Sylvestre and Clements ²⁹	Cohort	71	United States	To evaluate hepatitis C treatment of heroin users in maintenance treatment with methadone	Interferon (IFN)-a-2b + Ribavirin	Combined method: self-reporting + medication dispensation records	Predictors of non-adherence: regular substance use (p=0.03); pre-existing psychiatric disorder (p=0.04). Predictor of adherence: Starting psychiatric medication during treatment (p=0.02). Significant association between adherence and SVR
2008	Martin-Santos et al. ³⁵	Cohort	176	Spain	To investigate incidence of anxiety and depression, treatment of their symptoms and association with adherence to hepatitis C treatment	Interferon (IFN)-a-2b + Ribavirin	Took > 80% of the medication	36% incidence of depressive and anxiety disorder; greater in first four weeks of treatment. Immigrants showed greater incidence of depressive and anxiety disorder than non-immigrants (p=0.005). Predictor of non-adherence: Depressive and anxiety disorder (p<0.04).
2010	Melin et al. ²¹	Multi-centre cohort	1,860	France	To investigate SVR, adherence and quality of life in chemical dependents and in patients with no history of dependence	Interferon (IFN)-a-2b + Ribavirin	Self-reporting	Adherence, SVR and quality of life were similar in dependent and non-dependent patients.
2011	Grebely et al. ³³	Multi-centre cohort	163	Australia	To evaluate adherence to treatment in persons with a recent diagnosis of hepatitis C	Interferon (IFN)-a-2b with or without Ribavirin	PEG-IFN administration records	Predictor of adherence: Schooling (having higher education) (p=0.02).

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Chart 1. Characteristics of selected studies of factors associated with hepatitis C treatment adherence.

Year	Authors	Design	N	Country	Objective	Treatment type	Measurement used to assess adherence	Findings
2011	Marcellin et al. ²⁰	Multi-centre cohort	1,860	France	To evaluate adherence to treatment, identify factors associated with, and coherence between, adherence reported by patient and doctor	Interferon (IFN)-a-2b + Ribavirin	Self-reporting by patient + self-reporting by doctor	Self-reporting by patient and doctor disagreed, with doctors overestimating adherence by 20% to 30%. Predictors of adherence: virus genotype 3 (p=0.02); co-infection with HIV (p=0.003); first treatment (p=0.03); distance to referral centre (p=0.024); and abstinence during treatment (p<0.01).
2011	Re et al. ²⁶	Retrospective cohort	5,706	United States	To evaluate the relationship between adherence and early virological response, changes in adherence in the course of treatment and risk factors for non-adherence	Interferon (IFN)-a-2b + Ribavirin	Medication dispensation records	Early virological response was greater in patients with higher treatment adherence rates. Sustained virological response was greater in those with higher levels of adherence to interferon and ribavirin during the second, third and fourth adherence evaluation intervals for patients with genotypes 1 and 4.
2011	Wagner et al. ²²	Cohort	72	United States	To evaluate HIV co-infected patients' characteristics associated with adherence, conclusion of treatment and SVR	Interferon (IFN)-a-2b + Ribavirin	Self-reporting (analogical visual scale)	<i>Predictor of non-adherence: Psychiatric disorder (p=0.04).</i>
2015	Bonner et al. ³¹	Multi-centre cohort	401	United States	To identify associations between patient characteristics and self-efficacy expectations, before and during treatment, and association between self-efficacy expectations and adherence to treatment	Interferon (IFN)-a-2b + Ribavirin	Electronic monitoring	Self-efficacy expectations were associated with having a relationship, schooling, health insurance and being less depressed. More communication in week 24 reduced the risk of missing doses during weeks 24 to 48 of treatment.

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Chart 1. Characteristics of selected studies of factors associated with hepatitis C treatment adherence.

Year	Authors	Design	N	Country	Objective	Treatment type	Measurement used to assess adherence	Findings
2013	Evon <i>et al.</i> ³²	Cohort	48	United States	To identify patient characteristics associated with prevalence, missed doses and stopping treatment	Interferon (IFN)-a-2b + Ribavirin	Electronic monitoring	Predictors of non-adherence: Age (being younger) ($p < 0.001$); ethnicity (Afro-American) ($p < 0.001$); unemployed ($p < 0.001$); not being in a marital relationship ($p = 0.029$).
2013	Re <i>et al.</i> ²⁵	Retrospective cohort	333	United States	To examine for the presence of depressive disorder, bipolar disorder, schizophrenia and methadone maintenance treatment for chemical dependency as possible barriers to adherence in patients co-infected with HIV	Interferon (IFN)-a-2b + Ribavirin	Medication dispensation records	Predictor of non-adherence: Methadone treatment for dependency ($p = 0.04$).
2015	Batool and Kausar ²³	Cross-sectional	100	Pakistan	To examine changes in health-related behaviour before and after diagnosis and the relationship between these behaviours and adherence	Not stated	Self-reporting (Morisky scale)	Predictors of adherence: healthy diet, change in eating behaviour ($p < 0.01$). Predictor of non-adherence: fatigue ($p < 0.05$).
2017	Vieira-Castro and Oliveira ²⁷	Cross-sectional	121	Brazil	To evaluate the impact of alcohol consumption in patients in treatment for hepatitis C	Interferon (IFN)-a-2b + Ribavirin	Medication dispensation records	Predictor of non-adherence: Discontinuance of treatment was greater among patients who consumed alcohol during treatment (66.7% vs. 21.4%) and among those who were not abstinent for at least 6 months (72.7% vs. 15.4%).
2018	Cunningham <i>et al.</i> ²⁸	Multi-centre cohort	103	Australia	To study the association between adherence to treatment and recent use of injected drugs	Sofosbuvir and velpatasvir	Combined method: electronic monitoring + pill count + self-reporting	Predictor of non-adherence at baseline: Use of injected drugs (cocaine and amphetamines) in prior month ($p = 0.019$). Predictors of non-adherence during treatment: non-abstinent ($p = 0.023$); deviation from administration schedule ($p < 0.001$).

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Chart 1. Characteristics of selected studies of factors associated with hepatitis C treatment adherence.

Year	Authors	Design	N	Country	Objective	Treatment type	Measurement used to assess adherence	Findings
2019	Chehl et al. ³⁶	Retrospective cohort	1,328	United States	To ascertain whether adherence to treatment was greater among patients treated in an outpatient facility structured for hepatitis C than among those treated in a general hepatology clinic.	Sofosbuvir, sofosbuvir/daclatasvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, sofosbuvir/simeprevir, elbasvir/grazoprevir or dasabuvir/ombitasvir/paritaprevir/ritonavir with or without ribavirin	Show SVR	Predictors of adherence: Patients in treatment in a service structured for hepatitis C displayed greater adherence to treatment than those in treatment in a general hepatology service (p<0001). Other findings: age (being older) (p=0.0001); being female (p=0.05).
2014	North et al. ³⁷	Qualitative	48	United States	To examine barriers and facilitators to hepatitis C treatment as perceived by patients	Not stated	Did not evaluate adherence	Facilitators to treatment: Social support. Barriers to treatment: Stigma; not receiving appropriate information; problems communicating with the doctor; financial difficulties; logistical difficulties; the asymptomatic course of the disease; and undergoing difficult treatment with the possibility of not achieving the hoped-for response.
2015	Evon et al. ³⁸	Qualitative	21	United States	Perceptions of persons with hepatitis C about factors that facilitated or hindered adherence to treatment	Interferon (IFN)-a-2b + Ribavirin or direct-acting antivirals with Interferon (IFN)-a-2b and Ribavirin	Did not evaluate adherence	Facilitators to adherence: More knowledge and information about the disease and the importance of adherence; internal locus of control; optimistic thinking; social motivators, particularly relationship with the doctor. Barriers to adherence: being busy at medication time; family responsibilities; work; changes in daily routine upset medication, particularly being far from home without the medications; time of going to sleep/waking up; adverse events, mostly nausea, led some intentionally to avoid taking the medication.

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Chart 1. Characteristics of selected studies of factors associated with hepatitis C treatment adherence.

Year	Authors	Design	N	Country	Objective	Treatment type	Measurement used to assess adherence	Findings
2015	Sublette <i>et al.</i> ³⁹	Qualitative	20	Australia	Patients' perceptions of factors that influenced their decisions to start, adhere to and conclude treatment	Interferon (IFN)-a-2b + Ribavirin	Did not evaluate adherence	Starting treatment: Fear of death; stigma; shame. Facilitators to adherence: Social support; receiving personalised information and guidance with their needs and lifestyle. Barriers to adherence: Complexity of treatment; adverse events; lack of support social, stigma; limitations of health system.
2017	Sublette <i>et al.</i> ⁴⁰	Qualitative	40	Australia	To compare and contrast the views of patients and health personnel as to facilitators and barriers to treatment	Not stated	Did not evaluate adherence	Facilitators to adherence: Social support; communication between patient and health professional. Barriers to adherence: Stigma; difficulties in communicating between patient and health professional; limitations of health service.
2018	Gior-dano <i>et al.</i> ²⁴	Qualitative	12	United States	To explore the views of military veterans about facilitators to adherence to hepatitis C treatment	Direct-acting antivirals – not specified	Self-reporting (Morisky scale)	Facilitators to adherence: Knowing about the pros and cons of the new treatment as compared with the former treatment; the new treatment's offering realistic hope of cure; easier treatment; integrating the treatment into existing daily routines; developing behavioural strategies to manage adverse events from the treatment and treatment time; greater ability to manage adverse events; availability of medications; negative experience with the previous treatment; clear, honest communication with the doctor; good bonding with health personnel; trusting health personnel; social support; knowledge of value of medication and structure of health service.

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Chart 1. Characteristics of selected studies of factors associated with hepatitis C treatment adherence.

Year	Authors	Design	N	Country	Objective	Treatment type	Measurement used to assess adherence	Findings
2019	Patel et al. ³⁰	Qualitative	40	United States	To identify barriers and facilitators to adherence to treatment with direct-acting antivirals	Direct-acting antivirals – not specified	Combined method: self-reporting + pill count	Facilitators to adherence at pre-treatment interview: Possibility of incorporating the treatment into routine; high possibility of cure; trusting health personnel; feeling satisfied with the team; following guidance. Facilitators to adherence at post-treatment interview: Receiving positive results as to response to treatment and minimal adverse events. Barriers to adherence at pre-treatment interview: Unintentional forgetting; adverse events. Barriers to adherence at post-treatment interview: Difficulty in incorporating the treatment into routine; forgetting.
2019	Skolnik et al. ⁴¹	Qualitative	48	United States	Health personnel's and patients' perceptions about factors that contribute to conclusion of treatment	Direct-acting antivirals – not specified	Did not evaluate adherence	Facilitators Perceptions of current treatments and their side-effects as compared with prior experience; perception of improvement in symptoms attributed to starting the treatment; optimism in relation to SVR and/or possibility of improved health or longevity, so that they felt motivated to conclude the treatment; trusting health personnel, empathy, length of appointments and support from health personnel contributed to patients' concluding the treatment; descriptions of consistent curative habits and routines that contributed to the treatment, including social support, calendars and other strategies for adhering to medications and appointments. All facilitators reported by health personnel were reported by patients.

Source: Authors.

Chart 2. Distribution of articles published, by journal.

Journals	N
AIDS Behavior	1
AIDS Research and Treatment	1
Alimentary Pharmacology & Therapeutics	1
Annals of Internal Medicine	1
Arq Gastroenterol	1
BMC Health Services Research	1
Digestive Diseases and Sciences	2
European Journal of Gastroenterology & Hepatology	3
Journal of Clinical Gastroenterology	2
Journal of Behavioural Sciences	1
Journal of Health Psychology	1
Journal of Viral Hepatitis	1
Hepatology	1
Liver international: official journal of the International Association for the Study of the Liver	1
Medicine	1
Psychology & Health	1
International Journal of Drug Policy	1
The Qualitative Report	1
Total	22

Source: Authors.

Of the studies included in this review, the more recent, investigating variables associated with adherence to treatment with direct-acting antiviral agents, showed that the change in treatment could facilitate adherence in its multiple dimensions, by virtue of its being a less complex treatment and occurring in a shorter time^{24,30,41}. Adverse personal experiences with prior treatments using interferon and ribavirin were also found to facilitate adherence to the treatment prescribed currently and examined here^{24,30,41}.

In addition to these factors, knowing that there is a greater likelihood of cure with treatment using direct-acting antiviral agents, given their greater efficacy, facilitates adherence to the treatment^{24,30,41}, while treatments using interferon in association with ribavirin returned low efficacy, with sustained virological response rates of around 50%^{3,7}.

Adherence and individual factors

Twelve studies examined individual factors associated with treatment adherence. Nine

(41%) of the 22 studies investigated the association of mental disorder and/or depressive and anxiety symptoms with adherence, four (44%) finding statistically significant associations ($p < 0.04^{35}$; $p = 0.01^{34}$; $p = 0.04^{29}$; $p = 0.04^{22}$). However, Marcellin *et al.*²⁰ found that starting psychiatric treatment while depressive or anxiety symptomatology was present was associated with increased adherence. Three of these studies used validated scales for symptom screening: Symptom Checklist-90 Revised (SCL-90-R)³⁴, Hospital Anxiety and Depression Scale (HADS)³⁵, Beck Depression Inventory³⁵ and Patient Health Questionnaire (PHQ)²⁹. Another study in the United States obtained information about diagnosis of depression or other psychiatric disorder from patient records²².

Presenting with a mental disorder prior to and during treatment was the variable most investigated in the studies reviewed. This interest in assessing the influence of psychiatric problems on treatment adherence can be assumed to respond to the high prevalence of depressive symptoms in this population⁴², especially those receiving regimes (PEG-IFN+RBV) with significant psychiatric side-effects^{42,43}. It is also motivated by the association between psychiatric symptoms and non-adherence to treatment of other chronic diseases, as already evidenced in a meta-analysis with more than 18,000 participants regarding depression and adherence to medication in treatment of chronic diseases in the United States. In that study, the likelihood of a depressed patient being non-adherent was estimated to be 1.76 times greater than for a non-depressed patient⁴⁴.

Another aspect investigated as possibly relevant to adherence or non-adherence was psychoactive substance use. Three studies included in this review reported statistically significant associations between the regular use of psychoactive substances (heroin, stimulants, amphetamine, cocaine) and lower adherence rates ($p < 0.01^{20}$; $p = 0.03^{29}$; $p = 0.023^{28}$). These studies found lower adherence to treatment in persons who used injected drugs in the month prior to starting treatment and among those using during treatment. Another study showed an association of lower adherence in heroin users undergoing methadone treatment, also showing an association between a higher adherence rate and SVR²⁵.

The only study in Brazil included in this review indicated that alcohol use was also associated with higher rates of treatment dropout. That study found higher percentage treatment dropout in the group of patients who used >60

g/day of alcohol (32%) and an even higher percentage among patients who drank during treatment (66.7%, as against 21.4% in those who were abstinent) as well as among those who had not abstained from drinking for at least the prior 6 months (72.7%, as against 15.4% among those who had abstained). That study also found that persons co-infected with HIV and whose adherence was <80% failed to achieve SVR²⁷. Given the high prevalence of psychoactive substance use among persons with hepatitis C, this population is cause for major concern, because injected drug use is currently the main risk factor for infection with the hepatitis C virus in most of the developed countries¹⁰.

A cross-sectional study of a sample of 100 individuals in Pakistan²³ evaluated health care-related behaviour before and after a diagnosis of hepatitis C, as well as its possible relations to adherence as measured on the Morisky scale. The findings indicated that health-related behaviour improved significantly after the disease was diagnosed and that there was a significant association between good adherence rates and healthy diet ($p<0.01$) and modifying eating behaviour ($p<0.01$), while lower adherence rates were associated with fatigue ($p<0.05$).

Other studies have found that barriers to treatment were often related to missing doses and unintentional lateness. Being busy, forgetful, worried about family or work responsibilities or changing routine were signalled as unintentional barriers connected with non-adherence^{38,39}.

Adherence and socioeconomic factors

The association between socioeconomic factors and treatment adherence was investigated in 13 of the studies reviewed here. Investigations in the United States identified lower adherence associated with age, one of the studies showing lower adherence to use of PEG-IFN among younger individuals (OR=0.76 (0.66, 0.88), $p=0.003$) and even lower rates of adherence to RBV in the first 24 weeks of treatment. A five-year reduction in age was associated with 20% greater likelihood of missing doses (OR=0.80 (0.72, 0.88), $p<0.001$)³². One study of treatment with direct-acting antiviral agents found higher rates of adherence in older persons ($p=0.001$) and women ($p=0.05$)³⁶.

A cohort study in Australia found lower adherence to treatment among persons with less schooling (without higher education) ($p=0.02$)³³. A study in the United States indicated lower adherence rates among Afro-Americans (OR=2.22

(1.51, 3.27), $p<0.001$) than among Caucasians, among the unemployed (OR=2.57 (1.68, 3.92), $p<0.001$) than among the employed, and among those who were not in a conjugal relationship (OR=2.00 (1.23, 3.28), $p=0.029$)³².

Note that there is still controversy as to the influence of sociodemographic and economic conditions on adherence to treatment of other chronic diseases, and independent predictors of adherence were not found consistently among these conditions¹¹.

Patients in treatment for hepatitis C considered having social support to be important in facilitating adherence, which suggests the importance of being able to rely on people to fortify themselves and continue with the treatment at difficult times³⁷⁻⁴¹, which included those experienced from the side-effects of treatment with interferon and ribavirin. These findings corroborate those of other studies in the literature on adherence that point to perceived family support as the variable with the most significant associations with both adherence and mental health^{45,46}.

Patients also identified stigma, a socially-constructed condition^{47,48}, as a barrier to treatment and as a hindrance to obtaining social support^{37,39,40}. Some studies showed that patients in treatment for hepatitis C did not have to experience stigma in order to feel its effects: the fear of stigma was sufficient. They avoided talking about their illness and treatment for fear of discrimination in the workplace, which made it even more difficult to maintain regular dosage regimes and to refrigerate the medications (the complexity of the treatment with PEG-IFN+RBV entailed weekly injections and large numbers of tablets). Fear also prevented patients from socialising and broadening their support networks^{37,40}.

Studies of hepatitis C and stigma, by Butt *et al.*⁴⁷ and Stewart *et al.*⁴⁸, argue that persons with hepatitis C experienced stigma for a variety of reasons, prominent among which were misunderstandings as to the cause and transmission of the disease and its association with illicit drug use. Such stigma can undermine the ability to obtain social support, prejudicing relationships in the workplace and also influencing early treatment dropout^{47,48}.

Adherence and factors relating to the health service and health personnel

Issues connected with the health service and health personnel were discussed in nine of the 22 studies examined here and were associated with

both the treatment with interferon and ribavirin and the current treatment. Higher adherence rates were found among persons undergoing treatment in hepatitis C referral services with specific treatment protocols ($p < 0.001$)³⁶. The analysis of the articles selected also found a significant association reported between greater adherence and distance between place of residence and health service (OR=1.003 (1.000-1.006), $p = 0.024$)²⁰.

One qualitative study observed that having to miss work in order to wait a long time for a doctor's appointment was an important barrier for employed patients and this circumstance was considered a limitation of the health service^{39,40}.

The quality of the relationship between health personnel and patient has been associated with high levels of motivation and facilitation in adhering to treatment. Good bonding and trust in the health professional show the importance of establishing clear, honest communication and receiving appropriate information on disease and treatment; in the studies reviewed here, these are the factors considered facilitators of adhesion to the treatment process^{24,30,37-41}.

The main characteristics of communication identified by patients in treatment for hepatitis C and by health personnel in Australia were appointment time, use of medical jargon, the quality and quantity of information provided and whether or not personalised clinical feedback was provided^{39,40}. Authors also concluded that receiving detailed clinical information during treatment, coupled with a visualisation of the effects of the treatment, gave patients a better perspective on their health and helped them feel better informed and in control of the treatment⁴⁰. Corroborating these findings on the importance of communication and the doctor-patient relationship to treating patients with hepatitis C, studies have highlighted the importance of trust, of the health professional's being sensitive to the experience the patient is going through, with a view to establishing a relationship of empathy in which it is possible to listen to patients and share in finding strategies that will help them adapt to the lifestyle demanded by the disease^{11,13,49,50}.

Adherence and disease-related factors

Three studies addressed factors relating to the disease and two of them found significant associations with treatment adherence. One study pointed to a relationship between co-infection with HIV ($p = 0.003$), the presence of the geno-

type 3 virus ($p = 0.01$) and greater treatment adherence²⁰. Its authors argued that the association between co-infection with HIV and greater hepatitis C treatment adherence may possibly also be related to adherence to treatment for HIV, which is routinely emphasised in patient care and may thus have contributed to greater adherence to treatment for hepatitis C as well²⁰. There is a long history of studies, discussions and interventions directed to increasing HIV treatment adherence, which posed a challenge for individual and public health, and these are advancing in understanding and addressing the process of non-adherence^{51,52}.

A study using focal discussion groups suggested that hepatitis C's being an asymptomatic disease may hinder adherence³⁷. The literature indicates that having a disease with no specific symptomatology^{11,13,53}, such as arterial hypertension^{54,55}, can hinder adherence to treatment, as was found in this study.

Limitations of the study

One possible limitation of this study may have been that it did not include studies or other relevant material that failed to meet the inclusion criteria (only publications in Portuguese, English and Spanish and indexed in specific data bases), and the fact that it excluded dissertations, theses and official documents.

Final remarks

The articles reviewed were not always guided by the multidimensional view of adherence behaviour; rather the predominant perspective was that adherence is a particularly patient-centred difficulty. Adherence behaviour seems to result, in each case, from a singular interaction of multiple factors⁵³. This broader view does not seem to have been contemplated yet, especially in the quantitative studies. Only where the study design was qualitative was it possible to identify important points, such as the characteristics of communication by health personnel with patients, interaction with the health team, and the conditions of the health service and the treatment.

It can also be concluded that the major differences in methodological approach among the articles reviewed here also frustrated the possibility of arriving at more objective and uniform conclusions about the variables that may have influenced low adherence, pointing to a need for further research in this area.

Most of the studies included in this integrative review evaluated factors associated with adherence to treatment with therapeutic regimens that still used interferon and ribavirin, which – from when they were discovered in 1989 until 2014 – were the only medications that existed to combat the hepatitis C virus. Treatment with these medications was lengthy, caused numerous adverse side effects and offered less efficacy than current medications. In this review, these problems were identified to be barriers associated with lower rates of adherence. Corroborating these factors' importance, studies that have evaluated adherence to the new treatment with direct-acting antiviral agents have shown that the treatment's lesser complexity is a significant facilitator of adherence.

In addition to the significant associations between adherence and factors connected with the complexity of treatment with interferon and ribavirin, other variables also proved important to the phenomenon of adherence to hepatitis C treatment with these medications. The following factors associated with non-adherence to hepatitis C treatment stood out and should be identified before and during treatment: the presence of psychiatric disorder and depressive symptoms and the use of alcohol and/or illicit drugs are factors that need to be explored further with the new treatment in order to receive attention, specialised treatment and guidance. Also associated with non-adherence were: schooling (not having higher education); age (being younger); ethnicity (Afro-Americans); being unemployed; marital status (not having a fixed partner); distance from the health service; lack of information about the disease and treatment; unintentional forgetting; the fact that the disease is asymptomatic; limitations of the health service; and the presence of stigma relating to the disease.

Adherence to treatment with interferon in association with ribavirin was favoured by: receiv-

ing treatment for psychiatric disorders identified during treatment; changing lifestyle; starting to eat healthily; having social support; gaining information and knowledge about the disease and treatment; good bonding between health personnel and patient; presenting with genotype 3 virus; being in treatment for the first time; and being in treatment for HIV.

This integrative review also identified factors associated with adherence to treatment with direct-acting antiviral agents. There was a significant association between greater adherence and being female; age (being older); social support; receiving treatment in a service set up and specialised to treat hepatitis C; receiving information about the disease and treatment; having information and knowledge about the treatment; and bonding between health personnel and patient. There was also a significant association between use of injected drugs and lesser adherence to direct-acting antiviral agents.

Further research is needed to contemplate the treatment currently indicated^{4,10} – which constitutes an important milestone in treating hepatitis C, even though access still poses considerable challenges to treatment^{5,6,7} – and all the variables that may influence adherence: those relating to the individual, to the disease, to the treatment, to family and community factors and to health personnel, as well as those reflecting aspects of health service organisation¹¹.

This integrative review underscores the importance of exploring our thinking about the meanings and complexity of hepatitis C treatment adherence behaviour in greater depth. Studies for that purpose, which are still so lacking in the literature, can contribute to the introduction of measures coordinated among researchers, health personnel, managers and policymakers to address the very important issue of adherence to treatment.

Collaborations

LT Côco completed a Master's Degree thesis in Public Health, which provided the basis for the article. She contributed with the research planning and data collection, as well as data analysis, and the writing of the manuscript. ATAR Cerqueira was the study advisor, participated in the interpretation and analysis of the obtained data and in the writing of the manuscript. GF Silva was the co-advisor of the study, contributed with the study planning, and supported the data analysis and writing of the manuscript. FG Romeiro contributed to the writing of the manuscript.

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