**STRATEGIES TO REDUCE THE HIGH COST OF HEPATITIS C ANTIVIRAL TREATMENT: A LITERATURE REVIEW**

by

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**ABSTRACT**

 Hepatitis C infection is a chronic, debilitating disease with complications such as liver cancer and liver cirrhosis. In the United States, hepatitis C infection can be cured only with direct acting antiviral treatment. However, the cost of hepatitis C antiviral treatment is expensive, hindering many Americans from receiving treatment. Insurance companies and pharmaceutical companies control access to hepatitis C antiviral treatment as out-of-pocket costs are unaffordable for most individuals. A literature review was conducted to investigate strategies to reduce the high cost of hepatitis C antiviral treatment using PubMed database. The research question of “What are current or future strategies that could reduce the high cost of hepatitis C antiviral treatment in the US market to increase access?” focused this literature review’s purpose. Relevant studies were those published from 2013 to present that included strategies to decrease the cost of hepatitis C antiviral treatment. Articles were excluded if they included a genotype other than genotype 1, represented studies conducted in a country other than the United States, or a specific clustering of individuals in the title such as injection drug users, at-risk populations, and prison inmates. Thirty-one studies met the criteria for inclusion in this literature review. Fifteen articles indicated increased market competition (48.3% of the total included articles) as a strategy to decrease the cost of hepatitis C antiviral treatment. Modifications to the pharmaceutical industry were emphasized in 12 articles (38.7% of the total included articles) such as promoting competition, research of equivalent drugs, and partnerships with other pharmaceutical companies as a means of decreasing hepatitis C antiviral treatment costs. Eleven articles suggested that stakeholder involvement (35.5% of the total included articles) could help to reduce hepatitis C antiviral treatment costs. Eight studies suggested that business/finance industry modifications (25.8% of the total included articles) could lower hepatitis C antiviral treatment costs. These studies assist in developing strategies to reduce the high financial burden on people living with hepatitis C and furthering public health significance in reducing hepatitis C transmission.

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preface

With sincere gratitude and appreciation, I thank my academic advisor, Dr. Mackey Friedman, and Dr. Mary Hawk, for their guidance, support, and assistance during this master’s essay preparation and development.

# Introduction

Hepatitis C is the United States’ most prevalent blood borne infection (Trooskin, Reynolds, and Kostman, 2015) and the leading cause of liver transplantation, liver failure and liver cancer in the United States (Chhatwal, 2015 and Edlin, 2016). It affects 3.2 to 5.2 million individuals annually (Trooskin, Reynolds, and Kostman, 2015). Between 1999 and 2007, more people died annually from hepatitis C infection than from human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) infection in the United States (Ly et al., 2012), indicating that annual hepatitis C deaths are increasing compared to HIV/AIDS deaths.

Hepatitis C infection is caused by the hepatitis C virus, which invades and infects the hepatocytes of the liver. Once in the hepatocytes, the virus replicates, causing liver inflammation (Zhu, Qian, Zhao, and Qi, 2014). If no antiviral treatment is initiated, acute hepatitis C progresses to chronic hepatitis C 75% to 85% of the time. Because of the progression of the disease to advanced stages and the increasing trend of hepatitis C infection fatalities (Zoulim et al., 2015), the importance of obtaining treatment for hepatitis C is high. About 20 to 30% of individuals with hepatitis C develop liver cirrhosis, which is widespread scarring of the liver (Thornton, 2015). After cirrhosis of the liver, some infected individuals progress to the most severe stage of the natural history of hepatitis C, which is end stage liver disease and hepatocellular carcinoma. This occurs in about 2 to 7% of individuals suffering from liver cirrhosis (Thornton, 2015). People suffering from hepatitis C who have liver cancer or liver cirrhosis will succumb to hepatitis C infection 1 to 5% of the time (Magnifico, 2016).

Treatment of hepatitis C is crucial to stopping the progression from acute to chronic hepatitis C. As there is no vaccine available (National Institute of Diabetes and Digestive and Kidney Diseases, 2017), drug therapy is recommended for treatment of hepatitis C infection (Yilmaz, Yilmaz, and Leblebicioglu, 2016). In the past, pegylated interferon medications were administered; these medications resulted in side effects and longer periods of drug therapy (Sebhatu and Martin, 2016). With the introduction of direct acting antivirals into the market beginning in 2013 (World Health Organization, 2016), hepatitis C is curable. Direct acting antivirals have decreased side effects, shorter treatment periods, and a higher sustained virologic response than pegylated interferon medications (Rosenthal and Graham, 2016). The sustained virologic response is about 90% (Sebhatu and Martin, 2016) when treated with direct acting antivirals. While these results are promising to people living with hepatitis C infection, the cost of direct acting antivirals is very expensive with a 12-week regimen of the drug valued at $84,000 USD in the United States (Marseille and Kahn, 2016). In fact, estimated healthcare costs of hepatitis C treatment in the United States are projected to exceed 10.7 billion dollars between 2010 and 2019 (Reilley, 2014), indicating that hepatitis C is a very expensive illness to treat. The treatment cost of these direct acting antiviral medications serves as a barrier to treatment availability and access in the United States (Rosenthal and Graham, 2016). This financial difficulty causes a decrease in access to these medications for people living with hepatitis C (Rosenthal and Graham, 2016). The goal of this literature review is to discuss strategies to reduce the high cost of pharmaceutical treatment for hepatitis C in the United States.

## the pharmaceutical industry in the united states

The pharmaceutical industry in the United States ranks as one of the most significant sectors in the United States economy (International Trade Administration, 2016). One of the pharmaceutical industry’s roles is research and development for new drugs and modifications to existing drugs. Research and development is vital for new drugs to be identified, tested, approved and allowed to be placed on the market for purchase. Partly because of the long process required for a new drug to be approved by the Food and Drug Administration, research and development of drugs is very expensive. Over the past decades, research and development costs have increased with $50 billion being invested in research and development alone (International Trade Administration, 2016). In addition, pharmaceutical companies rely on the research and development process for clinical trials and the potential of drug interactions.

American pharmaceutical industries utilize the nation’s free enterprise system where drugs are priced freely with minimal interference from the federal government (Edlin, 2016). Pharmaceutical companies within the United States increase the price of drugs domestically in order to cover decreased international profits and to increase revenue for research and development costs (International Trade Administration, 2016). One of the methods pharmaceutical companies utilize is to file patents. Patents prohibit the production and sale of generic drugs by other companies in the United States market for twenty years (Amin and Kesselheim, 2012). In other words, the pharmaceutical company that has produced the drug such as direct acting antivirals has exclusivity in the market where they can produce profits solely for twenty years.

## drug pricing in the United states

 While the United States has the potential to eradicate hepatitis C virus due to the introduction of potent direct acting antivirals (Edlin, 2014), hepatitis C continues to be a public health issue because access to treatment serves as a barrier to care (Zoulim et al., 2015). Patients living with hepatitis C have a medical necessity to seek treatment while insurance companies and pharmaceutical companies retain the right to operate as businesses of a free enterprise economic system. As the United States has no universal healthcare system, the cost of hepatitis C treatment falls primarily on individual patients, private insurance companies, Medicare, and Medicaid for most Americans.

 Drug pricing in the United States is complex, with many different industries and professionals influencing the final drug price and the price that consumers will be required to pay for the drug. Drug pricing begins with pharmaceutical companies, which consult with pharmacy benefit managers. Pharmacy benefit managers represent mostly health insurers and patients. Their role is to negotiate drug discounts with pharmaceutical companies. As an incentive to pharmaceutical companies, which provide their drugs to pharmacy benefit managers at a reduced price, pharmacy benefit managers give exclusivity to pharmaceutical companies (Linas, 2016) and priority to their drug on the formulary list (Rosenthal and Graham, 2016). Nondisclosure agreements allow for pharmaceutical companies to sell their drug to payers such as health insurers and governments; these representatives are prohibited from disclosing the price of the discounted drug to other individuals in the drug negotiation process (Linas, 2016). Medicare cannot negotiate drug prices, although Medicaid and private health insurers have the option to negotiate with pharmacy benefit managers if they choose (Linas, 2016). With the United States government and private insurers purchasing the most drugs in the country (Daniel, 2016), most Americans turn to their private insurers to assist in financing hepatitis C treatment. The price of prescription medications in the United States is the highest in the world and there are no regulations on drug prices (Edlin, 2016). In the case of direct acting antivirals for hepatitis C, prices range from $83,320 USD to $94,500 for a 12-week duration of treatment and can increase for combination medications (Edlin, 2016).

 The United States government is prohibited from price bargaining, allowing for decreased competition and increasing drug prices (Jaffe, 2015). As a result of skyrocketing prices, Medicaid rations treatment for patients with the most advanced hepatitis C disease, thereby decreasing Medicaid costs. Rationing is necessary to project financial budgets and to allocate limited funding for hepatitis C treatment options. However, rationing contradicts the American Association for the Study of Liver Diseases’ recommendation that everyone diagnosed with hepatitis C should be provided with pharmaceutical treatment (Gentile et al., 2016). Patients’ hepatitis C must have progressed to advanced liver disease (F3 or F4) in order for Medicaid to pay for treatment. Private insurers ration hepatitis C antiviral treatment and also require prior authorization (Canary et al., 2015). Prior authorization consists of private insurers approving if treatment will be covered; prior authorization can also require criteria such as no alcohol or drug use for the individuals seeking treatment. Additional criteria further decreases the number of people living with hepatitis C who are able to obtain and afford treatment.

 As a result of the current pricing mechanisms for hepatitis C antiviral treatment, strategies are needed to decrease the high price of hepatitis C treatment in order to increase the number of people living with hepatitis C who are receiving treatment.

# methods

 This substantive literature review was conducted using English speaking, peer reviewed, and full text articles, reports, reviews, and commentaries from PubMed, which was conducted beginning in June 2017. Due to direct acting antivirals being introduced for hepatitis C treatment in 2013 (World Health Organization, 2016), the literature review focused on information present from 2013 to present. In order to account for the vast quantity of relevant articles that address hepatitis C, a research question was developed to narrow the literature review. The research question is, “What are current or future strategies that could reduce the high cost of hepatitis C treatment in the US market to increase access?”

 The phrases, “(hepatitis c [title]) AND (access OR access to treatment OR access to therapy) AND cost effectiveness),” “(hepatitis c) AND affordability),” “(hepatitis c) AND market prices,” and “(hepatitis c [majr] or hepatitis c virus [majr]) AND (united states OR us) AND (drug costs AND (price OR affordability)” located relevant articles to answer the question, ““What are current or future strategies to reduce the high cost of hepatitis C treatment in the US market to increase access?” The phrases, “(hepatitis c [mesh] AND access [title]) NOT HIV) NOT coinfection [title]) NOT comorbidity),” “(hepatitis c [majr]) AND united states) AND insurance) AND access,” “(hepatitis c [majr]) AND high cost) AND united states) AND pharmaceutical,” and “(hepatitis c [mesh] AND access [title])) NOT HIV) NOT coinfection [title])) NOT comorbidity),” further located articles relevant to the research question.

 Selection criteria for the articles consisted of any mention in the article of ways to reduce the cost of hepatitis C antiviral treatment in the United States. Articles were included if they were published from 2013 to present. Exclusion criteria consisted of a foreign country, a specific population, or a comorbidity in the article’s title. As this substantial literature review pertains to the United States, a foreign country, a specific population, or a comorbidity in the title indicates research that is not contextual to hepatitis C in the United States. As genotype 1 is the most prevalent genotype in the United States accounting for 70% of hepatitis C infections (Bickerstaff, 2015), articles with other genotypes in their title were excluded from this literature review for relevancy purposes. The inclusion and exclusion of articles is displayed in Figure 1.

(hepatitis c) AND affordability)- 36 articles

(hepatitis c [title]) AND (access OR access to treatment OR access to therapy) AND cost effectiveness)- 37 articles

32 excluded

28 excluded

4 included

9 included

(hepatitis c [majr] or hepatitis c virus [majr]) AND (united states OR us) AND (drug costs AND (price OR affordability)- 20 articles

(hepatitis c) AND market prices- 12 articles

14 excluded

10 excluded

2 included

6 included

(hepatitis c [majr]) AND united states) AND insurance) AND access- 21 articles

(hepatitis c [mesh] AND access [title]) NOT HIV) NOT coinfection [title]) NOT comorbidity)- 58 articles

20 excluded

52 excluded

1 included

6 included

(hepatitis c [mesh] AND access [title]))) NOT HIV) NOT coinfection [title])) NOT comorbidity)- 68 articles

(hepatitis c [majr]) AND high cost) AND united states) AND pharmaceutical- 8 articles

67 excluded

6 excluded

1 included

2 included

Figure : Flow Chart of Literature Review Searches

# results

 The search, “(hepatitis c [title]) AND (access OR access to treatment OR access to therapy) AND cost effectiveness),” resulted in 37 articles. There were 9 articles that met inclusion criteria for the literature review while 28 were excluded. The phrase, “(hepatitis c) AND affordability)” yielded 36 articles with 4 being included in the literature review and 32 meeting exclusion criteria. The search for “(hepatitis c) AND market prices” resulted in 12 articles and 2 met inclusion criteria while 10 were excluded. The phrase, “(hepatitis c [majr] or hepatitis c virus [majr]) AND (United States OR us) AND (drug costs AND (price OR affordability)” yielded 20 articles, of which 6 met literature review inclusion criteria and 14 were excluded. The search, “(hepatitis c [mesh] AND access [title]) NOT HIV) NOT coinfection [title]) NOT comorbidity),” yielded 58 articles with 6 meeting inclusion criteria and 52 being excluded. The search, “(hepatitis c [majr]) AND united states) AND insurance) AND access,” resulted in 21 articles: 1 article met inclusion criteria and 20 were excluded. The phrase, “(hepatitis c [majr]) AND high cost) AND united states) AND pharmaceutical,” yielded 8 articles with 2 being included and 6 being excluded. The search, “(hepatitis c [mesh] AND access [title]) NOT HIV) NOT coinfection [title])) NOT comorbidity),” yielded 68 articles with 1 selected for inclusion and 67 being excluded.

Resulting data from this substantive literature review comprised 31 articles, each of which detailed strategies to reduce the high cost of hepatitis C antiviral treatment in the United States (Table 1). The most commonly recommended strategies to reduce hepatitis C treatment costs included increased competition (48.3% of the total included articles), modifications provided by the pharmaceutical industry (38.7% of the total included articles), engaging stakeholders more systematically (35.5% of the total included articles), and changes in business and financial practices (25.8% of the total included articles) (Figure 2). Competition leads to decreased prices because it allows businesses to determine their prices with pressure from other competitors. The pharmaceutical industry influences cost because pharmaceutical companies own the patents that control distribution and sale of pharmaceutical medications. Stakeholders can impact decisions made by drug manufacturers and distributors, consumers, and governments by positively or negatively influencing policy decisions regarding hepatitis C antiviral treatment costs. Business and finance practices include adjustments to financial markets and economies that can impact hepatitis C treatment costs.

Table : List of Literature Review Articles

|  |  |  |  |
| --- | --- | --- | --- |
| **Authors and Publication Year** | **Research Design** | **Subjects** | **Results** |
| Chidi, Bryce, Donohue, et al., 2016 | Longitudinal study | 45, 50, and 55-year-old Medicaid patients | * No restrictions regarding Medicaid coverage
* Use early stage hepatitis C treatment
 |
| Jayasekera et al., 2017 | Longitudinal study | 1,000 U.S. patients with hepatitis C | * Task shifting allows decreased reimbursement rates for non-specialists compared to specialists
* Increased competition
 |
| Kamal-Yanni, 2015 | Comment | Not applicable | * Generic drugs
* Drug negotiation by governments
* Tiered pricing, voluntary licensing, and compulsory licensing
 |
| Rosenthal and Graham, 2016 | Review | Not applicable | * Similar hepatitis C program for financial assistance like the AIDS Drug Assistance Program
* Increased regulations and transparency
* Better cost-effectiveness analysis to educate patients and policy makers
 |
| Chhatwal, Chen, and Kanwal, 2015 | Comment from the Editor | Not applicable | * Competition from drug manufacturers
 |
| Sonnenreich and Geisler, 2016**Table 1 Continued** | Editorial | Not applicable | * Value-based formulary and copayment changes
* Copayment modifications allow pharmaceutical savings
* Patient centered system is more cost-effective than a supply driven system
* 340B drug discount program reforms
* Value-based insurance methods
 |
| Vernaz, Girardin, Goossens, Brugger, Riguzzi, Perrier, and Negro, 2016 | Retrospective study | Electronic data of sustained virologic response and US hepatitis C drug prices  | * Pharmaceutical industry, payers, and stakeholders can find new drug pricing options
 |
| Sebhatu and Martin, 2016 | Review | Not applicable | * Assisting in initiation of patient financial assistance programs
 |
| Bickerstaff, 2015 | Review | Not applicable | * Competition reduces hepatitis C treatment prices
* Increased drug manufacturing for pharmaceutical companies to compete
* Using older hepatitis C treatments
 |
| Edwards et al., 2015**Table 1 Continued** | Review | Not applicable | * Competition between hepatitis C treatment options
* Competition between generic drugs
* Price discounting
* Tiered pricing
* Licensing agreements of drugs; pharmaceutical companies must be flexible so generic medications can lower hepatitis C treatment prices
* Equal pricing and/or voluntary licensing should be considered early in a drug’s research and development phases
* Business transactions in voluntary licensing and generic manufacturers should be considered early
* Increased engagement of diverse stakeholders is needed to increase affordability of hepatitis C treatment
 |
| Trooskin, Reynolds, and Kostman, 2015  | Viewpoint  | Not applicable | * Implement federal programs similar to the AIDS Drug Assistance Programs to assist with price negotiations and cost
* Generic drug competition
* Government can utilize nonvoluntary licensing according to eminent domain guidelines to increase generic drug competition

  |
| Craxi et al., 2016**Table 1 Continued** | Report | Not applicable | * Increasing competition
* Discounting options
* Patent expiration
* Clinical evaluation and pharmaco-economical analysis of direct acting antivirals will assist cost effectiveness analysis and negotiations available to lower treatment costs
* Policies detailing the use of interferon and interferon-free regimens to lower treatment costs
* Cooperation between different stakeholders is needed
* Ethical and appropriate profit margins
* Early treatment
 |
| Barua et al., 2015 | Retrospective study | Electronic data of Medicaid reimbursement criteria | * Remove Medicaid restrictions to increase access to hepatitis C treatment, lowering long term costs
 |
| Reilley et al., 2014 | Prospective study | Electronic survey (n=48) | * Patient assistance programs by pharmaceutical companies
* Multi-stakeholder collaboration at the state, federal, and community organizations
 |
| Van Nuys et al., 2015 | Report | Not applicable | * Early stage treatment
 |
| Yilmaz, Yilmaz, and Leblebicioglu, 2016**Table 1 Continued** | Review | Not applicable | * Research of equivalent drugs by pharmaceutical companies
* Widespread support (domestic, international, and private) is needed to compact hepatitis C and lower prices
* Pharmaceutical companies should not charge for raw materials and can reduce the cost of the drugs for purchase
* Generic competition
* Non-governmental organizations can work to decrease treatment prices by developing policies
 |
| van de Ven et al., 2015**Table 1 Continued** | Prospective study | Clinical trials of hepatitis C direct acting antivirals  | * Generic competition
* Increased productivity in obtaining raw materials and production methods for drug ingredients
* Governments can use Trade-Related Aspects of Intellectual Property Rights policy
* The Trade-Related Aspects of Intellectual Property Rights policy can become stricter on patent applications to increase generic drug competition
* Pangenotypic drugs
* Increased demand
* Cheaper raw materials and more effective raw materials lower treatment costs
* Pricing and procurement methods can assist in reducing treatment costs using many stakeholders
* Patent holders can authorize discounts, voluntary licensing agreements, tiered pricing, and standard pricing
* Donor organizations have bargaining power to reduce treatment costs
 |
| Roy and King, 2016**Table 1 Continued** | Report  | Not applicable | * Profits should be invested towards research, not shareholders
* Drug development costs should be transparent
* Increased rebates
* Increased bargaining power
* Discounts
* Restricting pharmaceutical buybacks related to reinvestment
* Research and development costs become unrelated to drug prices so governments and other entities can license manufacturing rights for medications to be produced according to the correct production cost
 |
| Meyer et al., 2015 | Prospective study | Questionnaire (n=49) | * Price negotiations
* Voluntary licensing agreements
* Generic competition
* Patents should be stricter to obtain
* Compulsory agreements
 |
| Edlin, 2016**Table 1 Continued** | Personal view | Not applicable | * Competition
* Price discounts
* Negotiation of drug prices by payers and pharmaceutical companies
* Physicians can advocate for lower prices
* Pharmaceutical companies, federal, and state governments need to fund programs for hepatitis C treatment
* Drug companies can lower prices
* Government can lower prices by drug negotiation by public and private health insurers
* Non-voluntary licensing by governments
* Generic competition
* Policy experts can lobby governments for price reductions on hepatitis C treatment
* Class action lawsuits have pressured hepatitis C prices to drop
* State legislators can pressure pharmaceutical companies to lower hepatitis C treatment costs
 |
| Linas, 2016**Table 1 Continued** | Perspective | Not applicable | * Treat hepatitis C infection in the early stages of the disease
* Competition
* Use current data to pressure insurance companies to cover hepatitis C treatment costs
* Practitioners communicate ways to appeal hepatitis C treatment denial, decreasing hepatitis C treatment costs for patients
 |
| Linas et al., 2016 | Retrospective study | Hepatitis C Cost Effectiveness Model; hypothetical 1 million patients per patient type and treatment strategy | * Price negotiations between payers
* Lower drug costs for noncirrhotic patients
* Competition
 |
| Gentile et al., 2016 | Perspective | Not applicable | * World Health Organization can negotiate with stakeholders to lower hepatitis C prices
* Discounts on treatment costs
* Treat early stage hepatitis C sufferers
* Development of new hepatitis C drugs
* Utilizing international reference pricing
* Drug companies and national authorities need to prioritize affordable hepatitis C treatment
* Policies to reduce drug prices
* New deals with pharmaceutical companies
 |
| Zoulim et al., 2015**Table 1 Continued** | Report | Not applicable | * New financing options to fund hepatitis C treatment
* Limit treatment access to lower treatment costs
* Decrease drug costs
* Generic competition of direct acting antivirals
* Increase in combination drug therapies
* Advocacy groups can lower hepatitis C drug prices
* Voluntary licensing agreements
* Differential pricing
* Patent oppositions
* Compulsory licensing
 |
| Waheed, 2015 | Letter to the Editor | Not applicable | * Drug price negotiations
* Generic competition
 |
| Lynch and Wu, 2016 | Review | Not applicable | * Government can negotiate with pharmaceutical companies to reduce treatment costs
* Voluntary licensing agreements to increase generic competition
* Drug companies can work with governments for negotiations of generic medications
* Increased transparency is needed in the drug pricing process for cost-effectiveness analysis
* Increased public investment can assist control of hepatitis C treatment costs
 |
| Iyengar et. al., 2016**Table 1 Continued** | Retrospective study | 30 countries’ published data | * Restrict hepatitis C treatment to reduce costs
* Use tiered pricing agreements
* Voluntary licensing agreements allow for generic competition
* Negotiate drug pricing
* Import drugs from other countries
* Receive hepatitis C treatment overseas
* Compulsory licenses
* Pricing system must be modified
* Stakeholders (governments and corporations) can create pricing structures that lowers cost for hepatitis C treatment
 |
| Gornall, Hoey, and Ozieranski, 2016 | Report | Not applicable | * Reforms are needed to allow improved deal making, transparent pricing, and new payment processes
 |
| Bichoupan et al., 2014 | Retrospective study | Patients administered telaprevir-based triple therapy (n=147) | * Better combination therapies
 |
| Rein, Wittenborn, Smith, Liffman, and Ward, 2015 | Retrospective study  | US population over 20 years old (n = 229,185,985) | * Lower price alternatives exist

(Harvoni and Viekira Pak) |
| Hagan, 2014 | Question and answer | Not applicable | * Competition
* Generic medications
* Compulsory licensing
* Bulk purchasing decreases treatment cost through available discounts
* Activism and advocacy can generate support for reduced treatment costs
* Pay-for-performance pricing enables drug price negotiations by drug companies based on drug effectiveness
* Newer treatment options need to be more cost-effective than older ones to reduce future costs
 |

**Table 1 Continued**

Figure . The Top 4 Strategies for Hepatitis C Treatment Cost Reduction

(percentage of articles in review)

## financial strategies

Changes in business and finance practices can serve as strategies to reduce hepatitis C antiviral treatment costs. Eight of the studies (25.8% of the total included articles), which consisted of Rosenthal and Graham (2016), Sonnenreich and Geisler (2016), Craxi et al. (2016), van de Ven et al. (2014), Gentile et al. (2016), Zoulim et al. (2015), Iyengar et. al. (2016), and Hagan (2014) discussed this strategy.

Examples of changes in business and finance practices are clinical evaluation and pharmaco-economic analysis of direct acting antivirals can assist cost-effectiveness analysis and negotiations available to lower treatment costs. As a result, cost-effectiveness analyses can benefit policymakers, insurance firms, and the pharmaceutical industry to understand evidence that can be used to influence increased options to reduce hepatitis C antiviral treatment costs. Better cost-effectiveness analysis to educate patients and policy makers, new financing options to fund hepatitis C treatment expense, and need for pricing systems to be modified was suggested to decrease hepatitis C treatment costs (Zoulim et al., 2015, van de Ven et al., 2015, and Craxi et al., 2016). Another method of pharmaco-economical analysis, pay-for-performance pricing, is when payment for hepatitis C treatment accounts for drug effectiveness in the cost of the drug. This is important for drug price negotiations by drug companies based on drug effectiveness, international reference pricing, appropriate profit margins, and an increase in demand. Pricing and procurement methods, a patient-centered system that saves more costs than a supply driven system, and value based insurance systems are other strategies to decrease hepatitis C treatment costs. Pricing drugs based on value and the benefit of the drug in treating hepatitis C rather than on mostly pricing mechanisms allows for increased effectiveness of the drug in influencing treatment outcomes. A patient-centered system values the needs of the patient over the needs of corporations (Sonnenreich and Geisler, 2016).

Market competition, competition between hepatitis C treatment options, and generic drug competition were discussed in fifteen articles (48.3% of the total included articles). Jayasekera et al. (2017), Chhatwal, Chen, and Kanwal (2015), Bickerstaff (2015), and Edwards et al. (2015) discussed competition and its estimated effects on hepatitis C treatment costs. Other studies that addressed this topic were: Trooskin, Reynolds, and Kostman (2015), Craxi et al. (2016), Yilmaz, Yilmaz, and Leblebicioglu (2016), van de Ven et al. (2014), Meyer et al. (2015), Edlin (2016), Linas (2016), Linas et al. (2016), Zoulim et al. (2015), Waheed (2015), and Hagan (2014).

Eight studies (25.8% of the total included articles), Edwards et al. (2015), Craxi et al. (2016), Roy and King (2016), Edlin (2016), Gentile et al. (2016), Zoulim et al. (2015), Linas et al. (2016), and Rein, Wittenborn, Smith, Liffman, and Ward (2015), suggest that utilizing price discounts, utilizing lower price alternatives, and lowering drug costs for noncirrhotic patients may alleviate expensive hepatitis C treatment.

Price and drug negotiations are another strategy to reduce hepatitis C treatment costs. Five studies (16.1% of the total included articles) reported this finding: Meyer et al. (2015), Edlin (2016), Linas et al. (2016), Waheed (2015), and Iyengar et. al. (2016).

Different types of regulatory agreements by pharmaceutical companies are ways to decrease hepatitis C antiviral treatment. Licensing agreements were discussed by 7 studies (22.6% of the total included articles) according to Kamal-Yanni (2015), Edwards et al. (2015), Meyer et al. (2015), Zoulim et al. (2015), Lynch and Wu (2016), Iyengar et. al. (2016), and Hagan (2014).

The influence of patents also plays a role in the pricing of hepatitis C treatment. Four studies (12.9% of the total included articles), Craxi et al. (2016), van de Ven et al. (2014), Meyer et al. (2015), and Zoulim et al. (2015), reported that patent expiration, patent holders authorizing discounts, voluntary licensing agreements, tiered pricing, standard pricing, and patent oppositions can reduce hepatitis C treatment costs. Patent oppositions are when countries deny an existing patent due to the patent not producing a large enough pharmaceutical effect to treat medical illnesses (Zoulim et al., 2015). On the other hand, when patents expire, generic drugs are permitted to be produced and sold on the market, increasing competition and decreasing hepatitis C costs. Voluntary licensing agreements authorize generic medications (Meyer et al., 2015). As patents control the production of hepatitis C treatment drugs, they also influence prices because whoever owns the patents to the drugs owns the rights to them as well. Patent-holding starts the process of authorizing discounts, voluntary licensing agreements, tiered pricing, and standard pricing.

## institutional strategies

Twelve studies (38.7% of the total included articles), Kamal-Yanni (2015), Vernaz, Girardin, Goossens, Brugger, Riguzzi, Perrier, and Negro (2016), Bickerstaff (2015), Yilmaz, Yilmaz, and Leblebicioglu (2016), van de Ven et al. (2014), Rosenthal and Graham (2016), Gentile et al. (2016), Zoulim et al. (2015), Lynch and Wu (2016), Bichoupan et al. (2014), Hagan (2014), and Edlin (2016), reported that pharmaceutical industry modifications can moderate the high costs of hepatitis C treatment. Examples of pharmaceutical industry-based interventions and/or modifications include research of equivalent drugs, utilizing pan-genotypic drugs and generic drugs, and new deals involving pharmaceutical companies and, possibly, domestic and international health organizations. Other possibilities to lower hepatitis C treatment costs are newer treatment options, increasing the number of drug manufacturers and competition, and increasing the number of combination drugs available. Drug companies can work with the government to lower prices, and, along with payers and stakeholders, can implement more affordable drug pricing options. To account for the desire to increase profits, various entities can work together to develop a sustainable solution that will benefit all parties by compromising on solutions that benefit all interested parties. Transparency, which is the availability of pharmaceutical data such as pricing information on drugs during the payment process by payers (Rosenthal and Graham, 2016), can also be used to reduce hepatitis C treatment costs.

Three articles (9.7% of the total included articles), Sonnenreich and Geisler (2016), Roy and King (2016), Hagan (2014), stated that potential changes involving pharmaceutical companies in order to reduce hepatitis C treatment costs include value-based formulary and copayment changes, copay modifications, bulk purchasing, increased rebates, and restriction of buybacks. A value-based formulary organizes medications based on their value or cost-effectiveness. Health insurers are not required to pay if the medications do not improve patient health, decreasing their overall annual costs (Sonnenreich and Geisler, 2016).

Research and development changes to the pharmaceutical industry were analyzed by four studies (12.9% of the total included articles), Edwards et al. (2015), Roy and King (2016), van de Ven et al. (2014), and Yilmaz, Yilmaz, and Leblebicioglu (2016). These findings suggested that equal pricing and/or voluntary licensing should be considered early in a drug’s research and development phases and business transactions in voluntary licensing and generic manufacturers should be considered early. Other relevant strategies are that drug development costs should be more transparent; profits and research and development costs should become unrelated to drug prices so governments and other entities can license manufacturing rights for drug production. Increased productivity in obtaining raw materials and production methods for drug ingredients, cheaper, more effective raw materials, and pharmaceutical companies decreasing drug production by not charging for raw materials can reduce hepatitis C antiviral treatment costs (Yilmaz, Yilmaz, and Leblebicioglu, 2016 and van de Ven et al., 2015).

Seven articles (22.6% of the total included articles), Jayasekera et al. (2017), Kamal-Yanni (2015), Edwards et al. (2015), Zoulim et al. (2015), Iyengar et. al. (2016), Chidi, Bryce, Donohue, et al. (2016) and Barua et al. (2015) discuss the influence of insurance industries in the reduction of hepatitis C treatment costs. These include task shifting, which details the preferences of physicians screening individuals for treatment need and other staff monitoring the individuals in their treatment process. Task shifting reduces the costs of hepatitis C treatment by allowing other medical staff to oversee patients rather than physicians, which is cheaper (Jayasekera et al., 2017). This allows for decreased reimbursement rates for non-specialists.

Five articles (16.1% of the total included articles), Kamal-Yanni (2015), Trooskin, Reynolds, and Kostman (2015), van de Ven et al. (2014), Edlin (2016), and Lynch and Wu (2016) suggested that the United States government could assist with reducing hepatitis C treatment costs. Methods by the government consist of drug negotiation, the Trade-Related Aspects of Intellectual Property Rights policy, and non-voluntary licensing including the use of eminent domain specification.

Seven studies (22.6% of the total included articles), Rosenthal and Graham (2016), Sonnenreich and Geisler (2016), Craxi et al. (2016), Yilmaz, Yilmaz, and Leblebicioglu (2016), van de Ven et al. (2014), Gentile et al. (2016), and Gornall, Hoey, and Ozieranski (2016), stated that non-governmental organizations can develop policies involving both interferon and interferon-free regimens, and increased regulations. In addition, a 340B drug discount program, using the Trade-Related Aspects of Intellectual Property Rights policy for stricter patent applications, and reforms to improve deal making, transparent pricing, and new payment processes can result in a decrease in hepatitis C treatment costs. Having increased transparency improves the drug negotiation process by allowing entities to better understand market competition. The Trade-Related Aspects of Intellectual Property Rights policy allows for permission to market and sell generic medications (van de Ven et al., 2014). The 340B drug program permits low-income and underserved individuals to buy drugs free of charge. Hospitals buy the drugs at a subsidized rate and then charge the health insurer the full price for the drug. The cost savings provide additional revenue to the hospital or clinic (Barlas, 2017).

Two studies (6.5% of the total included articles), Gentile et al. (2016) and Iyengar et. al. (2016), report that utilizing other countries’ services can decrease hepatitis C treatment costs. These strategies consist of receiving hepatitis C treatment overseas, if possible, and reimporting drugs from lower-cost countries.

## stakeholder and potential interventions

Stakeholder involvement can play a critical role as stakeholders influence actions and directions of individuals and companies. Eleven articles (35.5% of the total included articles), Edwards et al. (2015), Craxi et al. (2016), Reilley et al. (2014), Yilmaz, Yilmaz, and Leblebicioglu (2016), Edlin (2016), Linas (2016), Gentile et al. (2016), Zoulim et al. (2015), Lynch and Wu (2016), Iyengar et. al. (2016), and Hagan (2014) emphasized the role of stakeholders in influencing hepatitis C treatment costs. Examples include increased public investment, increased engagement of stakeholders, stakeholder cooperation/collaboration, advocacy groups, and stakeholder-created pricing systems. Advocacy from physicians, practitioners advocating successful appeals, and widespread support of domestic, international, and private entities for hepatitis C treatment cost reductions are also methods to reduce hepatitis C treatment costs. Physicians can communicate their successful strategies with other practitioners such as filing appeals for patients to reduce the cost of hepatitis C treatment. Stakeholders can collaborate together to develop methods to reduce the high cost of hepatitis C treatment. In addition, the World Health Organization can negotiate with stakeholders by using common values and similarities between organizations to assist in lowering hepatitis C treatment prices. Drug companies and national authorities can prioritize affordable hepatitis C treatment by compromising with each party.

Five articles (16.1% of the total included articles), Rosenthal and Graham (2016), Sebhatu and Martin (2016), Trooskin, Reynolds, and Kostman (2015), Reilley et al. (2014), and Edlin (2016), suggested that providing programs for assistance, patient financial assistance programs, federal programs, and patient assistance programs initiated by pharmaceutical companies decreases hepatitis C treatment costs. These programs assist out-of-pocket costs for people living with hepatitis C and costs for health insurers. Another important strategy is for pharmaceutical companies, state, and federal governments to fund programs for hepatitis C treatment.

Two studies (6.5% of the total included articles), Edlin (2016) and Linas (2016), suggested that political pressure can be used to lower hepatitis C treatment costs. These include policy experts lobbying governments for price reductions and filing class action lawsuits. State legislators can pressure manufacturers to decrease hepatitis C treatment prices. Also, current dataon the rejection rates of prior authorization requests for hepatitis C treatment by insurers can be used to pressure insurance companies to cover hepatitis C treatment costs.

An increase in bargaining power, specifically by donor organizations was mentioned in two studies (6.5% of the total included articles): van de Ven et al. (2014) and Roy and King (2016). Bargaining power is beneficial because it is a measure of influence on various stakeholders. An increase in donor organizations’ bargaining power can have a greater impact on reducing hepatitis C treatment costs.

## treatment changes

Five studies (16.1% of the total included articles), Chidi, Bryce, Donohue, et al. (2016), Craxi et al. (2016), Van Nuys et al. (2015), Linas (2016), and Gentile et al. (2016), believed that early treatment for hepatitis C infection will lower the price of treatment. Bickerstaff (2015) suggested that using older hepatitis C treatments and developing policies about interferon and interferon-free treatment is important for decreasing hepatitis C costs.

Two studies (6.5% of the total included articles), Zoulim et al. (2015) and Iyengar et. al. (2016), suggested that limiting treatment access will reduce hepatitis C treatment costs. Limiting treatment access decreases costs; however, morbidity and mortality may increase as a result of limiting antiviral treatment access.

# DISCUSSIOn

Results of this literature review indicate that modifications to current practices within both the pharmaceutical industry and insurance industry with assistance from stakeholders, governments, and non-governmental organizations will help in alleviating the high burden of hepatitis C antiviral treatment costs. These are important methods to alleviate the barriers to care produced by the current hepatitis C treatment costs. Hepatitis C treatment is cost-effective (incremental cost-effectiveness ratio of $50,000-$150,000 per quality adjusted life year gained) to treat hepatitis C at any stage, especially the earlier stages, due to decreased medical costs in the future when hepatitis C progresses to the later stages of the disease (Chahal et al., 2016). Treating hepatitis C in the second or third stage is associated with less than $50,000 per QALY gained (Chahal et al., 2016). The incremental cost-effectiveness ratio is a quantitative measure of a health intervention and the quality adjusted life year gained measures the quality of life of an individual as an assessment of disease progression. These are used to measure the value of health interventions (Cohen and Reynolds, 2008).

The pharmaceutical industry is one of the profitable industries in the world (Denaro and Martin, 2016), but its profitability is one of the reasons why people suffering from hepatitis C have difficulty receiving treatment due to affordability concerns. As the pharmaceutical industry owns the rights to hepatitis C treatment medications, health insurers must negotiate with drug manufacturers for a purchasing price. As a result, drug costs will decrease and larger numbers of patients with hepatitis C will be able to afford treatment. Budgets of governments, industries, or organizations should be developed with increased flexibility toward hepatitis C treatment cost reductions.

One of the most significant barriers to affordable hepatitis C antiviral treatment in the United States relates to the ways drugs are produced and placed on the market for sale. The pharmaceutical industry in the United States develops the drugs and awaits approval by the Food and Drug Administration. The approval process for drugs is long and complex as pharmaceutical companies are required to provide evidence of drug efficacy and safety (US Food and Drug Administration, “Development,” 2017). As an additional barrier, the free market system of the United States permits pharmaceutical companies to determine their own drug prices. Research and development costs of drugs are expensive and pharmaceutical companies desire to profit from their endeavors before their patents expire. While the cost of research and development of drugs is expensive, this does not justify the high price of drug costs in the United States (Yu, Helms, and Bach, 2017), including hepatitis C treatment costs. In addition, due to the free market system in the United States and increased competition, the pharmaceutical industry protects its interests and ideas through patents, which prohibit other companies from developing and manufacturing similar drugs for usually twenty years (Amin and Kesselheim, 2012). The United States government, in general, does not produce pharmaceutical products nor does it have any impact on what drugs are produced. These decisions belong to pharmaceutical companies.

Competition is needed to decrease hepatitis C treatment costs and allow for increased discounts to be granted to those seeking hepatitis C treatment (Bickerstaff, 2015). While competition is gradually increasing with the introduction of new drugs such as Viekira, Pak, Zepatier, Epclusa, and Mavyret (American Liver Foundation, 2016 and Porter, 2017), additional competition is still needed. A way to increase competition is to change the regulatory system so larger numbers of drugs are approved faster (Daniel, 2016). While this change is feasible, the Food and Drug Administration, who has the authority to approve new pharmaceutical drugs for the market, must be involved to ensure the scientific process, safety, and effective delivery of drugs is not compromised. With the recent designation of Fast Track by the Food and Drug Administration implemented in March 2017, pharmaceutical companies can request their drug to have this designation if the drug is treating a condition where there is limited therapy and a strong need for the drug. Part of the criteria that the Food and Drug Administration uses to approve the drug to be designated Fast Track is a public health need has not been reached (US Food and Drug Administration, “Fast,” 2017). By giving priority to unmet needs, pharmaceutical companies will be able to have their drugs on the market for purchase and consumers will have drugs available quicker for their medical conditions. Another strategy to increase competition is to implement programs and policies to increase awareness of prescription medications and their pricing methods (Daniel, 2016). New pricing methods can decrease hepatitis C treatment costs by increasing flexibility for Medicare and other programs that assist with drug pricing. Medicare and other programs can advocate for drug bulk purchasing agreements, which is cheaper (Daniel, 2016). This is important to maintain a level playing field in the pharmaceutical industry and the insurance industry where both industries must compromise in order for increased access to hepatitis C treatment.

The insurance industry was reported as an area of significance in this literature review with the potential to influence hepatitis C treatment prices. The insurance industry is involved in many strategies to decrease hepatitis C treatment costs. Insurances can work with stakeholders, the financial community, and pharmaceutical industries to allow for improved pricing and ways to reduce the cost of hepatitis C treatment. Establishment of programs and policies can assist this cause. The [American Association for the Study of Liver Diseases](https://en.wikipedia.org/wiki/American_Association_for_the_Study_of_Liver_Diseases) and the [Infectious Diseases Society of America](http://www.idsociety.org/) recommends that all sufferers from hepatitis C be considered for treatment (Do et al., 2015). To adhere to this recommendation, the insurance industry can assist people living with hepatitis C by decreasing treatment prices for those insured and providing programs for those who are uninsured.

This literature review has detailed proposed strategies to decrease the expensive cost of hepatitis C antiviral treatment. In understanding why hepatitis C treatment is difficult to obtain due to cost, it is beneficial to learn from similar diseases with high treatment cost. When HIV/AIDS treatment was first introduced to the market, it was very expensive and there was decreased availability to sufferers without means to afford the cost of treatment. As a result, advocates from the HIV/AIDS community collaborated together, placing political pressure on drug manufacturers and legislatures to propose strategies to combat HIV/AIDS infection and provide sustainable treatment at a reasonable cost (Zoulim et al., 2015).

Advocacy played a large role in influencing pharmaceutical companies, health insurers, and policymakers to act on the growing urgency to provide HIV/AIDS treatment to people suffering from HIV/AIDS. Advocacy was reported in many of these articles and is important in bringing awareness to public health causes, including high hepatitis C treatment costs. Advocacy develops partnerships (Henry and Younossi, 2016) between individuals, industries, and organizations that can work together to alleviate public health concerns, facilitate price negotiations with pharmaceutical companies to benefit hepatitis C sufferers (Hagan, Wolpe, and Schinazi, 2013), and improve pricing of hepatitis C treatment (Chhatwal, 2015). To decrease the costs of hepatitis C treatment, programs need to be implemented similar to the Ryan White Care Act and the AIDS Drug Assistance Program (ADAP) (Carter and Aronsohn, 2017) to decrease hepatitis C treatment costs.

Limitations of this literature review include geographic coverage: not all states in the United States were represented in the literature review. Similar connotations of the search phases that could generate relevant results for inclusion in this literature review were not performed. These similar connotations could have generated different relevant studies for inclusion. This literature review is restricted to only the results generated by the search strategies guided by the research question. The results contain overlap from articles generated by the search phrases. Only one search engine, PubMed, was used to generate the literature review’s results. Using a broader array of search engines could result in a wider range of journal articles, increasing the breadth of the literature review.

This literature review provides additional information on ways to increase access to hepatitis C treatment by reducing the cost of the treatment. It is important to note that from a public health perspective, individual finances should not be considered a hindrance to receiving hepatitis C treatment as hepatitis C is a curable disease. There are strategies to reduce the cost of hepatitis C treatment and these strategies should be implemented from a policy standpoint. It is the responsibility of various stakeholders including local, state, and federal entities to collaborate on effective funding of hepatitis C treatment. In addition, the scientific community should be more proactive and serve as vocal advocates for changes in drug pricing (Hagan, Wolpe, and Schinazi, 2013).

# CONCLUSION

 Reducing hepatitis C treatment costs is an important first step to improve the lives of people living with hepatitis C. Hepatitis C infection is a serious illness that presents the possibility to develop liver cancer and liver cirrhosis. This literature review highlighted some of the many strategies and techniques necessary for decreasing the high cost of hepatitis C treatment. Without increased access to important hepatitis C treatment drugs, the goal of hepatitis C eradication will not be achieved (Hagan, Wolpe, and Schinazi, 2013). From a public health perspective, eradication of hepatitis C is possible with assistance from health insurers, pharmaceutical companies, and changes in business/financial practices. In addition, many stakeholders and policymakers are needed to facilitate decreasing hepatitis C treatment costs. With perseverance, the cost of hepatitis C treatment can be lowered by implementation of various strategies.

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