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A Systematic Review and Meta-Analysis of Studies Evaluating the Effect of Medication Treatment for Opioid Use Disorder on Infectious Disease Outcomes

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The opioid epidemic has fueled infectious disease epidemics. We determined the impact of medications for opioid use disorder (MOUD) on treatment outcomes of opioid use disorder (OUD)-associated infectious diseases: antiretroviral therapy (ART) adherence, human immunodeficiency virus (HIV) viral suppression, hepatitis C virus (HCV) sustained virologic response, HCV reinfection, new hepatitis B virus infections, and infectious endocarditis-related outcomes. Manuscripts reporting on these infectious disease outcomes in adults with OUD receiving MOUD compared with those with OUD "not" receiving MOUD were included. Initial search yielded 8169 papers; 9 were included in the final review. The meta-analysis revealed that MOUD was associated with greater ART adherence (odds ratio [OR] = 1.55; 95% confidence interval [CI] = 1.12–2.15) and HIV viral suppression (OR = 2.19; 95% CI = 1.88–2.56). One study suggested a positive association between MOUD and HCV sustained virologic response. There is significant support for integrating MOUD with HIV treatment to improve viral suppression among persons with HIV (PWH) and OUD. Treatment of OUD among PWH should be a priority to combat the opioid and HIV epidemics.

Keywords. endocarditis; HCV; HIV; medication treatment; opioid use disorder.

The increase of opioids prescribed for pain in the 1990s initiated the US opioid epidemic, leading to an increase in persons diagnosed with opioid use disorder (OUD) [1]. Despite declines in opioid prescribing rates since 2012, injection of heroin and the synthetic opioid fentanyl has accelerated across the United States [1–3]. The Centers for Disease Control and Prevention (CDC) reported >81 000 overdose deaths in May 2020, the highest number to be recorded in a 12-month period, driven primarily by injection of synthetic opioids and stimulants [2]. This increase in injection drug use (IDU) of heroin, fentanyl, and stimulants (methamphetamine and cocaine) [2] combined with restrictions on syringe service programs (SSPs) [4] has resulted in a surge of infectious diseases, including human immunodeficiency virus (HIV), hepatitis C virus (HCV), and infectious endocarditis [3, 5].

Shared or used injection equipment increases the transmission of blood-borne viral infections, such as HIV and hepatitis B and C, and increases the risk of bacterial and fungal infections that can cause endocarditis [3, 6]. In 2018, 10% of new HIV diagnoses were attributed to IDU or male-to-male sexual contact and IDU [6]. In the past decade, viral hepatitis, HIV, and bacterial and fungal infections due to IDU have increased [7]. In a 2019 study, infective endocarditis accounted for 14% of bacterial or fungal infections in persons who inject drugs [8]. In addition to SSPs that decrease outbreaks of infectious diseases [4], medication treatments for OUD (MOUD) have also been identified as avenues of infectious disease harm reduction.

Medication treatment for OUD is the most effective form of treatment for OUD (eg, buprenorphine [BPN], methadone, and extended-release naltrexone [XR-NTX]), because they reduce opioid craving, use, overdoses, and death [1]. However, only 15% of those with OUD receive MOUD [9], despite evidence that it can lead to reductions in HIV and HCV risk behaviors and bacterial and fungal infections. Furthermore, few persons with OUD are offered MOUD with harm reduction strategies or MOUD with integrated infectious disease treatment [1, 5, 10–13]. Because of this, experts in addiction medicine and

infectious disease [5, 10–13] recommend integrating MOUD with infectious disease prevention and treatment services to reduce incidence of new HIV, HCV, and other related infections. Medication treatment for OUD improves adherence to antimicrobial treatment [5], HIV and HCV treatment, and reduces HIV risk behaviors [3, 12]. Thus, it is critical to understand the impact of MOUD on infectious disease-related outcomes.

We conducted a systematic review and meta-analysis to explore the relationship between MOUD and 4 of the most prevalent OUD-related infectious diseases that are published in the literature (HIV, hepatitis C viral infection, hepatitis B viral infection, and infection-related endocarditis) and their associated treatment outcomes: antiretroviral therapy (ART) adherence and HIV viral suppression in persons with HIV (PWH), sustained virologic response and reinfection in persons with HCV, and new hepatitis B virus (HBV) infections. For endocarditis, antimicrobial treatment completion, surgery and surgical outcomes, and reinfection were assessed. This systematic review and meta-analysis seeks to provide empirical evidence to supplement the expert recommendations that MOUD integrated with infectious disease prevention and treatment can lead to better infectious disease outcomes.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statements for reporting were used for this study [14]. The protocol was registered with PROSPERO before title and abstract review (CRD42020166964).

Data Sources and Searches
A systematic search of the literature was conducted in Cochrane Library, Google Scholar, Ovid Embase, Ovid Medline, Ovid PsychInfo, Pubmed, Scopus, and Web of Science Core Collection databases to find relevant articles published from inception of database to the date of final searches, June 25, 2020. The search was peer-reviewed by a second researcher using PRESS (Peer Review of Electronic Search Strategies) [15]. Databases were searched using combinations of controlled vocabulary and keywords for MOUD (buprenorphine, methadone, or extended-release naltrexone) and HBV, HCV, HIV, or endocarditis. Details of the full search strategy are in Appendix A.

Study Selection and Inclusion Criteria
All citations were imported into EndNote X9 (Clarivate Analytics), where duplicates were removed. The deduplicated results were imported into Covidence [16] for screening and data extraction. Studies were not limited to English language, and Google Translate was used in each step to read non-English texts. At least 2 independent screeners reviewed each study in title and abstract and full-text screening for inclusion with a third reviewer to resolve conflicts.

The population studied in this review included patients with (1) a diagnosis of OUD or opioid dependence and (2) at least 1 of the following infectious diseases: HIV, HCV, HBV, and/or endocarditis. Studies had to examine the effect of MOUD on ART adherence, HIV viral suppression, HCV sustained virologic response or reinfection, new HBV infection, or antimicrobial treatment completion, surgical outcomes, and reinfection for infection-related endocarditis. Studies were excluded if the population was defined as "PWID" or "IDU," because several of these studies included persons who exclusively injected drugs other than opioids. Studies were excluded if they did not have a comparison group of persons with OUD not on MOUD. Other filters included human subjects and subjects 18 years or older.

Data Extraction
At least 2 independent reviewers extracted all study data: publication year, enrollment period, country, study design, study method, study population, setting of population, recruitment methods, number of participants, sex of participants, mean or median age of participants, duration of participation, and HCV and/or HIV treatment type, if applicable. Information on (1) the type, frequency, duration, and compliance of MOUD and (2) infectious disease outcomes being studied was also extracted. A third reviewer resolved any discrepancies in the data extraction.

Risk of Bias
Risk of bias was independently assessed by at least 2 reviewers who reviewed the methodological quality of the studies included using the Newcastle-Ottawa Scale (NOS) [17] for nonrandomized cohort studies and the Cochrane risk-of-bias tool (RoB2) [18] for the randomized controlled trial (RCT) [19]. The NOS is used for nonrandomized studies to assess the selection of the study groups, comparability of groups, and the ascertainment of the outcome of interest [17]. The Cochrane RoB2 includes questions about randomization, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and overall bias [18]. Each domain was assessed as either "high" or "low" bias per study for each scale.

Meta-Analysis
Meta-analysis was possible for HIV viral suppression and ART adherence outcomes. Depending on the measure reported, we expressed the measures of the effect of MOUD on the different outcomes as risk ratios (RRs) or odds ratios (ORs). For studies that did not report these estimates, we calculated unadjusted RR/OR and their corresponding 95% confidence intervals (CIs) based on available data. Using the METAANAL Macro [20] in SAS 9.4, we used DerSimonian-Laird [21] random-effects and fixed-effects models to conduct meta-analysis and the Q-test to test for heterogeneity.

To assess publication bias, we conducted funnel plots and Egger's and Begg's tests in Stata/SE 16.1.

Patient Consent Statement

This systematic review and meta-analysis was nonhuman subjects research. It conforms to the ethical standards currently applied within the United States.

RESULTS AND FINDINGS

The search resulted in 17 180 articles; after duplicates were removed, 8169 remained for title/abstract screening, and 364 articles met the criteria and were reviewed in full text (Figure 1). We included a total of 9 articles in the final review (Table 1).

For the HIV viral suppression outcome, the only outcome with relatively enough studies available to assess publication bias, the symmetry of the funnel plot (*P* for Egger's test = 0.971 and *P* for Begg's test = 0.851) (Supplemental Figure 1), suggested no evidence of publication bias. All of the cohort studies had good quality as rated by the NOS, and the one RCT was rated as low risk of bias overall (Supplemental Table 1). Results between studies were homogenous for the 2 outcomes for which meta-analysis was possible (Table 2): HIV viral suppression and ART adherence. This review did not identify any studies of the effect of MOUD on new HBV infections.

Human Immunodeficiency Virus Viral Load and Viral Suppression

All 5 studies that analyzed the effect of MOUD on HIV viral suppression reported a significant relationship (Table 1) [19, 22–25]. Reddon et al [22], Roux et al [23], and Socías et al [24] reported significant effects of methadone treatment on viral suppression at 6 months. Both studies by Springer et al [19, 25] reported viral suppression to be HIV-1 ribonucleic acid (RNA) <50 copies/mL with statistically significant improvement with BPN or XR-NTX. Springer et al [25] found that receiving methadone was not found to be significantly associated with achieving maximal viral suppression. Analyses of viral load values of <400 copies/mL were also used, and researchers found no significant differences between the non-BPN/naloxone (NLX) group, the BPN/NLX
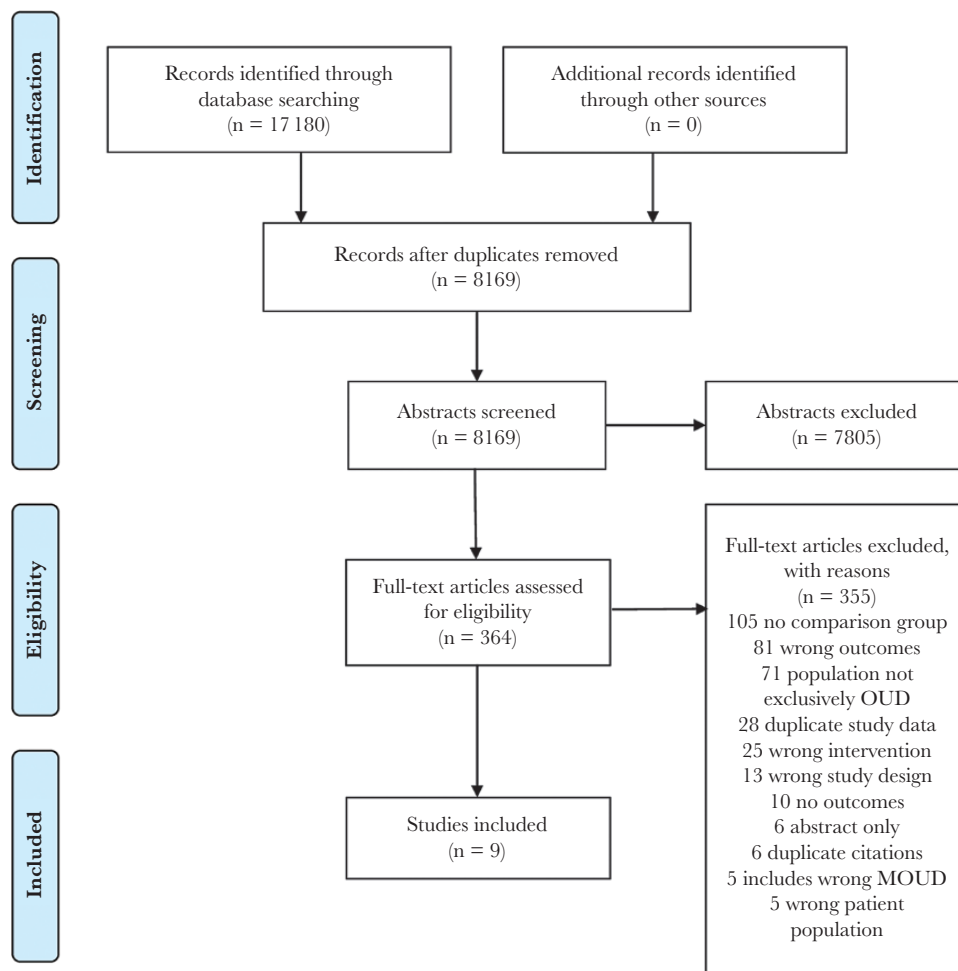

Figure 1. PRISMA flow chart. MOUD, medication for opioid use disorder; OUD, opioid use disorder.

Table 1. Summary of Included Studies

First Author	Study Design	Population Type	Population Number	Study Enrollment Period	MOUD Evaluated	ID Outcome Evaluated	Results
Mazhnaya et al [26]	Case Control/Cohort Study	PWID with HIV, OUD, and prescribed MOUD	520	2014–2015	Methadone and buprenorphine	ART adherence	Receiving MOUD was associated with 4.29-fold increased odds for optimal ART adherence
Reddon et al [22]	Case Control/Cohort Study	ART-exposed PWH and history of opioid use	408	1996–2008	Methadone	Viral suppression	878 (81.6%) of 1076 viral load assessments of those receiving ART and MTD achieved VS compared with 718 (65.81%) of 1091 assessments among those prescribed ART without MTD (P = .001)
Rosenthal et al [11]	Case Control/Cohort Study	OUD with chronic HCV, injection of opioid within 3 months	100	2017–2018	Methadone, buprenorphine, XR-naltrexone	SVR	82/100 reached SVR, but not significantly associated with MOUD vs non-MOUD (62/68 on MOUD, 20/32 non-MOUD)
Roux et al [23]	Case Control/Cohort Study	PWH as a result of IDU, receiving HAART, and indicated for MOUD	113	1995–1996	Methadone and buprenorphine	Viral suppression and ART adherence	Relationship between retention in MOUD and nonadherence was not statistically significant. Patients who received MTD were significantly more likely to achieve VS than those not on MOUD (odds ratio no treatment = 1; odds ratio MTD = 3.66 [95% CI = 1.39–9.61, P = .011.) Patients who received BPN were more likely to achieve VS than those not on MOUD, but this was not significant (odds ratio BPN = 1.75 [95% CI = 0.8–3.85, P = .16]).
Socías et al [24]	Case Control/Cohort Study	ART-exposed PWH	397	2015–2014	Methadone	Viral suppression	Being on MTD significantly increased patient odds of achieving viral suppression (OR = 1.99, 95% CI = 1.49–2.66)
Springer et al [19]	Randomized Controlled Trial	Incarcerated PWH, OUD, and willing to be randomized to receive XR-NTX	93	2010–2015	XR-naltrexone	Viral suppression	XR-NTX significantly improved to VS (HIV RNA ≤50 copies/mL) from baseline (37.9%) to 6 months (60.6%) (P = .002), whereas the placebo group did not (55.6% at baseline to 40.7% at 6 months P = .294)
Springer et al [25]	Case Control/Cohort Study	Incarcerated PWH starting ART	94	2005–2010	Buprenorphine/naloxone	Viral suppression	Those who were retained on BPN/NLX for 24 weeks were significantly more likely to achieve maximal VS (14/17, 82.4%) than either the non-BPN/NLX group (24/44, 54.6%) or those who were not retained on BPN for the full 24 weeks (16/33, 48.5%); (OR = 4.32; CI = 1.15–16.2).
Suzuki et al [28]	Case Control/Cohort Study	OUD hospitalized with endocarditis	26	2013–2015	Methadone and buprenorphine	Completed endocarditis-antimicrobial course, endocarditis readmission	No significant difference found in antibiotic completion (14/16 on MTD or BPN vs 10/10 not on MOUD) or repeat episode of endocarditis (6/16 on MTD or BPN vs 4/10 on no MOUD) between those on MTD or BPN and those not on MOUD.
Uhlmann et al [27]	Case Control/Cohort Study	ART-naive PWH using opioids	231	1996–2008	Methadone	ART adherence	MTD was significantly associated with antiretroviral adherence compared with those not on MTD (OR = 1.49; 95% CI = 1.07–2.08; P = .019)

Abbreviations: ART, antiretroviral therapy; BPN, buprenorphine; CI, confidence interval; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ID, infectious diseases; MOUD, medication for opioid use disorder; MTD, methadone; NLX, naloxone; OUD, opioid use disorder; PWH, persons with HIV; PWID, people who inject drugs; RNA, ribonucleic acid; SVR, sustained virologic response; VS, viral suppression; XR-NTX, extended-release naltrexone.

Table 2. Meta-Analysis Results

Outcome and Studies	Measure of Association	Estimate (95% CI)	RE% Weights[a]
HIV Viral Suppression			
Roux et al [23] BPN	OR	1.81 (0.82–4.00)	9.41
Roux et al [23] MTD	OR	3.91 (1.48–10.33)	6.26
Springer et al [25]	OR	1.36 (0.59–3.15)	8.42
Reddon et al [22]	OR	2.30 (1.89–2.81)[b,c]	
Socías et al [24]	OR	1.99 (1.49–2.66)	70.35
Springer et al [19]	OR	2.90 (1.04–8.14)	5.56
FE overall (Q = 3.78, *P* = .580)		2.19 (1.88–2.56)	
RE overall		2.19 (1.88–2.56)	
FE overall (excluding Reddon et al [22]) (Q = 3.18, *P* = .527)		2.03 (1.60–2.59)	
RE overall (excluding Reddon et al [22])		2.03 (1.60–2.59)	
ART Adherence			
Uhlmann et al [27]	OR	1.49 (1.07–2.08)	79.58
Mazhnaya et al [26]	OR	4.29 (0.87–22.59)	20.43
FE overall (Q = 1.55, *P* = .212)		1.55 (1.12–2.15)	
RE overall		1.85 (0.80–4.26)	
HCV Sustained Virologic Response			
Rosenthal et al [11]	RR	1.46 (1.10–1.93)[b]	NA
Endocarditis (Readmission)			
Suzuki et al [28]	RR	0.94 (0.35–2.52)[b]	NA
Endocarditis (Antibiotic Completion)			
Suzuki et al [28]	RR	0.88 (0.73–1.05)[b]	NA

Abbreviations: ART, antiretroviral treatment; BPN, buprenorphine; CI, confidence interval; FE, fixed effects; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MTD, methadone; NA, not applicable; OR, odds ratio; RE, random effects; RR, risk ratio.

NOTE: Meta-analysis: estimates and 95% CIs for the associations between medication for opioid use disorder treatment and infectious disease outcomes.

[a]For viral suppression outcome, RE weights are presented after excluding Reddon et al [22].

[b]Unadjusted estimates and 95% CI calculated based on information presented in the article.

[c]Unadjusted estimates and 95% CI calculated using information from viral load assessments instead of subjects.

group retained for 24 weeks, and the BPN group not retained for 24 weeks [25]. Reddon et al [22] and Socías et al [24] used HIV-1 RNA <500 copies/mL as the cutoff for viral suppression. Roux et al [23] measured viral suppression to be "HIV-1 RNA level below the lower limit of detection of the assay"; the assay used was not specified.

Springer et al [19] was the only RCT that met all of the inclusion criteria for this review. This study reported a significant increase in viral suppression at 6-month follow-up (60.6%) compared with baseline (37.9%) for participants randomized to XR-NTX. The placebo group showed decreased viral suppression levels after 6-months, but this was not statistically significant (55.6% at baseline and 40.7% at 6 months). The full 24-week retention on BPN/NLX was statistically significantly associated with participants achieving viral suppression after being released from prison [19].

Overall, our meta-analysis found that being on MOUD increased the odds of achieving viral suppression (OR = 2.19; 95% CI = 1.88–2.56; Q = 3.78; *P* = .580) (Table 2). We also conducted meta-analysis excluding Reddon et al [22] because their calculated effect estimates were unadjusted and based on data by HIV-RNA assessments instead of by subjects.

After excluding Reddon et al [22], MOUD use remained significantly associated with viral suppression (OR = 2.03; 95% CI = 1.60–2.59).

Antiretroviral Treatment Adherence

Three studies discussed the effect of MOUD on antiretroviral treatment (ART) adherence (Table 1) [23, 26, 27]. Although 2 studies demonstrated a positive association between being on MOUD and adherence to ART [26, 27], 1 study, which did not report effect estimates, found no significant relationship between MOUD treatment and adherence to ART [23].

Mazhnaya et al [26] and Uhlmann et al [27] defined being optimally adherent to ART as taking >95% of prescribed doses, whereas Roux et al [23] evaluated 100% adherence to ART. The methods of collecting ART adherence data were also different, although all used validated measures. Mazhnaya et al [26] and Roux et al [23] used validated self-report questionnaires for adherence over the past 30 days. Uhlmann et al [27] assessed ART adherence with prescription refill data from the past 6 months. Our meta-analysis found that being on MOUD increased the odds of being adherent to ART (OR = 1.55; 95% CI = 1.12–2.15) (Table 2).

Hepatitis C Virus Sustained Virologic Response

One study assessed the effects of buprenorphine on achieving HCV sustained virologic response (Table 1) [11]. Rosenthal et al [11] demonstrated that participants with HCV and OUD who started and continued buprenorphine were significantly more likely to achieve sustained virologic response (measured by HCV RNA level) at 12 weeks (92%) than those who were never on buprenorphine (64%) and those who started but stopped buprenorphine (63%). This remained true even after adjustment for HCV treatment adherence (P = .008) [11].

Infectious Endocarditis Readmission

One study investigated infectious endocarditis readmission rates or repeat episodes of endocarditis and their association with MOUD (Table 1) [28]. Suzuki et al [28] found that 6 (37.5%) of the 16 participants who initiated MOUD at their initial hospital admission for endocarditis had a repeat episode within the follow-up period (45 months). This did not significantly differ from those who declined MOUD during initial hospitalization and had a repeat episode (4 of 10, 40%). The groups were defined by who started MOUD during hospitalization, but 50% of those who declined MOUD at first admission were reported to be using MOUD during follow-up, and only 68.8% of those who started with MOUD during hospitalization continued it during follow-up.

Infectious Endocarditis Antimicrobial Completion

One study evaluated infectious endocarditis antimicrobial completion (Table 1) [28]. Suzuki et al [28] noted that there was no significant difference in completion of antimicrobial course for endocarditis in those on MOUD compared with those not on MOUD. Of the 16 participants who initiated MOUD at the index hospitalization, 14 (87%) completed the course of antimicrobials, whereas all 10 (100%) of the non-MOUD participants completed the antimicrobial course. As previously mentioned for this study, 50% of the non-MOUD participants were on MOUD during follow-up, which may have affected these results.

DISCUSSION

Although opioid-related outcomes of MOUD have been extensively reported as well as the impact of MOUD on HIV risk behaviors [3, 29], to our knowledge this is the first systematic review and meta-analysis to empirically analyze the impact of MOUD on ART adherence, HIV viral suppression, HCV sustained viral response, HCV reinfection, new HBV infection, endocarditis treatment completion, and reinfection. Overall, we found a significant impact of MOUD on HIV viral suppression as well as ART adherence, which suggests that MOUD increases the probability of a PWH achieving viral suppression and ART adherence. Despite our extensive search, we found too few or no articles to make conclusions on the effect of MOUD on HCV sustained virologic response, HCV reinfections, new HBV infections, endocarditis antimicrobial completion, or endocarditis readmission rates.

Our results support the importance of integrating HIV and OUD treatment to increase likelihood of achieving viral suppression. Persons who are actively using drugs are historically less likely to be adherent to ART, and the incorporation of OUD treatment in HIV care can be crucial to medication adherence and thus achieving viral suppression [30]. Given that the most important goal of HIV treatment is to attain viral suppression for reduction in individual morbidity and mortality and improvement of public health through reduction in transmission (Undetectable = Untransmittable, U = U), integration of OUD and HIV treatment is critical [3, 10, 12, 13]. This systematic review and meta-analysis adds to the existing compelling evidence that it is possible and encouraged to address the intersectionality of the opioid and HIV epidemics. Long-term care strategies and standardized guidelines have been suggested [3, 5] and should be used to integrate treatment for OUD and HIV to maximize treatment success and improve healthcare quality.

Improving ART adherence is a vital step toward combatting the HIV epidemic [3]. Some studies did not meet our eligibility criteria for inclusion criteria but presented important results about the effect of MOUD on ART adherence that are worth mentioning. Palepu et al [31] demonstrated that methadone maintenance therapy was significantly associated with ≥95% ART adherence, but they did not specify whether the nonmethadone group had OUD. Another study looked at how differences in methadone dosage affected ART adherence and found that those taking a higher dose (≥100 mg/day) were significantly more likely to achieve ≥95% adherence to ART [32]. Coadministration of ART and MOUD impacts health outcomes in these vulnerable populations by improving adherence and viral suppression [32].

Few studies were identified with our search inclusion criteria to evaluate the impact of MOUD on HCV sustained virologic response and reinfection. Several studies were not eligible due to the lack of a control group but demonstrated that sustained virologic response can be achieved in patients maintained on MOUD [33, 34]. People with OUD are suitable candidates for HCV treatment with curative direct-acting antivirals (DAAs) and demonstrate comparable sustained virologic response posttreatment to those without OUD [34]. Despite this evidence, few people with OUD and HCV are receiving DAA treatment, in part due to abstinence-based substance use restrictions for HCV DAA medication according to 2017 Medicaid regulations in several states [35]. Government-funded resources and standardized care guidelines to integrate HCV and OUD care could allow for better treatment access [35].

There were no studies identified that evaluated the effect of MOUD on HCV reinfection. However, some studies did find

that persons who received MOUD experienced low rates of re-infection with HCV [36, 37], although these studies were ineligible for our review because the population receiving MOUD was compared with those without OUD or among an entire study population of those on MOUD. In addition to integration of MOUD and HCV treatment, increases in SSPs could help to reduce reinfection rates [35], especially given the increase in injection of stimulants such as methamphetamine and cocaine, leading to new infectious disease epidemics across the United States [2]. To address both HCV and OUD, care should be integrated that includes MOUD, DAA, and SSPs [5, 35].

Only 1 article was identified that discussed antimicrobial completion for infectious endocarditis and rehospitalization outcomes. We did identify studies that reported promising results despite not meeting our search criteria. Barocas et al [38] noted a significant difference in 1-year, all-cause rehospitalization between persons with endocarditis who received MOUD and a group who did not receive MOUD. Another study [39] reported that most persons who received buprenorphine and were hospitalized for an injection-related infection completed their antimicrobial course (19 of 20, 95%). Suzuki et al [40] reported no significant difference in 30-day readmission between those who were on MOUD before and/or during hospital stay and those who were not. These studies did not limit their results to endocarditis and thus were excluded. Previous research, as described, suggests that receipt of MOUD can significantly improve endocarditis-related outcomes. More research for strategies to engage persons with OUD in MOUD during endocarditis hospitalization might prevent rehospitalization, increase antimicrobial completion, improve surgical outcomes, and reduce mortality.

This review did not identify any studies of the effect of MOUD on new HBV infections. Our criterion for new HBV infection studies included reporting a negative hepatitis B surface antigen (HBsAg) before MOUD initiation and then a new positive HBsAg after initiating MOUD. To our knowledge, only 1 study presented this data, but there was no control group [41].

Limitations

This review has several strengths including the comprehensive search of multiple databases, the screening of 8169 papers, and the risk of bias assessments. However, there are some limitations to this review. First, few studies compared our desired infectious disease outcomes among persons with OUD on MOUD compared with those not on MOUD. We found several articles pertaining to our outcomes in observational studies in which all participants were on MOUD or studies that compared those on MOUD with non-OUD populations. To assure specificity of our results, we excluded articles that did not clearly identify their population as having OUD or opioid dependence. These excluded studies that described their population as "PWID" or "IVDU," which may

have included those who use cocaine or methamphetamine without any opioid use. These populations would not be an appropriate non-MOUD control to compare the effect of being on MOUD on infectious disease outcomes in persons with OUD, and they would bias our results. Thus, additional data may exist that are not presented in this review due to our more specific search criteria. It is notable that persons who opted out of MOUD likely were very different than those who chose to use MOUD for their OUD, leading to selection bias and distortion of true treatment effects. Ideally, more RCTs should be conducted to address this; however, because MOUD is the recommended standard of care for treatment of OUD, it would be unethical to offer a non-MOUD control group. Furthermore, because of the small sample size, we were unable to conduct a meta-analysis on HCV sustained virologic response and endocarditis-related outcomes. Finally, the purpose of this review was to determine the effectiveness of MOUD in general on infectious disease outcomes, not differences in type of MOUD on these outcomes. Future research could investigate comparative analyses of these infectious disease outcomes based on type of MOUD.

CONCLUSIONS

This systematic review found a significant impact of MOUD on HIV viral suppression and ART adherence. These results are particularly relevant given the intersecting opioid and HIV epidemics. There exists compelling evidence that MOUD treatment leads to improved HIV outcomes. Despite the extensive search, this review found too few articles for the effects of MOUD on HCV sustained virologic response, HBV infections, endocarditis antimicrobial completion, and endocarditis readmission rates to yield meaningful results. Some strategies for incorporation of OUD and infectious disease treatments include standardized OUD screening protocols in infectious disease prevention and treatment programs, linkage to or direct integrated provision of MOUD, increased access to SSPs, and integration of OUD and infectious disease prevention and treatment training programs for all healthcare students and providers. Implementation research is needed to evaluate how to best improve such treatment integration within different contexts.

Supplementary Data

Supplemental Figure 1. Funnel plots of reviewed studies for the HIV viral suppression outcome. HIV viral suppression was the only outcome with relatively enough studies available to assess publication bias. Results suggest no evidence of publication bias. The Funnel plot, Egger's and Begg's tests in Stata/SE 16.1 were used to assess publication bias.
Supplemental Table 1. Risk of bias results.

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