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Hepatitis C Treatment for Substance Users in North Dakota

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HEPATITIS C TREATMENT FOR SUBSTANCE USERS IN NORTH DAKOTA

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Abstract

In the 1960's, the hepatitis C virus (HCV) epidemic began mainly through the transmission of blood transfusions. By the time screening was implemented, millions had already become infected worldwide. After a decade of declining infection rates, a second wave started in the midst of the opioid epidemic in 2010. Prior to 2014 and the application of curative direct-acting antivirals, treatment was expensive, had low efficacy, many side effects, and long treatment durations. Advances in medicine have allowed for HCV elimination with shorter treatment durations, less side effects, and higher treatment rates. Unfortunately, treatment is not offered to all HCV patients due to current Medicaid restrictions and drug and alcohol abstinent requirements. This literature review aimed to investigate the effectiveness of treating HCV in active substance users. A comprehensive literature review was performed using electronic search databases PubMed, Embase, and CINHAL. Keywords used, along with MeSH words, included: hepatitis C, drugs, alcohol, economics, prevention and control, psychology, health care disparities, statistics and numerical data, health care quality, access and evaluation, and public health. The search results were limited to the last 10 years which yielded 30,397 articles. Exclusion criteria consisted of research on other variables with lacking data on substance use and HCV therapy completion. Studies with specific populations such as African Americans, pregnant patients and those with HCV/HIV co-infection were excluded. Research that was not completed in the United States (US) was also excluded. Current literature provides strong evidence in successful treatment regardless of substance use. Given the prevalence of those not receiving treatment and continual increase of HCV in the US, applying this research to clinical application could move us one step closer to HCV eradication.

Key Words: Hepatitis C, Direct Acting Antivirals, Drugs and Alcohol, Public Health

Introduction

Around the world, hepatitis C (HCV) is on the rise and continues to spread despite advances in medicine. In the 1960's, the HCV epidemic began primarily through the transmission of blood transfusions. By the time screening was implemented, millions of people had already become infected worldwide. National surveillance data reported that after a decade of declining HCV infection rates, a second wave started in the midst of the opioid epidemic in 2010. From 2010 to 2014, rates more than doubled with the largest increase in rural areas amongst persons aged 20 to 29 years of age. This was largely driven by the misuse of illicit drugs by sharing of injection equipment. Fortunately, newer medications have increased the cure rate of HCV to over 95%, however, not everyone who tests positive for HCV are receiving treatment. While advances in medicine have positively changed HCV treatment, challenges with treating patients continue. In many states in the US, Medicaid has specific restrictions on who can and cannot receive treatment. Currently, this strict regulation requires patients to be abstinent from drugs and alcohol three months prior to initiating HCV therapy. Unfortunately, this barrier often leaves vulnerable patients left untreated with the possibility of spreading to others. Because of the lack of treatment, eradication of the virus is nearly impossible. This literature review aimed to investigate the effectiveness of treating HCV patients who actively use drugs and alcohol.

Statement of the Problem

Unfortunately, access and barriers to treatment make it much harder for some with HCV to receive treatment. One major barrier to receiving HCV therapy is insurance. Currently, in many states in the US, Medicaid has strict guidelines that requires those who use substances to be abstinent from drugs and alcohol for three months prior to initiating treatment. This barrier

leaves many vulnerable, substance using patients are left untreated as sobriety is not within reach for many patients. It is also important to note that a vast majority of patients who use intravenous (IV) drugs are those that are isolated from society with little access to health care, live in poverty, are homeless, and have a higher rate of mental health issues. Unfortunately, because of these barriers, it is not uncommon for providers to consider people who inject drugs (PWID) to be non-compliant, poor candidates for HCV therapy, and do not offer them treatment. Although many patients are offered the opportunity to enroll in support programs prior to starting HCV treatment, it is not uncommon for patients to be discouraged and are often lost to follow up care because of the current requirements. Despite the great advances in HCV treatment and testing, the heavy barriers, limitations of current available therapies, and public health burdens are front and center as primary areas of need for better prevention and treatment strategies. However, eradication of the worldwide disease may be impossible if treatment is not provided for all, including those actively using drugs and alcohol.

Research Question

In the US, for HCV positive patients who actively use alcohol and illicit drugs, is abstinence prior to initiating treatment necessary to achieve a sustained virologic response (SVR) or a cure for HCV?

Methods

A comprehensive literature review was performed using electronic search databases PubMed, Embase and CINHAL. Keywords, used along with MeSH words, included: hepatitis C, drugs, alcohol, economics, prevention and control, psychology, health care disparities, statistics and numerical data, health care quality, access and evaluation, and public health. The search results were limited to the last 10 years as this time frame is more relevant to this

research. The search yielded 30,397 articles. Exclusion criteria consisted of research on other variables with insufficient data on substance use and HCV therapy completion. Many studies were excluded as they were performed on specific patient populations such as African Americans, pregnant patients and those with HCV/HIV co-infection. Research that was not completed in the US were also excluded.

Literature Review

A review of literature shows that HCV continues to increase across the world with an increased prevalence in the vulnerable population, such as homeless and incarcerated individuals. For the vulnerable population, access to health care and lack of insurance are both large barriers to receiving treatment. While treatment is not standardized across the country, this leaves many people with the inability to be treated due to barriers and discrimination. Although there currently is not an HCV vaccination, medical professionals around the world are advocating for broader use of treatment to aid in eradication of this potentially deadly virus. There have been various studies completed on treatment outcomes of those using substances versus those who remain sober or are in remission.

Pathophysiology of Hepatitis C

Hepatitis C is an enveloped, RNA virus with ten protein coding genes that is transmitted through blood-to-blood contact that primarily targets liver cells. The liver is a vital organ that fights infections and filters blood and nutrients. With damage and inflammation, the function of the liver is impaired. In roughly 50-80% of patients, HCV infection will progress to a chronic state, which means the virus is detectable after six months. If left untreated, it can lead to cirrhosis, fibrosis, end-stage liver disease, hepatocellular carcinoma or even death. In approximately 20-50% of patients, the body can be completely clear after an acute infection

(Vine et al., 2015). The mechanism that induces hepatocyte damage by HCV infection is not completely understood, however, it is thought to cause cell injury with a local immune-mediated response which causes a chronic inflammatory state. The metabolic processes interrupted by the viral replication facilitates liver steatosis and inflammation (Vine et al., 2015).

Hepatitis C Treatment

Once a patient has a confirmed HCV infection, disease staging is completed to assess the extent of liver damage, which determines if the patient is a candidate for treatment. Histopathological examination with a liver biopsy is most accurate at determining disease stage, however, ultrasound imaging-based transient elastography is used most often as it is less expensive, less invasive, and is moderately accurate in detecting and differentiating stages of liver fibrosis. Once identified as a candidate, appropriate therapy is determined by the provider based on HCV genotype. There are 7 known HCV genotypes (1-7) with genotype 1 being the most prevalent causing between 40% and 50% of HCV infections worldwide (Hopkins et al., 2020). In addition to the 7 genotypes, more than 70 subtypes have been found which is thought to arise from genetic variation from HCV's high rate of mutation. Determining HCV genotype is important as it allows for proper drug selection, dosage, and overall treatment duration (Hopkins et al., 2020).

Over the past decade, the drastic evolution of HCV treatment has the potential to make a big impact throughout the world. Prior HCV treatment consisted of medications that had low efficacy, many side effects as well as long treatment durations. The newest HCV medications, direct-acting antivirals (DAAs), have the capacity to achieve SVR within 8 to 12 weeks. SVR is defined as the absence of HCV after receiving treatment. Regardless of genotype, DAAs have proven to be more than 90% effective in curing HCV (Hopkins et al., 2020).

Prevention and Treatment Barriers

The Global Burden of Disease estimated that 39% of HCV burden is acquired via injecting of illicit drugs (Grebely et al., 2017). Unfortunately, PWID bear considerable stigma and discrimination. Lack of engagement in health services among this population can stem from discrimination experienced in past health care encounters. According to Grebely et al. (2017), a study that was completed in Thailand found that 26% of PWID reported avoiding health services due to factors associated with past experience of verbal abuse, being refused medical care, and experiencing barriers to accessing care.

Criminalization of drug use and presence of restrictive drug use policies among PWID has many unintended harms. For example, restrictions to DAAs with failure to intervene at early stages may result in costly long-term care, development of cirrhosis, decompensated liver disease, and liver cancer. While treatment is limited and PWID have the greatest risk of transmission, HCV treatment in this population should be a priority to have an impact on the global epidemic. It has been proven that DAA therapy is effective among PWID that are receiving opioid substitution therapy (OST), people with a history of injecting drug use, and recent PWID including those with HCV/HIV co-infection. HCV reinfection in PWID is low (0.0 to 5.3/100 per-year) with slightly higher rates among those with ongoing injecting drug use (4.9-6.4/100 person-year) (Grebely et al., 2017). Mathematical modeling suggests that HCV prevention could lead to reductions in prevalence among PWID. Increasing DAA treatment to 8 per 100 PWID would lower HCV incidence and prevent further transmission (Grebely et al., 2017).

In many countries, governments are restricting access to HCV treatment based on fibrosis staging, recent drug use, and prescriber type to reduce the budget impact of high-price therapies (Grebely et al., 2017). Compared to international guidelines, the World Health Organization (WHO) states that treatment should be made available for everyone despite their disease state or drug use history. To reduce both new infections and mortality by 2030, a dual focus approach among PWID and those with advanced disease is necessary (Grebely et al., 2017). However, this prioritization strategy must be built on a foundation that broadens access to DAAs while requiring pharmaceutical companies to lower DAA prices. Access to affordable, quality healthcare should be a basic human right despite one's drug or alcohol use status.

This research report pinpoints key actions that are needed to eliminate HCV infection. HCV is a global health threat and government investment accompanied by national strategies is necessary to ensure successful implementation. Grebely et al. (2017) recommends reforming drug policies, scaling up harm reduction services, making health services accessible for PWID while supporting community empowerment and community-based programs. While HCV elimination is achievable, it will require researchers, healthcare providers, policy makers, the affected community, advocates, pharmaceutical and diagnostic industries, and governments around the world to come together to make this happen (Grebely et al., 2017).

Arguably, one of the biggest barriers to HCV therapy is the cost. When DAAs were first released, one of the most effective and commonly used agents, Sofosbuvir, cost approximately $84,000 for a full treatment course. Over the past several years, multiple other regimens have been FDA approved and prices have come down significantly, however, even at the best price available on the market, a course of HCV treatment costs tens of thousands of dollars. When considering treatment, not only is it expensive but PWID with HCV often rely on public payers,

such as Medicaid, which places substantial stress on health care budgets. Unfortunately, while transmission is highest amongst PWID, the elimination challenge in this population is the most difficult. With effective treatment in hand, there is a tremendous potential to eliminate transmission, however, the challenge has now shifted from one of biology and how to cure a virus, to public health and how to treat over four million people in the US who have HCV (Linas & Nolen, 2018).

Linas and Nolen (2018) expressed the need for outcome measurement that considers both cost of HCV treatment as well as the benefit it provides to assess its value. Cost-effective analysis (CEA) is used to explore how to maximize public health benefits of HCV treatment. Cost-effectiveness was evaluated by using the incremental cost-effectiveness ratio (ICER). The ICER is interpreted by answering three questions: "What are the costs with new and old treatment? How much more will we spend? What are the benefits of the interventions?" This included the cost of new HCV treatments, as well as the cost of staging and evaluation. The importance of this study was to consider the costs that are avoided by preventing future complications from the disease. While the costs of HCV therapy are immediate, the future costs that would accrue from advanced liver disease could potentially be avoided. Measuring benefit of life expectancy is valuable, but only considering mortality benefits fails to recognize the value of HCV treatment and improving quality of life. To calculate quality of life, they used a measurement tool called quality-adjusted life year (QALY), that integrates longevity and quality of life which is ultimately the preferred outcome for CEA (Linas & Nolen, 2018).

CEA compared ICER for a specific treatment, such as HCV therapy, to a threshold value which can be rejected if treatments have an ICER greater than threshold which would be considered "not cost-effective." The threshold they used to compare the ICER is referred to as

"willingness-to-pay" threshold (WTP). WTP is not a value of how much they would be "willing" to pay to save a life and is not an ethical judgement of how much life is worth, but is an attempt to quantify the opportunity cost of a new treatment. The importance of WTP is a reflection in the return in QALY if available budget was used to provide treatment and instead used to invest in the current healthcare system. In the US, the WTP is considered $50,000 or $100,000/QALY gained. This number is country-specific and reflects resources available in a given area. The WHO defines ICER less than per-capita GDP for a country as "very cost-effective" and less than three times per-capita GDP as "cost-effective" (Linas & Nolen, 2018).

Linas and Nolen (2018) compiled data on over 20 studies that investigated the cost-effectiveness of HCV treatment over the past five years. The studies compared "treat all patients" to various forms of treatment restrictions. They consistently determined that "treat all" is a cost-effective approach. Cost-effective studies with DAAs included cost-effectiveness of DAA regimens compared to interferon-based treatments, cost and cost-effectiveness of HCV treatment restrictions, cost-effectiveness of implementation models to increased HCV treatment capacity, cost-effectiveness of HCV treatment in key populations such as PWID, and cost-effectiveness of HCV therapy in liver transplant patients. It was noted that some of the earlier studies with the list price of first available treatment regimens were determined not cost-effective, however, those conclusions did not reflect the substantial price reductions that have occurred over the past couple years.

Linas and Nolen (2018) questioned why more people aren't receiving treatment if treatment is considered cost-effective. Unfortunately, payers in the US. make their coverage decisions based on budgetary impact and not on economic "value." They found that businesses such as Medicaid assume a one-year to five-year perspective on budgets which directly impacts

decision making for HCV therapy. The cost of therapy through Medicaid accrues immediately but the benefits may not be apparent for decades. When considering offering treatment to all HCV positive patients, the future savings has very little meaning for Medicaid budgeting today. Even though research demonstrates an ICER <$100,000/QALY for HCV therapy, it does not address the reality of treatment expense and the likely responsibility of thousands of dollars of treatment cost for all HCV-infected people covered by their plan (Linas & Nolen, 2018).

The information that was gathered provides a foundation of evidence that providing HCV treatment for all persons has good economic value even though treatment is expensive. While the prices of medications have fallen, the price continues to limit access to care. This solidified that the wedge between affordability and cost-effectiveness stands front and center as a leading barrier to elimination of HCV (Linas & Nolen, 2018).

While treatment is the ultimate cure, harm reduction interventions are also vital for averting transmission of HCV and other blood-borne infections, such as HIV, amongst active PWID. Around the country, syringe service programs (SSPs) are available to provide education and clean equipment in exchange for used injection supplies. SSPs are crucial to public health as they access hard-to-reach, stigmatized communities while allowing easier linkage to healthcare, providing HCV testing, referrals for opioid substitution therapy, abuse treatment programs, access to overdose prevention tools in addition to reducing risky injection behaviors with clean injection supplies. Unfortunately, throughout the United States, there is considerable geographic inconsistency in the number and capacity of SSPs (Canary et al., 2017).

From July 1, 2015 to June 30, 2016, Canary et al. (2017) analyzed persons aged 15 to 29 years with a detectable HCV RNA at Quest Diagnostics (Quest) or Laboratory Corporation of America (LabCorp). The analyzed patients were mapped according to their residential zip code

associated with their earliest positive HCV RNA result. Some records were noted to miss a residential zip code and were recorded using the ordering providers zip code. In accordance with the Health Insurance Portability and Accountability Act (HIPAA), laboratory test results were obtained by the US Centers for Disease Control (CDC) (Canary et al., 2017).

Canary et al. identified programs that provided syringe services as of June 2016 through a directory maintained by the North American Syringe Exchange Network. All SSP's were geocoded based on zip code, city, and state. Distance, in miles, was calculated between zip codes of patient residences and location of SSPs. Distances less than 10 miles were defined as "near" and distances greater than 10 miles were defined as "far."

LabCorp and Quest analyzed a total of 29,382 people aged 15 to 29 with active HCV infections. Patients were tested in all 50 states of the United States, including Washington, DC. The overall median age was 25 years with 54% of patients being female and 46 percent male. The majority of persons, 86.8%, were mapped to a residential zip code and 13.1% were mapped to the ordering provider zip code. Those missing a zip code were excluded from the study and accounted for 0.1% of persons (Canary et al., 2017).

Overall, Canary et al. concluded that over the course of a one-year period, less than half of young persons with HCV were located near SSPs. They calculated a total of 23,494 persons had limited access to SSP services with a median distance of 37 miles. Interestingly, the proportion of patients residing near an SSP was highest in the West (35.8%) and lowest in the South (9.9%). In addition, proximity to SSPs varied across levels of urbanicity. Unfortunately, 98% of those living in rural areas lived far from SSPs. Given that injection drug use is the primary cause of HCV and the higher proportion of persons without access to SSPs live in rural areas, this highlights the continuous challenge of reaching PWID in remote settings. Using

location analyses, it was estimated that over 2200 additional programs would need to be established to reach almost 95% of persons residing far from an SSP. The large gaps in access to harm reduction services addresses the continual need for primary prevention of blood-borne diseases from unsafe injection drug use.

Evidence Based Medicine

In the US, substance abuse is a major public health problem and is disproportionately associated with HCV infection. Intravenous drug use (IDU) is the main mode of transmission and identified risk factor to HCV. Unfortunately, it continues to contribute to the increasing prevalence of acute infections. Globally, in 2015, there was a reported 1.7 million new HCV infections with approximately 23% of cases linked to injecting drugs (Grebely et al., 2017). In addition to substance use and HCV, alcohol can also promote disease progression in chronic liver disease. In those with HCV, alcohol abuse acts synergistically and can aggravate hepatic injury leading enhanced fibrosis, cirrhosis, and hepatocellular carcinoma. Substance and alcohol abuse has a higher prevalence in those with underlying, uncontrolled psychiatric comorbidities such as depression, anxiety, bipolar disorder, and schizophrenia to name a few (George et al., 2018).

Hepatitis C treatment has evolved immensely from the interferon era which was known to consist of a long treatment course that had several side effects. New DAA's have fever complications, drug-to-drug interactions, require less intense monitoring, and have a shorter treatment course to achieve SVR. Media advertising of the new HCV drug-development has attracted people with ongoing substance abuse seeking therapy. Although we have established effective treatment, the cost of medication continues to be a large barrier for those wanting to receive treatment. Studies continue to show that HCV is common amongst low income,

vulnerable populations, and it is this same population that commonly do not have insurance, income or means to pay for expensive medications. HCV treatment involves frequent clinic visits and medication compliance. With the inability to comply taking daily medications due to substance use, achieving SVR is not realistic. Newer medications have proven to be safe and effective among those who inject drugs, however it appears there is a concern that substance misuse may affect adherence to antiviral therapy.

George et al. (2018) completed a study to investigate recreational drug use (RDU) disclosure among those with HCV before and after educational intervention aiming to improve response rates. In addition, they investigated patterns of alcohol and coexisting psychiatric diseases. The study was completed at a specialty clinic that centralized care to all HCV patients. The primary goal was to characterize substance abuse and psychiatric profiles in addition to providing educational information to test whether it impacted commencement of antiviral therapy. To better portray each patient's psychosocial profile, all patients were provided with a questionnaire inquiring about the use of any intravenous (IV), snorted (S), other (O) RDU and cannabis (THC) use prior to their clinic visit. It also included a detailed prescription drug use and psychiatric survey with special attention on patterns of alcohol use. According to the Dietary Guidelines for Americans 2015-2020, U.S. Department of Health and Human Services and U.S. Department of Agriculture, defined moderate drinking as up to one drink per day and heavy drinking as eight or more drinks per week for women. For men, moderate drinking was defined as up to two drinks per day and heavy drinking as 15 or more drinks per week. Binge drinking was identified as four or more drinks for women and five or more drinks for men per drinking occasion per the NIAAA (National Institute on Alcohol Abuse and Alcoholism). A

retrospective chart review was performed in all cases to further investigate and cross reference any missing or incomplete data (George et al., 2018).

A total of 153 patients (mean age 50 ± 12 years, males 52%, females 48%) were selected from the Viral Hepatitis Clinic at the University of Arkansas for Medical Sciences. Prior to the clinic visit, 144 patients submitted the questionnaire while 13 (8%) declined to fill out the substance abuse portion despite being asked on a second occasion if they had anything to disclose. During the visit, the provider spent extra time with each patient to provide education on the clinical course of HCV, the impact RDU has on the transmission of HCV, with emphasis on the importance of disclosing accurate substance use history (George et al., 2018).

Although a thorough questionnaire was completed, a urine drug screen was performed in 123 patients (80%). Forty-five patients screened positive for at least one drug. Fourteen patients (31%) tested positive for methamphetamine, including one patient who adamantly denied any drug use. Twenty-nine patients (64%) tested positive for THC, including eight patients who adamantly denied THC use. After educational intervention, in all cases except O-RDU, all patients revised their statements revealing a significant increase RDU and THC use. The net gain in drug disclosure in was 11/28 (39%) for any RDU, 7/58 (12%) for IV-RDU, 15/71 (21%) for S-RDU, 4/108 (4%) for O-RDU, and 17/54 (31%) for THC. For O-RDU, net gain in drug disclosure was 26 (59%) in methamphetamine smoking, 11 (25%) in cocaine smoking, four (9%) in use of hallucinogens (mushrooms and LSD) and one (2%) in non-prescribed opioids/benzodiazepines. In 83% of cases, other risk factors for HCV transmission were acknowledged despite IV-RDU or S-RDU not being identified. Other risk factors included blood transfusions, tattoos, household contacts, needle sticks, prison, and high-risk sexual behavior (George et al., 2018). Data on alcohol use was also collected in 136 patients. Prior to being

tested, current and prior ethanol use was reported in 118 patients with 38 being current drinkers. The median daily consumption for all 118 patients was 59 g/d (23 to 137 g/d) with a mean duration of 20 (9 to 32) years (George et al., 2018). Regarding drinking patterns, 51/104 patients reported heavy drinking, 49/99 reported daily drinking, and 15/104 reported binge drinking. In heavy and non-heavy drinkers, median daily ethanol use 88g/d (IQR 62 to 205) and 14g/d (IQR 5 to 24) (George et al., 2018). A psychiatric condition, of at least one prior or active condition, was positive in 84 patients. Twenty-seven patients reported having two psychiatric disorders while eight reported three psychiatric disorders. Sixty patients were using at least one psychiatric medication during the initial evaluation, 29 patients received two medications and six patients were on three psychiatric medications. Medications that were used among these patients included selective serotonin reuptake inhibitors (SSRI), selective serotonin norepinephrine reuptake inhibitors (SNRI), antipsychotics, tricyclic antipsychotics and others (George et al., 2018).

A total of 73 of 139 (53%) patients were eligible for antiviral therapy after a follow-up of 21 ± five months. Fourteen patients were eliminated from further analysis due to a spontaneously resolved infection or prior SVR at initial visit. Several antiviral regimens were used in this study including ledipasvir/sofosbuvir in 42 patients, sofosbuvir + ribavirin in 14 patients, paritaprevir/ombitasavir/dasabuvir ± ribavirin in nine patients, peginterferon + sofosbuvir + ribavirin in five patients and simeprevir + sofosbuvir ± ribavirin in three patients. Liver fibrosis staging was available in 92 patients, however, there were no differences in the rate of commencement across all stages (George et al, 2018). The remaining 66 patients did not start treatment as they were lost to follow-up (64%, n=42), denied by insurance or third payer (29%, n=19), and other reason (7%, n=5). On multivariable analysis, lack of commencement of

antiviral therapy was shown independently by only age (OR=1.04, 95% CT 1.01-1.08) and having a positive drug screen (OR=0.41, 95%, CI 0.19-0.92). Patients that tested positive were more likely to be denied by their insurance company or lost to follow-up than a patient with a negative screen (George et al., 2018).

Interestingly, medication noncompliance was identified in only 10/73 treated patients with just one instance of significant noncompliance (lapse of 2 weeks off medication) while the other nine cases missed no more than three doses. However, education on importance of medication compliance is unknown. Overall, George et al. (2018) found that all patients with available information, 57/58 (98%) patients achieved SVR12 which is considered a cure for HCV. In addition, they concluded that the most common reasons for not starting antiviral treatment were loss to follow-up and insurance denial. George et al. concluded that routine history taking, the use of questionnaires and reconciliation of patient-provided history, substance abuse data remains inaccurate. Although inaccurate, trained individuals who dedicate clinic time to obtain a thorough history and provide education in a non-judgmental, empathetic environment can increase yield by 6% to 30%. Considering only patients that provided a negative response, it was found that 39% of patients revised their statement and accepted RDU after their in-person clinic visit with a provider (George et al., 2018).

This study displayed that providing patients with a comfortable, confidential environment and treating them with respect can make a huge difference in building trust and long-term patient provider relationships. Good patient-provider relationships allow for thorough and accurate substance abuse evaluation which is proven effective in maximizing abstinence and minimizing behaviors with risks for reinfection. Ultimately, utilizing this strategy would increase the risk of

successful antiviral therapy while reducing transmission and reinfection rates (George et al., 2018).

Norton et al. (2017) conducted a study with 89 hepatitis C (HCV) patients between January 2014 and August 2015 in an urban primary care clinic in Bronx, NY with the intent to examine the impact of both drug use and participation in drug use (OAT) on HCV treatment outcomes. Patients with a positive HCV antibody were referred by their primary care provider (PCP) or from a community-based organization (SSP) to be evaluated by an HCV specialist. Thorough patient evaluation included past clinical history, current drug use and opioid agonist treatment (OAT), HCV viral load, genotype testing, complete metabolic panel, complete blood count, noninvasive liver assessments and abdominal ultrasound for those with cirrhosis. Those excluded from treatment those with impaired renal function (creatinine clearance <30mL/min), decompensated liver disease (Child Pugh Class B or C), or the presence of hepatocellular carcinoma (Norton et al., 2017). Those who were offered treatment attended an initial treatment visit which included initial evaluation and review of laboratory results. Follow-up visits included a baseline treatment visit where at least one HCV medication was started, a visit at treatment week two, four, eight, 12 (every month after this for those who were on 24 weeks of treatment) and a final visit at 12 weeks post treatment to determine SVR, which is considered a virologic cure of HCV. In addition to scheduled office visits, each patient was enrolled in a patient care program through the NYC Department of Health which funded and provided a full-time care coordinator that provided clinical-care coordination services to assist patients in completing treatment (Norton et al., 2017).

Median age of patients receiving treatment was 59 years with 63% male, 54% Latin American, and 39% African American. Eighty-four patients had genotype 1 HCV, three with

G2, one with G3 and one with G4. Additionally, 21% of patients had received prior HCV-treatment, 35% had cirrhosis and 24% were HIV/HCV co-infected. A psychiatric diagnosis presented in nearly half of the study group (48%) and 25% had used alcohol in the last 30 days. All patients enrolled were treated with sofosbuvir containing agents (Norton et al., 2017). Patients were identified in to four categories based on drug use and drug treatment. Categories included non-people who use drugs (PWUD) or OAT therapy, no active drug use and receiving OAT, active drug use not receiving OAT, and active drug use receiving OAT. Forty-three patients were categorized as non-PWUD or OAT and 46 patients were categorized as patients actively using drugs and/or receiving OAT. Active drug use was self-reported or was documented from a positive urine drug screen that was completed at the time of the study, however, urine drug screens were not universally performed for the purpose of this study. Of the 46 patients actively using drugs, 61% (n=19) were using opioids, 32% (n=10) were using cocaine, 39% (n=12) were using marijuana and 3% (n=1) were using amphetamines. Between the four drug and non-drug use categories, there were significant differences in age, sex, and prevalence of psychiatric disorders. Active drug users, not receiving OAT, were younger with a median age of 55 and 56 (active drug use receiving OAT) compared to a median age of 64 for those with not active drug use and not receiving OAT (Norton et al., 2017).

All 89 patients completed treatment, however, there were two patients that failed treatment (viral relapses) and two who were lost to follow-up. For those that had a viral relapse, one was actively using drugs and receiving OAT and the other was not actively using drugs or receiving OAT. Overall, the results of the study showed a total SVR rate of 96%. SVR rates for non-PWUD was 95% (n=41/43) and 96% for patients actively using drugs and/or receiving OAT

(n=44/46). There were no differences in SVR rates by drug use or drug treatment category (Norton et al., 2017).

This study supports treating all patients regardless of their drug use history. No clinical evidence was noted to justify restricting access to HCV for those actively using drugs and/or receiving OAT. This study also proved treatment success was achievable with care from an HCV specialist in addition using a care coordinator. There were several limitations to this study. The patients in this study were provided care coordination through special funding which is not generalizable to all settings. Furthermore, all patients in this study were referred by their PCP therefore may have been more motivated than others who do not have the same access to healthcare. In addition, this study had a small sample size while taking place in only one small, urban primary care clinic (Norton et al., 2017).

From 2003 to 2010, the National Health and Nutrition Examination Survey (NHANES) collected data on nearly 3.6 million noninstitutionalized people that were HCV positive in the US (Spradling et al., 2018). Approximately 2.7 million people had a chronic HCV infection, meaning an active infection lasting longer than six months. Unfortunately, only a small fraction received treatment with interferon (IFN) therapy and an even smaller fraction that achieved SVR. As of 2013, it was estimated that only 7% to 11% of all HCV infected patients had been treated and only 5% to 6% achieving SVR (Spradling et al., 2018).

Beginning in late 2013, the approval and release of DAA's revolutionized HCV treatment while offering the opportunity for widespread HCV infection reduction. Compared to IFN regimens, the newer agents have substantially shorter treatment durations, are well-tolerated and are highly effective. Spradling et al. (2018) completed a study to determine DAA uptake among HCV infected patients and determine patient characteristics associated with receipt of DAAs.

Spradling et al. collected data from patients 18 years and older with chronic HCV who were enrolled in the Chronic Hepatitis Cohort Study (CHeCS). The 2.7 million patients, who had at least one clinical service visit between January 1, 2006 and December 31, 2014, were studied across four geographically and demographically US sites. Information collected included patient demographics, medical encounters, receipt of and response to HCV therapy and laboratory and biopsy results through basic analysis of electronic health records and administrative data. Confirmation of chronic HCV infection was completed based upon chart review and one or more positive HCV-RNA test prior to starting antiviral treatment (Spradling et al., 2018).

To determine the number of persons eligible for treatment, the study was limited to patients who had at least one encounter at a hospital, clinic, pharmacy, or emergency department in 2013. As of December 13, 2013, those with no previous treatment and those who previously failed treatment were prescribed a DAA regimen between January 1 to December 31, 2014. Sociodemographic (study site, age, sex, race/ethnicity, insurance status, annual income according to census tract geocode) and clinical scores (pretreatment FIB4) of HCV positive patients were compared among those who did not start therapy. FIB4, a non-invasive marker for liver fibrosis, is calculated using patient age, serum aminotransferase levels and platelet count. Scores were stratified into four categories (<2.0, 2.0-3.23, 3.26-5.88, ≥5.88) and were validated as a predictive of cirrhosis in this study. Body mass index, HCV genotype, Charlson comorbidity score (number of medical comorbid diagnoses present during HCV diagnosis), liver transplant history and hepatitis B and human immunodeficiency virus (HIV) coinfection status were also compared among those who did and did not initiate therapy (Spradling et al., 2018).

Throughout the study interval (prescriptions prescribed during 2014 and initiated as late as August 31, 2015), they plotted the number of patients that initiated therapy during each month. Provider type (primary care, infectious disease practitioner, hepatologist, etc.) and time interval between DAA prescription and initiation were examined by <one month, one to three months and greater than three months periods. The regimens prescribed were sofosbuvir (SOF) ± simeprevir or daclatasvir ± ribavirin (RBV) and SOF with LDV±RBV (Spradling et al, 2018).

During 2006 to 2014, the CHeCS cohort comprised 17,650 patients with chronic HCV. Patients that were excluded from the study included those who died (2975), those who were treated and cured before January 1, 2014 (2238), and those without a clinical encounter during 2013 (3029). After exclusions, 9508 patients were eligible for DAA regimen initiation. The persons eligible for treatment initiation consisted of 58.7% males, 64.6% non-Hispanic white, and 23.1% non-Hispanic white respectively. The majority of patients were between the ages of 41 to 70 years of age (79.8%). An annual income of less than $30,000 was reported in 24.4% of patients and 27.3% had an income greater than $50,000. In regards to insurance, 46.0% reported having private insurance and 12.8% reported having Medicaid. Clinically, 17.5% had failed prior treatment, 3.3% were HIV coinfected, 78.4% had HCV genotype 1 infection, and 4.9% had a previous liver transplant. In addition, 13.7% had a pretreatment FIB4 score of 3.25 to 5.88 and 13.8% who had a FIB4 score >5.88 (Spradling et al., 2018).

From January 1, 2014 to August 31, 2015, 544 (5.7%) eligible patients initiated DAA treatment. Overall, they found that uptake of DAA therapy was associated with sociodemographic and clinical characteristics which included those with a higher annual income, higher FIB4 (8.6% of patients with a pretreatment score of 3.25 to 5.88 initiated treatment and 11.6% of patients with a score >5.88) scores, previously failed treatment, genotype 2 HCV

infection, and HIV coinfection. Although the American Association for the Study of Liver Diseases guidelines stated it was "most appropriate to treat those greater at risk of disease complications before treating those with less advanced disease," the overall uptake was even low among patients with moderate to severe liver disease. Among those with a lower likelihood of initiation of DAA therapy included non-Hispanic Black race, those with Medicaid and receipt of care at one of the study sites (Spradling et al., 2018).

While restricted access to DAA among Medicaid beneficiaries in the state of North Dakota is present, this study confirmed that indeed Medicaid patients have 50% reduced odds of receiving therapy compared to those with private insurance. In addition, Spradling et al. concluded that 30% of black patients have reduced odds of receiving therapy compared to white patients. Unsurprisingly, those with a lower income were less likely to receive therapy compared to those with a higher annual income. The highlight of their findings solidified the urgent need for targeted efforts to improve access to DAA therapy, especially in the state of North Dakota where several vulnerable, homeless, low income and Medicaid patients are not receiving treatment (Spradling et al., 2018).

This study did not include other patient-related information such as drug and alcohol use and mental health issues. Relying primarily on electronic health records made it difficult to quantify the effect of other barriers that may have affected uptake. Another limitation to this study was absence of SVR of those enrolled. While not having this data, it is possible that some patients could have been prescribed HCV therapy but left CHeCS before starting the regimen, thus falsely lowering the uptake percentage. Another limitation to this study was the time it was completed. This study was completed in the first year that the DAAs were approved. Since 2013, there have been changes in system barriers and access to medications throughout the US,

however, this study is specifically relevant to the state of North Dakota as Medicaid barriers continue to largely impact patient access. An advantage to this study is the data collected was from patients under real-world conditions in the absence of a study protocol. Additionally, the patients in this study represented a variety of backgrounds with patients that have access to both primary care and specialists.

Barriers to HCV therapy continue to limit the ability to eradicate HCV despite the availability of the highly effective DAAs. Wong et al. (2018) focused on race/ethnicity and insurance-specific disparities while evaluating rates and predictors of HCV treatment across four community-based health care systems in California, Louisiana, Texas and Virginia from January 1, 2011 to February 28, 2017. The adults in this study included a large proportion of ethnic minorities, broad payer mix and two safety-net systems. Overall, HCV treatment rates were calculated using Kaplan-Meier methods and multivariate logistic regression models to evaluate predictors of receiving treatment (Wong et al, 2018).

In the US, each state has their own Medicaid criteria and restrictions. A recent publication by the National Viral Hepatitis Roundtable and the Harvard Law School Center for Health Law and Policy Innovation compared state-specific Medicaid restrictions in 2014 and 2016 on access to HCV treatment. In 2014, known sobriety requirements of at least six months (abstinence from drugs and/or alcohol) existed in 49% of states. In 2016, 44% of states had this same restriction. In 2014, abstinence of six months was required in California and Virginia, 12-months in Louisiana and restrictions were unknown in Texas. In 2016, Texas required one month of abstinence, Louisiana required 12 months, Virginia only required screen and counseling and restrictions were unknown in California (Wong et al., 2018).

The patients that were included in this study were identified via electronic health record query using ICD-9 and ICD-10 codes and manual review of medical records. To confirm chronic HCV status, additional review was performed via assessment of HCV RNA. Some patients were already enrolled in HCV treatment clinical trials and were excluded from this study given inclusion would have confounded the ability to assess real-world access to HCV therapies. At the first patient encounter, each patient was assigned a study entry date at each health care organization during the set study period. At the time of entry, patient demographics and HCV-specific characteristics including sex, race/ethnicity, age at diagnosis, insurance status, severity of illness (e.g., stage of fibrosis, presence of cirrhosis, HCV genotype, prior treatment experience), presence of high-risk behaviors (e.g., alcohol use, drug use, high risk sexual behavior) and other medical co-morbidities were collected from patient files. High-risk behaviors with a past or present behavior were considered positive and were combined in to one variable in the multivariate model. To determine treatment status, patients were followed for a minimum of three months or until February 28, 2017, the end of the study period (Wong et al., 2018).

The results of the six-year study period that included 29,544 adults with HCV, revealed that 17.8% received treatment and 82.2% did not receive treatment. The male gender made up the majority of patients and were between the ages of 45 and 64. 55.9% of patients were white, 38.4% were black and 8.8% were of Hispanic ethnicity. Medicare (25.9%), was the most common source of health insurance followed by commercial (22.5%), indigent care (21.7%), and Medicaid (18.7%). History of current or past alcohol use was positive in 36.6% of patients, 25.6% had a history of current or past drug use, and 19.5% had a history of current or past high-risk sexual behavior (Wong et al., 2018).

When comparing patients who did not receive treatment vs. those who received treatment, those who received treatment were more likely to be older (15.5 vs. 9.7%, ≥65 years, $p<0.0001$), have Medicare (39.8 vs. 22.8%, $p<0.0001$) and more were likely to have commercial insurance (39.7 vs. 18.8%, $p<0.0001$). Those who did not receive treatment were more likely to have Medicaid and indigent care. Interestingly, HCV patients that had Medicaid or state insurance and those with indigent care/no insurance had similarly lower odds of receiving treatment. Higher rates of HIV ($p<0.0001$), psychiatric/mental/behavioral disorders ($p<0.0001$) and non-hepatocellular carcinoma ($p<0.0001$) were present in those who did not receive treatment (Wong et al., 2018).

Given that the study was focused on insurance-specific disparities in access to HCV treatment and the possibility that race/ethnicity, age and insurance status may be correlated, interaction between these two variables was analyzed. When comparing non-Hispanic whites to Hispanics, Hispanics were significantly less likely to receive HCV treatment (adjusted OR 0.48, 95% CI 0.39-0.60, $p<0.001$), whereas Asians/Native Americans were more likely to receive treatment (OR 1.43, 95% CI 1.22-1.67, $p<0.001$). Overall, a statistically significant interaction was observed between black race and having Medicaid/State insurance (Wong et al., 2018).

Across the study period, they sought to determine if there was a correlation of demographics and insurance status and the likelihood of receiving treatment. A cumulative KM curve was used and adjusted for various sociodemographic variables, sex, age, race, ethnicity and insurance status. At the end of the study, treatment rates for men and women were similar at 25% and rates increased with older age. Patients less than 45 years old had cumulative treatment rates of 16% compared to 27% for those aged 45-64 ($p<0.0001$) and 25% for those ≥65 years ($p<0.0001$). By race, treatment rates were also similar. Cumulative treatment rates were 18%

for blacks, 19% for whites and 22% for Asians. At 18%, Hispanics had significantly lower treatment rates than non-Hispanics with overall cumulative treatment rates at 28%. Overall, the treatment rates at the end of the study were associated with insurance status. Rates were lowest among indigent patients with no insurance (6%) and Medicaid insurance (9%). Patients with Medicare (30%) and privately insured HCV patients (34%) were among the highest rates of treatment. When comparing Medicaid to privately insured patients with HCV, those with Medicaid had a 25% lower rate of treatment (95% CI -22 to -28%, $p<0.0001$) and those with no insurance had a 28% lower rate of treatment (95% CI -24 to -31%, $p<0.0001$) (Wong et al., 2018).

This multi-centered real-world community-based study showed that overall access to HCV treatment remains low. Significant disparities were observed among the ethnically diverse population by age, race, ethnicity and most notable insurance status. In fact, TRIO network/Trio Health, a company working with providers and specialty pharmacies, found data for 3,841 patients that were prescribed a sofosbuvir-containing regimen. It was reported that 8% of patients did not start HCV therapy and 81% of patients reported financial or insurance-related barriers for not starting treatment. They also observed that Medicaid patients had the highest non-start rates (35%) while commercially insured patients were 6.5 times more likely to start treatment compared to Medicaid. It is important to note that the TRIO study only included nine months of the new DAA era (Wong et al, 2018).

This research study demonstrated that improvements have been made over the past several years, however, despite the improvements, payer-specific restrictions and access to treatment continue as barriers for HCV patients. The disparities that do not allow access to life saving HCV treatment emphasizes the need for more action to ensure equitable access across all

populations, particularly the most vulnerable ones. More advocacy is needed to affect policy changes to allow access to treatment for all those in need. While limited access remains, studies suggest that insurance-related processes and financial reasons are major reasons for delaying treatment (Wong et al., 2018).

A strength of this study was the large sample size with nearly 30,000 chronic HCV patients over the course of more than six years. This study spanned across four diverse states which included many different ethnic populations and patients with high-risk comorbidities. While some providers may not treat patients immediately and require a more extensive work up, this study could not accurately assess for these types of specific detail. While there were many patients enrolled in this study, more in-depth, patient specific details from each state were not available. Such information would have been helpful as each state has different Medicaid restrictions and criteria (Wong et al., 2018).

Discussion

When comparing North Dakota Medicaid with the rest of the US, there are several other states that provide HCV treatment to those actively using drugs and alcohol. While research has proven to show high SVR with the use of DAAs in all patient populations, it is likely that North Dakota's strict Medicaid restriction is in place due to concerns of poor medication compliance with the current inflated price of treatment. Improvements in treatment have made HCV curable, however, payer-specific restrictions and limited access to treatment continue as large barriers for HCV patients (Wong et al., 2018). In addition to limitations to health care access, Wong et al. concluded that insurance-related processes and financial reasons are major motives for delaying therapy. With the restricted access to DAA among Medicaid beneficiaries in the state of North Dakota, Spradling et al. (2018) confirmed that Medicaid patients have 50% reduced odds of

receiving therapy compared to those with private insurance. Unsurprisingly, those with a lower income were less likely to receive therapy compared to those with a higher annual income. The highlight of their findings solidified the urgent need for targeted efforts to improve access to DAA therapy which is relevant for the state of North Dakota where several vulnerable, homeless, low income, and Medicaid patients are not receiving treatment. Linas and Nolen (2018) provided a foundation of evidence that showed providing HCV treatment for all persons has good economic value even though treatment is expensive. The cost of HCV therapy is immediate and costly, however, restrictions to DAAs with failure to intervene at early stages may result in future, costly long-term care with the development of cirrhosis, decompensated liver disease, and liver cancer. Increasing access to DAAs can be helpful in decreasing HCV prevalence, but other interventions in primary prevention are needed. To reduce both new infections and mortality by 2030, a multifocal approach amongst researchers, health care providers, policy makers, the affected community, advocates, pharmaceutical and diagnostic industries, and governments around the world must come together to make this happen (Grebely et al., 2017). Correspondingly, providing patients with a comfortable, confidential environment can make a huge difference in building trust and long-term patient provider relationships. These relationships allow for thorough and accurate substance abuse evaluation which is proven effective in maximizing abstinence and minimizing behaviors with risks for reinfection (George et al., 2018). Ultimately, utilizing this multi-focused approach would lead to an increase in successful antiviral therapy while reducing transmission and reinfection rates.

Good patient-provider relationships and increasing access to DAAs will help in the HCV eradication process, but SSPs are also crucial to public health as they access hard-to-reach, stigmatized communities while allowing easier linkage to healthcare, providing HCV testing,

referrals for opioid substitution therapy, abuse treatment programs, access to overdose prevention tools in addition to reducing risky injection behaviors with clean injection supplies. SSPs and medication assisted treatment programs both have evidence-based strategies in the reduction of HCV, however, Canary et al. solidified that the large gaps in harm reduction services supports the continual need for primary prevention services.

One may argue that HCV patients have the potential to be lost to follow up care due to substance use, however, this is not a reasonable argument to support not treating every patient equally. Overall, treating HCV can be achieved by increasing access to DAA's; however, eradicating HCV needs to be viewed as a whole. Research solidifies that to successfully eliminate HCV, discrimination against patients based on their substance abuse history must first be dismissed.

Conclusion

The conclusion of this literature review suggests that there is strong evidence to support treating all HCV positive patients regardless of alcohol and drug use status. Given the prevalence of HCV in the US, along with those not receiving treatment because of the drug and alcohol use status, including this research in clinical application could move us one step closer to the eradication of HCV. Ultimately, when comparing non-substance using patients with active substance users, the data compiled revealed that abstinence prior to HCV treatment is not necessary to achieve SVR.

Applicability to Clinical Practice

Many of the patients with HCV are those who are actively using drugs and alcohol. In the state of North Dakota, it is continually observed that many patients are unable to receive treatment or are not interested in receiving treatment because of the Medicaid restrictions that are

currently in place. Health care access is already difficult for the vulnerable population, proving to be yet another barrier in successful eradication of HCV. With the ability to provide HCV treatment to all patients regardless of their substance abuse status, this would slow the spread of HCV substantially!

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