Cost-effectiveness of syringe service programs, medications for opioid use disorder, and combination programs in hepatitis C harm reduction among opioid injection drug users: a public payer perspective using a decision tree

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What is already known about this subject

- Harm-reduction strategies such as syringe service programs (SSPs) or medications for opioid use disorder (MOUD) are effective in reducing the risk of hepatitis C virus (HCV) acquisition.
- Using these harm-reduction strategies in combination is more effective than using them separately.

What this study adds

- The SSP+MOUD combination intervention dominated both MOUD and “no intervention” strategies when a public payer perspective was undertaken.
- All harm-reduction strategies yielded significant cost savings when compared with a no intervention strategy over a 1-year period.
- Among opioid injection drug users in the United States, the SSP+MOUD combination intervention is cost-effective if payers are willing to pay \$4,699 or more per HCV case avoided.

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ABSTRACT

BACKGROUND: The hepatitis C virus (HCV) prevalence rate among injection drug users (IDUs) in North America is 55.2%, with 1.41 million individuals estimated to be HCV-antibody positive. Studies have shown the effectiveness of syringe service programs (SSPs) alone, medications for opioid use disorder (MOUD) alone, or SSP+MOUD combination in reducing HCV transmission among opioid IDUs.

OBJECTIVE: To evaluate the cost-effectiveness of SSP alone, MOUD alone, and

SSP+MOUD combination in preventing HCV cases among opioid IDUs in the United States.

METHODS: We used a decision tree analysis model based on published literature and publicly available data. Effectiveness was presented as the number of HCV cases avoided per 100 opioid IDUs. A micro-costing approach was undertaken and included both direct medical and nonmedical costs. Cost-effectiveness was assessed from a public payer perspective over a 1-year time horizon. It was expressed as an incremental cost-effectiveness ratio (ICER) and an incremental

cost savings per HCV case avoided per 100 opioid IDUs compared with cost savings with “no intervention.” Costs were standardized to 2019 U.S. dollars.

RESULTS: The incremental cost savings per HCV case avoided per 100 opioid IDUs compared with no intervention were as follows: SSP+MOUD combination=\$347,573; SSP alone=\$363,821; MOUD alone=\$317,428. The ICER for the combined strategy was \$4,699 compared with the ICER for the SSP group. Sensitivity analysis showed that the results of the base-case cost-effectiveness analysis were sensitive to variations in the

probabilities of injection-risk behavior for the SSP and SSP+MOUD combination groups, probability of no HCV with no intervention, and costs of MOUD and HCV antiviral medications.

CONCLUSIONS: The SSP+MOUD combination and SSP alone strategies dominate MOUD alone and no intervention strategies. SSP had the largest incremental cost savings per HCV case avoided per 100 opioid IDUs compared with the no intervention strategy. Public payers adopting the SSP+MOUD combination harm-reduction strategy instead of SSP alone would have to pay an additional \$4,699 to avoid an additional HCV case among opioid IDUs. Although these harm-reduction programs will provide benefits in a 1-year time frame, the largest benefit may become evident in the years ahead.

Hepatitis C virus (HCV) is the leading cause of chronic liver disease, liver transplantation, and liver-related mortality and morbidity in the United States.¹⁻⁴ According to the Centers for Disease Control and Prevention (CDC), the estimated number of new HCV cases was 44,700 in 2017. The rate of acute HCV reported had increased from 0.7 per 100,000 people in 2013 to 1.0 per 100,000 people in 2017.⁵ The HCV prevalence rate among injection drug users (IDUs) in North America is 55.2%, and about 1.41 million are estimated to be HCV-antibody positive.⁶ Approximately 2.4 million people in the United States are living with HCV infection.⁷ In 2017, there were 17,253 HCV-related deaths in the United States, which is about 4.13 deaths per 100,000 people.

IDUs are at greater risk of developing HCV infection, and the growing number of HCV cases in the United States is attributed largely to opioid misuse.^{8,9} In 2018, the total economic cost of the opioid crisis was estimated at \$696 billion (3.4% of the gross domestic product) and more than \$2.5 trillion from 2015 to 2018.¹⁰

HCV infections can be reduced through syringe service programs (SSPs) and medications for opioid use disorder (MOUD). SSPs involve the distribution of sterile syringes and other injecting equipment to patients, increasing the number of clean syringes in circulation and reducing the number of contaminated syringes, consequently reducing the risk of acquisition of HCV and other diseases acquired by needle sharing.¹¹ SSP programs can be implemented in a fixed or nonfixed setting on a local community level. While there is very low-quality and insufficient evidence on the effect of SSP on HCV acquisition risk in North America, there is evidence of reduced HCV acquisition risk with SSPs by 56% in Europe, after stratification by region.^{12,13} MOUD such as methadone or buprenorphine are used in an effort to decrease illicit opioid use or misuse as well as injection-risk behaviors.¹⁴ MOUD programs have been

shown to reduce HCV acquisition risk by 50%.¹² Recent studies have suggested that a combination of SSP and MOUD programs has an additive effect in reducing HCV and HIV transmission. The combination of harm-reduction strategies resulted in a 6- to 7-fold decrease in the risk of HCV seroconversion and a 2- to 3-fold decrease in the risk of HIV seroconversion.¹⁴⁻¹⁷ A study by Turner et al. (2011) in the United Kingdom suggested that the combination of SSP and MOUD reduced the odds of new HCV infections by almost 80%.¹⁸ Despite these results, no study in the United States has examined the cost-effectiveness in terms of the incremental cost savings per HCV case avoided compared with cost savings with “no intervention.”

The purpose of this project was to develop an economic model comparing the costs and effectiveness of SSP and MOUD as standalone interventions and SSP+MOUD in combination as harm-reduction strategies for the prevention of HCV infection in opioid IDUs. The study was conducted from a public payer perspective and considered both direct medical and nonmedical costs associated with injection-risk behaviors. The analysis was done to assist local community and public payers in decision making regarding adoption of harm-reduction strategies to prevent HCV infections and reduce the burden associated with HCV.

Methods

The target population studied in this analysis consisted of opioid IDUs in the United States not currently engaged in any harm-reduction strategy. The model considered a hypothetical population of patients and was designed using prevalence-based model inputs. A 1-year time period was chosen to capture the time patients engaged in the intervention, antiviral treatment, and antiviral retreatment in cases of treatment failures.

The primary outcome measure used in this cost-effectiveness study was the number of HCV cases avoided per 100 patients in the SSP, MOUD, and SSP+MOUD combination groups compared with the no intervention group. Several cost-effectiveness studies on infectious diseases similarly assessed their outcomes in terms of “cases of infection avoided or averted.”¹⁹⁻²¹

A decision tree analytic model was built in Microsoft Excel 2016 (Microsoft, Redmond, WA), as pictured in Figure 1. The model explores the question, “Which is most cost-effective: the combination of SSP and MOUD, SSP alone, MOUD alone, compared with no intervention?” Effectiveness was assessed as a dichotomous measure: no HCV versus HCV. According to the model, opioid IDUs could be enrolled in only 1 of the interventions. There is then a probability, based on the effectiveness of the intervention, that they

FIGURE 1 Decision Tree of the Cost-Effectiveness of SSP vs. MOUD vs. SSP+MOUD Combination vs. No Intervention

Note: Opioid IDUs going through each decision path would incur the corresponding costs and number of HCV cases shown at the terminal node. HCV=hepatitis C virus; IDUs= injection drug users; MOUD=medications for opioid use disorder; SSP=syringe service program.

would continue or discontinue engagement in injection-risk behaviors, except for the no intervention group. If patients continued to engage in injection-risk behaviors, there was a probability, which was different across intervention strategies, that they either developed or did not develop HCV. Opioid IDUs discontinuing their engagement in injection-risk behaviors also either developed or did not develop HCV.

The outcomes data for this analysis were obtained from a PubMed literature search using the following search terms: “needle exchange programs,” “syringe exchange programs,” “needle and syringe programs,” “opioid substitution treatment,” “injection drug users,” “opioid or opioids,” “people who inject drugs,” and “hepatitis C,” in various combinations. Additional articles were included after reviewing the literature search. Clinical data from randomized controlled trials, cost-effectiveness studies, systematic reviews and meta-analyses, and review articles were included in the

analysis. Data retrieved from the literature search pertaining to the effectiveness of harm-reduction strategies were summarized in Table 1. Effectiveness data for the base-case analysis were obtained from prior systematic reviews and meta-analyses.^{12,22} The probability of injection-risk behaviors for each intervention was obtained from systematic literature reviews and meta-analyses and secondary sources.^{18,23-26}

Both costs and effectiveness measures were estimated from a public payer perspective to capture the public payer’s interest in the growing issue of opioid misuse, given that interventions were likely to be sponsored by a public entity.

Opioid IDUs who developed HCV incurred the following costs: HCV screening, biopsy, computerized tomography (CT), magnetic resonance imaging (MRI), antiviral treatment, antiviral treatment complication, HCV treatment monitoring, hepatitis A-B vaccine (3 doses). On the other hand,

TABLE 1 Key Base-Case Assumptions for Model Parameters, Sources Used, and Variation Introduced in Sensitivity Analysis

Model Inputs, Clinical		Base Case	Range	Source
Risk reduction of HCV with SSP	56%	0.56	Varied $\pm$ 50%	Platt et al. ⁴³ Cotter et al. ²²
Risk reduction of HCV with MOUD	50%	0.50	Varied $\pm$ 50%	Platt et al. ⁴³
Risk reduction of HCV with combination (SSP+MOUD)		0.60 ^a	0.3-0.66	Platt et al. ⁴³ Assumption
Probability of NO HCV with no intervention (HCV naturally cleared)		0.30	Varied $\pm$ 50%	WHO ²⁶ Assumption
Probability of injection-risk behavior with SSP	OR=0.5	0.33	Varied $\pm$ 50%	Sawangjit et al. ²⁴ Aspinall et al. ²³
Probability of injection-risk behavior with MOUD		0.45	Varied $\pm$ 50%	Gowing et al. ²⁵
Probability of injection-risk behavior with combination (SSP+MOUD)	AOR=0.52	0.34	Varied $\pm$ 50%	Turner et al. ¹⁸
Probability of HCV for SSP users engaging in NO injection-risk behavior		0.11 ^b		Calculated
Probability of HCV for MOUD users engaging in NO injection-risk behavior		0.06 ^b		Calculated
Probability of HCV for SSP+MOUD combination users engaging in NO injection-risk behavior		0.09 ^b		Calculated

^aThe base case is a more conservative estimate than the 74% risk reduction originally reported by Platt et al.¹² It varied up to 0.66, the maximum upper limit that allows other probabilities in the model to fall within a reasonable range (i.e., 0-1). This seems reasonable given that the 95% CI for the 74% estimate was 11%-93%.

^bSee [Supplementary Material](#) (available in online article) for sample calculation.

AOR=adjusted odds ratio; HCV=hepatitis C virus; MOUD=medications for opioid use disorder; OR=odds ratio; SSP=syringe service program; WHO=World Health Organization.

opioid IDUs who did not develop HCV did not incur these costs. We assumed that those engaging in injection-risk behaviors and those in the no intervention group also incurred the direct nonmedical costs due to injection drug use-related crime.

Cost data were collected from public data sources, primary literature sources, and recently published cost-effectiveness studies (Table 2).²⁷⁻

³⁴ The per-person-per annum cost of SSP and MOUD were obtained from literature sources.²⁷⁻²⁹ Direct costs of CT and MRI were obtained from the 2019 National Physician Fee Schedule, while the cost of hepatitis A-B vaccine for 3 doses was obtained from

the CDC.^{29,30} Other direct medical costs such as costs of HCV screening, biopsy, HCV antiviral, and HCV treatment monitoring were obtained from literature sources, including recently published cost-effectiveness studies.^{31,32} Similar to the approach of previous studies and due to the perspective chosen for this study, the base-case analysis considered direct nonmedical costs such as criminal justice expenditures related to substance use.³¹ The public payer perspective analyses included the costs associated with the criminalization of substance use, comprising the costs of policing, court, corrections, and criminal victimization. These cost inputs were

obtained from a retrospective, administrative data-based cohort study with comprehensive information on drug treatment and criminal justice system interactions.^{31,33} All costs were standardized to 2019 U.S. dollars, using the medical Consumer Price Index.³⁵

In developing the model, several assumptions were made. Considering the natural prevalence of HCV in patients with opioid IDU (70%), we postulated the following:

1. The probability of no HCV with no intervention is 0.30, the proportion of patients who do not seem to be infected by HCV virus or naturally clear the virus from the body. We also assumed that all participants (100%) receiving no intervention were engaging in injection-risk behaviors and were exposed to HCV.
2. Opioid IDUs enrolled in one of the harm-reduction strategies and still engaging in injection-risk behaviors had the same probability of developing HCV as those receiving no intervention since injection-risk behaviors are the primary means by which HCV is transmitted. If the injection-risk behavior is not decreased, then the risk of HCV is not decreased.
3. Opioid IDUs enrolled in one of the harm-reduction strategies no longer engaging in injection-risk behaviors had a lower probability of developing HCV when compared with those in the no intervention group.
4. Similar to the study by Stevens et al. (2019), we assumed that patients were retreated with antivirals for treatment failures.³¹
5. Those engaging in injection-risk behaviors incurred the cost of injection drug use-related crimes.
6. Although the risk reduction of HCV for the SSP+MOUD combination group was estimated at 74%, the confidence interval was broad from 11% to 93%.¹² As a result, we assumed a conservative estimate of

TABLE 2 Direct Medical and Nonmedical Costs Associated with HCV (in 2019 USD)

Model Inputs, Costs	2016 \$	Base Case, 2019 \$, Adjusted	Source
Cost of SSP, annual per person	774.30	840.99	Teshale et al. ²⁷
Cost of MOUD, annual per person (2013) ^a	14,468.00	17,496.00	Mohlham et al. ²⁸ NIDA ²⁹
Cost of combination (SSP+MOUD), per annum	15,242.30	18,336.99 ^b	Calculated
Cost of injection drug use-related crime (direct nonmedical costs), annual per person	35,494.00	38,550.00	Stevens et al. ³¹ Krebs et al. ³³
Cost of HCV screening	111.58	121.00	Stevens et al. ³¹
Cost of biopsy	762.00	828.00	Stevens et al. ³¹
Cost of computerized tomography	N/A	463.00	2019 National Fee Schedule ³⁴
Cost of MRI	N/A	525.00	2019 National Fee Schedule ³⁴
Cost of HCV antiviral	61,020.00	66,275.00	Stevens et al. ³¹ Barbosa et al. ³²
Cost of HCV antiviral, complication	61,020.00	66,275.00	Stevens et al. ³¹ Barbosa et al. ³²
Cost of HCV treatment monitoring (12 weeks), per person	358.50	390.00	Barbosa et al. ³²
Cost of hepatitis A-B vaccine (3 doses)	N/A	249.00	CDC ³⁰

^aCost standardized from 2013 to 2019 using the medical Consumer Price Index.

^bCalculation: Cost of combination (SSP+MOUD)=cost of SSP+cost of MOUD.

CDC=Centers for Disease Control and Prevention; HCV=hepatitis C virus; MOUD=medications for opioid use disorder; MRI=magnetic resonance imaging; N/A=not applicable; NIDA=National Institute on Drug Abuse; SSP=syringe service program; USD=United States dollar.

60% to avoid other key probabilities in the model from falling outside a reasonable range (i.e., 0-1).

The cost-effectiveness findings were expressed in terms of cost per IDU and per 100 IDUs, number of HCV cases per 100 IDUs, number of HCV cases avoided per 100 IDUs, cost per HCV case avoided per 100 IDUs, incremental cost savings per HCV case avoided (per 100 IDUs) compared with no intervention, and incremental cost-effectiveness ratio (ICER).

A 1-way sensitivity analysis was conducted on all cost inputs considered in the model to test the robustness of the base-case cost-effectiveness analysis. The risk reduction of HCV for SSP, MOUD,

and SSP+MOUD combination; the probabilities of injection-risk behavior for SSP, MOUD, and SSP+MOUD combination; the probability of no HCV infection with no intervention; and all cost inputs were varied by $\pm 50\%$, according to accepted modeling research practices.³⁶

Results

Figure 1 shows the costs and effectiveness associated with each arm of the decision tree. The costs for the SSP and MOUD groups were summed to derive the costs for the combination program. As a result, those enrolled in the combination program who engaged in injection-risk behaviors

and who developed HCV incurred the largest cost, \$192,013.

Results of the base-case cost-effectiveness analysis are shown in Table 3. The SSP+MOUD combination was the most effective intervention as it avoided 72 HCV cases among 100 opioid IDUs, while SSP alone was the least expensive as it cost \$5,518,130 for 100 opioid IDUs. The ICER for the combined strategy was \$4,699 per additional case of HCV avoided compared with the SSP group. In other words, the combined intervention would cost public payers an additional \$4,699 to avoid an additional case of HCV when compared with SSP. In addition, SSP alone had the highest incremental cost savings per HCV case avoided at \$363,821, compared with no intervention. Both MOUD alone and no intervention were dominated by SSP alone and SSP+MOUD combination interventions. For the SSP+MOUD combination strategy to become the most cost-effective intervention, the probability of injection-risk behavior for SSP alone would have to increase to 0.52 or the risk reduction of HCV for SSP alone would have to decrease to 0.41.

The sensitivity analysis varied all cost and clinical variables using the ranges presented in Tables 1 and 2. The results of the sensitivity analyses are presented in Figure 2 and in the [Supplementary Material](#) (available in online article). When varying the risk reduction of HCV infection to +50%, an upper limit of 1 (probability [risk reduction]=100%) was considered. When the risk reduction of HCV infection with SSP was increased to 0.84, SSP was the dominant intervention. At the lower range of the risk reduction of SSP (0.28), the SSP+MOUD combination was the dominant intervention. When all the cost variables were varied within their ranges, there were only 2 meaningful changes in the outcomes. These were the cost

TABLE 3 Expected Costs (in 2019 USD), Effectiveness, and Cost-Effectiveness Ratios of SSP, MOUD, SSP+MOUD Combination, and No Intervention in Base-Case Analysis

Intervention	Cost per Opioid IDU, \$ ^a	Cost per 100 Opioid IDUs, \$	Number of HCV Cases ^b	Number of HCV Cases Avoided ^b	Cost per HCV Case Avoided Ratio, \$ ^b	Incremental Cost Savings per HCV Case Avoided ^b (Compared with No Intervention), \$	ICER, \$ ^a	Dominates
Combination (SSP+MOUD)	69,279.27	6,927,927	28	72	96,221	347,573	4,699 (compared with SSP)	MOUD alone No intervention
SSP	55,181.30	5,518,130	31	69	79,973	363,821	–	MOUD alone No intervention
MOUD	82,137.60	8,213,760	35	65	126,366	317,428	–	No intervention
No intervention	133,138.20	13,313,820	70	30	443,794	–	–	–

^aPer opioid IDU.

^bPer 100 opioid IDUs.

HCV=hepatitis C virus; ICER=incremental cost-effectiveness ratio; IDU=injection drug user; MOUD=medications for opioid use disorder; SSP=syringe service program; USD=United States dollar.

of MOUD and the cost of HCV antiviral. As the tornado diagram in Figure 2 shows, the ICER between SSP and the SSP+MOUD combination strategies was most sensitive to the probabilities of injection-risk behavior for the SSP and SSP+MOUD combination groups, probability of no HCV with no intervention, and costs of MOUD and HCV antiviral. The shift in the base-case cost-effectiveness was minimal for all other parameters tested. Discounting was not performed because both costs and outcomes occurred within a 1-year time horizon.

Discussion

This study indicates that the SSP+MOUD combination program is an effective harm-reduction strategy to prevent HCV cases among opioid IDUs and is cost-effective if payers are willing to pay \$4,699 or more per avoided case of HCV. There is evidence to support the effectiveness of these harm-reduction strategies in reducing injection-risk behaviors as well as reducing HCV and HIV transmission.^{17,18} The base-case analysis suggested that (a) the combination strategy, compared with SSP alone, would cost \$4,699 to avoid an additional HCV case; (b) the combination and the SSP-alone groups dominated both the MOUD-alone and no intervention groups; and (c) the MOUD-alone group dominated the no intervention group.

Most of the recent studies on the cost-effectiveness of SSP and MOUD alone and in combination were conducted

outside the United States, were conducted from a societal or health care system perspective, did not directly compare the interventions used in the base case, had moderate evidence of the cost-effectiveness in some sites, estimated the outcome in terms of quality-adjusted life years, and did not examine the number of cases avoided in a 1-year time horizon.^{19,31,32,37–39} To date, studies have not examined the cost-effectiveness of these harm-reduction strategies in terms of incremental cost savings per HCV case avoided, and none has undertaken a public payer perspective in the United States.

Based on the analysis, the combination of MOUD and SSP appears to be the most effective policy, from a public health perspective. By including both the direct medical and nonmedical costs due to injection drug use-related crime in the calculation, the combination program will save public payers \$347,573 per HCV case avoided compared with costs for no intervention. SSP-alone and MOUD-alone interventions will also save public payers \$363,821 and \$317,428, respectively. Given that the total direct economic burden of HCV-related liver disease in the United States is estimated to be \$6.5 billion (\$4.3 to \$8.2 billion) annually and 2.4 million people in the United States live with an HCV infection, these interventions could dramatically reduce HCV-related annual costs.^{7,40,41} The savings associated with these interventions would allow public institutions to redirect funds toward other health care services or public service investments. In addition, the results indicated that

FIGURE 2 Tornado Diagram on the Incremental Cost-Effectiveness Ratio Between SSP and Combination (SSP + MOUD)

Note: Costs are in 2019 U.S. dollars.

HCV=hepatitis C virus; ICER=incremental cost-effectiveness ratio; MOUD=medications for opioid use disorder; MRI=magnetic resonance imaging, SSP=syringe service program.

all the harm-reduction strategies were less costly and more effective than no intervention even though they required some up-front investments. It is also important to point out that the largest benefits could occur in the future. This is because HCV-related liver disease such as cirrhosis and hepatocellular carcinoma may take several years to occur, and SSPs are associated with reducing the risk of other diseases transmitted via needle sharing, such as HIV.^{23,26}

The 1-way sensitivity analysis shows that the base-case cost effectiveness analysis was sensitive to the probabilities of injection-risk behavior for the SSP and SSP+MOUD combination groups, probability of no HCV with no intervention, and costs of MOUD and HCV antivirals. Despite varying the model parameters by $\pm 50\%$, the base-case ICER was not sensitive to a majority of the key variables in the model. Considering that the cost for the combination intervention was assumed to be the sum of the costs of the SSP and MOUD individual interventions, our results can be considered as conservative estimates, given that in reality, savings and economies of scale can be achieved by a combination of efforts.

LIMITATIONS

Several limitations could affect the results of this analysis. Given the lack of evidence on the probability of HCV among opioid IDUs who are receiving no intervention, we assumed that 30% would not have HCV since they would naturally clear the HCV.²⁶ However, varying this variable by $\pm 50\%$ resulted in an ICER between SSP and combination interventions that ranged from \$4,429 to \$7,454 compared with the base-case ICER of \$4,699. The micro-costing approach of this cost-effectiveness study could have omitted other important cost inputs. There is also weak and insufficient data on the effect of SSP on HCV transmission in North America and the effectiveness of combination programs in reducing injection risk behaviors; thus, we used outcomes data from Europe. Finally, not all populations in the studies from which our input estimates came were the same.

FUTURE RESEARCH

This research reports the cost-effectiveness of several harm-reduction strategies: SSP alone, MOUD alone, and SSP+MOUD combination program, compared with no intervention in preventing HCV cases in the United

States during a 1-year time horizon. Additional research should be performed on the cost-effectiveness of other harm-reduction strategies to examine their role in preventing HCV cases among opioid IDUs. These include antiretroviral therapy, condom programs for IDUs and their sexual partners, and targeted information, education, and communication.⁴² The cost-effectiveness of harm-reduction strategies could also be examined in nonopioid IDUs. Finally, future studies should also examine the cost-effectiveness of these harm-reduction strategies from a societal perspective by including indirect costs such as costs due to lost productivity.

Conclusions

This study provides evidence that compared with no intervention, SSP, MOUD, and the SSP and MOUD combination are cost-effective and cost-saving harm-reduction strategies. The base-case scenario of the model found the combination program to be cost-effective if payers were willing to pay \$4,699 or more per case of HCV avoided. Although these harm-reduction programs will provide benefits in a 1-year time frame, the largest benefit may become evident in the years ahead.

DISCLOSURES

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