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Diversity Inclusion in United States Opioid Pharmacological Treatment Trials: A Systematic Review

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Abstract

Pharmacological treatments for opioid use disorders (OUDs) may have mixed efficacy across diverse groups (i.e., sex/gender, race/ethnicity, socioeconomic status [SES]). The present systematic review aims to examine how diverse groups have been included in U.S. randomized clinical trials examining pharmacological treatments (i.e., methadone, buprenorphine, or naltrexone) for OUDs. PubMed was systematically searched according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The initial search yielded 567 articles. After exclusion of ineligible articles, 50 remained for the present review. Of the included articles, 14.0% (n = 7) reported both full (i.e., accounting for all participants) sex/gender and race/ethnicity information; only two of those articles also included information about any SES indicators. Moreover, only 22.0% (n = 11) reported full sex/gender information, and 42.0% (n = 21) reported full racial/ethnic information. Furthermore, only 10.0% (n = 5) reported that their lack of subgroup analyses or diverse samples was a limitation to their studies. Particularly underrepresented were American Indian/Alaska Native, Asian, Native Hawaiian/Other Pacific Islander, and multiracial individuals. These results also varied by medication type; Black individuals were underrepresented in buprenorphine RCTs but were well represented in RCTs for methadone and/or naltrexone. In conclusion, it is critical that all people receive efficacious pharmacological care for OUDs given the ongoing opioid epidemic. Findings from the present review, however, support that participants from diverse or marginalized backgrounds are underrepresented in treatment trials, despite being at increased risk for disparities related to OUDs. Suggestions for future research are advanced.

Keywords

opioid use disorder; methadone; buprenorphine; naltrexone; diversity

Of the 20.5 million Americans who met criteria for any substance use disorder in 2015, 10% specifically had an opioid use disorder (OUD); for example, misuse of opioids for purposes other than prescribed, or non-prescription use of opioids (SAMHSA, 2019). Opioid misuse is associated with numerous negative consequences including health (e.g., HIV, [Willner-

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Reid et al., 2008], coma, [Khansari et al., 2013], and premature death [APA, 2018]), legal (e.g., criminal justice involvement; Winkelman et al., 2018), and economic consequences (Birnbaum et al., 2011). While the "opioid epidemic" (DEA, 2017) has affected all races/ethnicities, age groups, sexes/genders, and socioeconomic statuses (SES; Pletcher et al., 2008), specific demographic groups are disproportionately affected. For instance, prevalence rates of OUDs tend to be highest among individuals ages 18–25 and younger (0.9–1.3%) and these rates decrease with age across the lifespan, with the lowest rates seen among adults age 65 years and older (0.09%; APA, 2013; SAMHSA, 2019). OUD prevalence rates are also higher among those who are unemployed or of a low socioeconomic status (SES; Han et al., 2017). Moreover, research reports mixed findings in terms of rates of OUD across gender groups; however, findings support that women tend to progress from use to dependence more quickly than men and have more use-related social and psychological consequences (Back et al., 2011). Nationally representative data also suggest there are differences by race/ethnicity; American Indian/Alaska Native (AI/AN) and multiracial individuals are most likely to report opioid misuse, followed closely by White and Hispanic/Latinx individuals, while Black and Asian individuals report less misuse (Nalven et al., 2020; SAMHSA, 2019). Of additional concern, research suggests that minoritized groups (e.g., racial/ethnic, low SES) may be the most likely to experience negative consequences and health disparities related to opioid misuse (King et al., 2014; Singh et al., 2019); these disparities may be related to access to and utilization of pharmacological treatments.

Pharmacological Treatments for OUD

There are currently three medications approved by the U.S. Food and Drug Administration (FDA) for use in OUD treatment: methadone, buprenorphine, and naltrexone (FDA, 2019). Methadone, an opioid agonist, prevents or reduces withdrawal, craving, and opioid misuse relapse by occupying opioid mu receptors and diminishing euphoric effects (Salsitz & Wiegand, 2016). Methadone must be administered daily at specialty clinics by personnel who monitor an oral liquid or pill administration (Samet at al., 2018). Buprenorphine, a partial mu-opioid agonist and kappa-opioid receptor antagonist, is thought to be as effective as methadone but has lower misuse and overdose potential (Johnson et al., 1992; Ling et al., 1994). Buprenorphine typically results in less analgesia, euphoria, and respiratory depression than methadone (Whelan & Remski, 2012) and, therefore, may be a preferred treatment for OUDs. Buprenorphine has several methods of administration including as buccal film (in the cheek), sublingual film or tablet (under the tongue), as a subdermal implant (under the skin), or as a subcutaneous injection; it can be prescribed such that physician visits are progressively less frequent over an individuals' course of use (i.e., rather than requiring daily, or even weekly visits), thus increasing access compared to methadone (SAMHSA, 2020). Finally, naltrexone, an opioid antagonist, functions by blocking opioid postsynaptic receptors and the related euphoric effect from opioids but does not assist with withdrawal symptoms. Naltrexone is typically administered daily as an oral pill or every four weeks as an intramuscular injection and can be prescribed by health care providers that can prescribe medication (e.g., nurse practitioners, physician assistants, physicians) as it has less misuse potential then methadone and buprenorphine (SAMHSA, 2020). Though found to be effective and safe for treatment of OUDs, naltrexone has poor adherence rates because it can

result in severe withdrawal and concomitantly blocks the desired effects of opioid use (e.g., euphoria or pain relief; Jarvis et al., 2018).

It is important to note that pharmacological treatments utilized for OUDs have been found to differ in efficacy across demographic subgroups; however, many of these findings are preliminary and require further exploration and replication. These differences are likely due to biological, environmental, and psychosocial factors, among others. Younger individuals, those with lower SES, and females tend to report worse outcomes following pharmacological treatment for OUD compared to older individuals, those with higher SES, and males (Barbosa-Leiker et al., 2018; Hillhouse et al., 2013; Parran et al., 2010). Although some research suggests there may be specific gene polymorphisms (i.e., variations in the formation of genes) of the OPRD1 gene that are associated with worse buprenorphine treatment outcomes among females but not males (Clarke et al., 2014), these findings are equivocal and need to be replicated in larger, more diverse samples. Further, a systematic review of 26 articles focused on buprenorphine concluded that findings were inconsistent across studies and small sample sizes (with only 26% female participants in included articles) did not allow for definitive statements regarding sex differences in outcomes (Ling et al., 2019). Regarding racial differences, Pro et al., (2020) conducted a retrospective, cross-sectional study and found that the effects of medication for OUD varied widely based on race, such that AI/AN women were most likely to benefit from medication while White men were the least likely. Their study did not account for differing treatment mechanisms making it impossible to determine precise explanations for their findings; however, the authors theorized that AI/AN individuals may be participating in culturally adapted OUD treatment that may have better success within their communities. Moreover, Crist et al., (2013) found a specific polymorphism on the OPRD1 gene was associated with worse outcomes following buprenorphine treatment for Black (but not White) individuals, despite the fact that the polymorphism occurred among both racial groups. It is important to note, however, that these genetic findings are correlational in nature and inconclusive.

While further exploration is necessary concerning the efficacy of pharmacological treatments for OUDs, it is evident that certain demographic groups have barriers to accessing and receiving efficacious treatment. For example, Wu and colleagues (2016) found that, among the National Surveys on Drug Use and Health dataset that is considered to be nationally representative, adolescents, uninsured people, and Black or Asian individuals underutilized opioid pharmacological treatment. Other studies have found that Black individuals with an OUD were only half as likely to enroll in a methadone or buprenorphine maintenance treatment (Potter et al., 2015) and Hispanic/Latinx and incarcerated individuals were less likely to utilize OUD pharmacological treatment (Evans et al., 2019) than their White or non-incarcerated counterparts. Beyond lack of recruitment, Black, Hispanic/Latinx, low-income individuals, and women with an OUD are prescribed opioid pharmacological treatment less often than White, higher-income individuals, and men (Lagisetty et al., 2019; Lapham et al., 2021). Rates of retention in pharmacological opioid treatment have also been found to be lower for patients who were younger, Black, Hispanic/Latinx, or unemployed (Weinstein et al., 2017). Other possible barriers to treatment for marginalized groups may include a lack of trust in research and/or medical professionals, stigma involved in accessing care (Harris et al., 1996; Pacheco et al., 2013; Schick et al., 2020), or limited access

and poor quality of care (Stein et al., 2018); however, it is clear that there are disparities in ability to be successfully treated with pharmacological treatment for an OUD among people from certain demographic groups. Moreover, while there is evidence to support these disparities among relatively larger marginalized racial groups (e.g., Black, Asian, Latinx), there is a lack of research to support or refute the evidence that disparities exist among groups less-well represented in research, such as AI/AN, Native Hawaiian/Other Pacific Islander (NH/OPI), and multiracial groups; this lack of support suggests more research is necessary. In summary, the limited body of existing literature suggests there are demographic group differences in OUD prevalence, disparities, and pharmacological treatment and efficacy; yet, it remains unclear the extent to which diverse sample have been represented in trials of medication treatments for OUDs.

Present Study

The gold standard of research methodologies for interventions, randomized controlled trials (RCTs) are a scientifically robust method of testing intervention efficacy. Participation in RCTs by members of diverse groups is important as it allows for a better understanding of potential differences in efficacy of treatments that may be important for targeted pharmacological interventions. Furthermore, participation in such trials provides opportunities for marginalized and underserved groups to receive potentially greater efficacious medical care (Klein et al., 2015). Concerningly, reviews examining pharmacological treatment for other conditions have found that inclusion of individuals from underrepresented groups is lacking (Chen Jr et al., 2014; Schick et al., 2020). Such underrepresentation is of concern, as it is difficult to conclude how effective a given treatment is within a group for which it has not yet been adequately assessed. Yet, it is important to also note that overrepresentation of vulnerable groups (e.g., those who are economically disadvantaged) is exploitative, hence, it is critical that studies employ fair and equitable recruitment procedures (DHEW, 1979). It remains unclear, however, the extent to which diverse demographic groups have been included in pharmacological treatment trials for opioid use disorders.

Gatzke-Kopp (2016), Clark and colleagues (2019) and others have called for more diverse representation in psychophysiological and pharmacological research, and a clearer understanding of the current state of diversity inclusion in the OUD literature is needed. Therefore, the present study aims to examine the extent to which diverse groups (i.e., age, sex/gender, race/ethnicity, SES) have been included in U.S. RCTs examining the efficacy of pharmacological treatment for OUDs (i.e., methadone, buprenorphine, and naltrexone). We specifically focus on the U.S. because people of color and of lower SES have experienced historical and contemporary inequities (e.g., access to resources and adequate healthcare) that have resulted in notable health disparities (Kreps, 2006; Williams, 2012). Moreover, while the authors recognize that sex is a biological variable and gender is a social construct encompassing the characteristics and roles of femininity and masculinity, these variables are analyzed together in the present review because no articles reported on both variables or provided information on how the data was collected so that we could ascertain whether sex and gender were being accurately represented.

Materials and Method

This systematic review followed guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (PROSPERO registration # CRD42020192077), which ensures the accuracy and quality of conducting and reporting a systematic review (Liberati et al., 2009; Moher et al., 2009). The PRISMA statement includes a 27-item checklist specifying information required to be reported and a four-phase flow diagram that details the identification, screening, eligibility, and inclusion of relevant articles.

Search Strategy

PubMed, selected to collect articles representing trials funded by the National Institutes of Health, was searched for peer-reviewed manuscripts in the English language on March 31, 2020 using the search terms: (“opioid use disorder” OR “opioid dependence”) AND (“randomized controlled” OR “randomized trial” OR “clinical trial”) AND (“methadone” OR “buprenorphine” OR “naltrexone”). All papers generated using search criteria were compiled into a Microsoft Excel database. Abstracts were screened by two independent coders from the initial search to assess inclusionary criteria, and a third coder resolved any discrepancies in coding. The search strategy is illustrated in the flow diagram (see Figure 1).

Eligibility Criteria

Articles were restricted on the basis of six pre-defined criteria: (1) reporting in English language; (2) conducted in the U.S.; (3) assignment of at least five participants per condition (consistent with prior systematic review methodology; Bouza et al., 2004); (4) intent of the paper was to test the efficacy of methadone, buprenorphine, or naltrexone for opioid dependence or OUD; and (5) assessment of at least one opioid use outcome (i.e., uranalysis, self-report; Moeller et al., 2008; Palamar et al., 2019).

Data Extraction and Synthesis

The remaining full-length articles were reviewed and information relevant to study goals was extracted and compiled into a table (see Table 1). The following information was extracted from each article: (1) funding source; (2) sample size; (3) reporting of sample demographics including age, sex/gender, race/ethnicity, SES; (4) sample demographic information (e.g., number and percent of participants that were members of various demographic groups); (5) subgroup analysis by demographic group; and (6) discussion of the inclusion/diversity in article limitations. Variables that were coded to represent SES include employment status (e.g., full-time, part-time, unemployed, etc.), income, and living situation (e.g., living with homelessness, unstable living situation, etc.).

Results

Search Results

The search strategy yielded 567 articles. After removing duplicates, the search resulted in 560 unique articles. After the initial abstract review, 494 were excluded for failing to meet inclusion criteria. Following the procedures outlined previously, the remaining 66 articles

were reviewed. Of those 66, 16 articles were deemed to be ineligible after full-text review (i.e., did not randomize participants to conditions, were not peer-reviewed, or were not conducted in the U.S.). The remaining 50 full-text articles were reviewed and included in the present study. These final articles were subsequently examined, and relevant information pertaining to study goals was extracted. Information regarding reported sample demographic breakdowns, subgroup analyses conducted, and mention of cultural inclusion in limitations sections for each article were then compiled into a table (see Table 1).

Summary of Included Articles

In total, 50 articles met all criteria; a summary of reporting and inclusion by demographic factors, subgroup analyses inclusion, and lack of inclusion as a limitation are presented in Table 2 for the full sample and by medication. The total number of participants included in all articles was 9,124, with a weighted average age of 36.2 years old. Three articles were conducted with adolescents or young adults (i.e., ages 13–24 years old), while the others reported average ages between 30 and 47 years old. Most articles (80.0%, n = 40) were funded, at least in part, by the NIH and of the 10 remaining articles, six were funded by pharmaceutical companies, four were funded by United States Public Health Service grants, and one article had no reported funding source. While 98.0% (n = 49) of the articles included at least some information on sex/gender and 96.0% (n = 48) included some information of race/ethnicity, only 14.0% (n = 7) of the articles reported both full (i.e., accounting for all of the participants) sex/gender and race/ethnicity information and only two of those articles (i.e., 4.0% of the articles included in the present review) also included information about any SES indicators. Moreover, 22.0% (n = 11) included full sex/gender information and 42.0% (n = 21) included full racial/ethnic information. Furthermore, only 16.0% (n = 8) of articles conducted subgroup analyses by any demographic factor and 10.0% (n = 5) reported that their lack of subgroup analyses or diverse samples was a limitation of their study.

Regarding sex/gender, of the 9,124 total participants in included articles, 6,192 (67.9%) participants' sex/gender were reported. Only 34.0% (n = 17) of articles mentioned the inclusion of females/women, while 86.0% (n = 43) indicated the number or percent of male/men participants. Of the 6,192 participants whose sex/gender were reported, male/men individuals were the largest included group, representing 77.7% (n = 4,812) of all individuals whose sex/gender was reported in the articles, while females/women represented only 22.3% (n = 1,380). None of the articles differentiated between biological sex and gender as unique factors in their demographics and many used them interchangeably. Moreover, no articles mentioned the inclusion of transgender or non-binary gender individuals in their samples.

Regarding race, of the 9,124 total participants in included articles, 6,994 (76.7%) participants' races were reported (excluding ethnicity and "other" categories). Of these 6,994 participants, White individuals were the largest included group, representing 72.5% (n = 5,071) of all individuals whose race was reported in the articles, followed by individuals who identified as Black (n = 1,909, 27.3%). Less than 1% were identified as Asian (n = 8) or AI/AN (n = 6). While some articles categorized non-White individuals into an "other"

category, no articles included mention of participants that were either Native Hawaiian/Other Pacific Islander or multiracial. Moreover, while 64.0% (n = 32) of articles reported on the inclusion of Black participants, less than 1% of articles reported on the inclusion of Asian or AI/AN participants, and no articles mentioned the inclusion of NH/OPI or multiracial participants. Regarding ethnicity, less than half (n = 24, 48.0%) of the articles reported on participant ethnicity or described the percent of their population that was Hispanic/Latinx.

Regarding SES, 72.0% (n = 36) of articles reported on participants' employment status, 10.0% (n = 5) reported some measure of income (typically sample mean income), and 12.0% (n = 6) reported on number/percent of participants who were experiencing homelessness or without a stable living arrangement. Only 20.0% (n = 10) did not report on any variables related to SES (e.g., employment, income, living situation). Of the 36 articles that reported on the percent of their participants that were employed (versus not; n = 24, 48.0%), 35.5% (n = 1,491) of participants were employed. Of the five articles that reported a mean income, the weighted mean monthly income was $1,136.70.

Methadone Findings

A total of eight articles specifically assessed outcomes for methadone treatment, with 1,234 participants included. Only one article reported on the number of female/women participants (the rest reported only on the percent male/men). Only two of the methadone articles reviewed reported on issues of inclusion and diversity in their limitations section (i.e., two mentioned SES and one mentioned race). Notably, in one of the two articles, the authors stated that having predominately Black and unemployed participants in their sample may mean their findings are limited in their generalizability (this article reported to have 58% Black participants, 41% White participants, and 1% Hispanic participants, while 37% of participants were reported to have been employed in the past 30 days).

Buprenorphine Findings

A total of 24 articles specifically assessed outcomes for buprenorphine treatment, with 4,792 participants included. Three of these articles specifically focused on adolescents or young adults (notably, no articles focused on other medications used samples of adolescents/young adults). Only 16.1% (n = 617) of participants with an identified race in these articles were reported to be Black, Asian, or AI/AN.

Naltrexone Findings

A total of nine articles specifically assessed outcomes for naltrexone treatment, with 1,072 participants included. Only one of these articles reported on the number of females/women included. The only article that discussed demographic composition of the sample as a limitation to the study had enrolled 100.0% males and noted that failure to recruit female participants was a constraint of the study. Of importance, 61.4% (n = 475) of all participants with an identified race in these articles were reported to be Black.

Discussion

The present study systematically examined the inclusion of individuals from diverse backgrounds with respect to sex/gender, race/ethnicity, and SES in RCTs examining methadone, buprenorphine, and naltrexone efficacy for OUDs. Fifty eligible articles were identified, with a majority of articles including at least partial information about sex/gender, race/ethnicity, and SES for their samples; however, participants from diverse backgrounds were not routinely nor representatively included and a majority of participants were male/men and White. These findings are consistent with findings of Gatzke-Kopp (2016) and Clark and colleagues (2019), who reported underrepresentation of diverse participants in psychophysiological research with regard to demographic factors such as sex/gender, race/ethnicity, and SES.

A relative strength of the reviewed articles was that all but two articles reported, to some extent, on both sex/gender and race/ethnicity. Furthermore, the majority of articles reported on some indicator of SES, such as employment status, income, or homelessness. Further, the samples in the reviewed articles may represent a lower than average SES population, which is consistent with the population of individuals with OUDs – a critical factor to consider because this group experiences a high level of health disparities related to OUDs (King et al., 2014; Singh et al., 2019). These findings are important given that research suggests that females, people of low SES, and racially/ethnically minoritized individuals experience significant health disparities related to opioid use and may not respond as well to pharmacological treatment (Barbosa-Leiker et al., 2018; Crist et al., 2013; Parran et al., 2010; Pro et al., 2020). Moreover, people who are both low SES and from a minoritized racial/ethnic background may experience even greater, additive or multiplicative risk for harm related to OUD. Recognition that all people have multiple groups with which they identify underlines the need for subgroup analyses to examine the ways in which identities may interact with each other (Crenshaw, 2017). Such investigations would allow for fine-grained analyses to examine how pharmacological treatments work for people from a range of backgrounds. Reporting on demographic factors and conducting subgroup analyses by such factors would allow readers to better understand the unique sample with whom the study was conducted and may help care providers to determine which medication(s) for OUD is/are appropriate for their patients or client populations.

This review also highlights several weaknesses of the literature with respect to inclusion and diversity in OUD pharmacological treatment studies. Few articles (n = 17, 34.0%) reported the percent of females/women included in their samples, and of the participants with an identified sex/gender, only 22.3% of participants were females/women (compared to 77.7% males/men identified). This finding contrasts with nationally representative data that has found females misuse opioids at similar rates (3.3% past year prevalence) compared to males (4.1% past year prevalence; SAMHSA, 2019). Of particular concern, none of the reviewed studies reported on the inclusion of gender diverse (e.g., transgender or gender non-binary) individuals. It is further problematic that articles did not differentiate between biological sex and socially constructed gender, as biological sex may differ from expressed gender, but sex can affect efficacy of medications for OUD, making it critical to know

whether reported samples are reflecting biological sex or gender identity (Barbosa-Leiker et al., 2018).

Another weakness in the existing literature is that of the 6,994 participants with a race reported between all 50 articles, only eight Asian, six AI/AN, and zero NH/OPI or multiracial participants were identified; there may have been additional participants that were included in the reviewed articles, but their races were not identified. These findings are particularly problematic given that AI/AN and multiracial individuals report the highest rates of opioid misuse (Nalven et al., 2020; SAMHSA, 2019) and experience disproportionate health disparities due to OUD compared to other racial groups (King et al., 2014; Singh et al., 2019). Moreover, these findings are inconsistent with nationally representative data that found that 5.2% of multiracial, 5.1% of AI/AN, 3.8% of White, 3.7% of Hispanic/Latinx, 3.4% of Black, 2.8% of NH/OPI, and 1.6% of Asian individuals misuse opioids (SAMHSA, 2019). In contrast, our study found that White individuals are the best represented in clinical trials of medications for OUD, followed by Black participants, while less than one percent or no Asian, AI/AN, NH/OPI, or multiracial individuals were reported to be included.

While the present manuscript is unable to determine the specific reasons for a lack of reporting diverse racial/ethnic inclusion in the reviewed articles, it is plausible that this pattern is consistent with the systemic racism and implicit bias that surrounds the disparities in prescriptions of opioids to marginalized groups (e.g., through racist media portrayal and physician bias; Anderson et al., 2009; Santoro & Santoro, 2018; Tait & Chibnall, 2014). Research has further indicated that Black, compared to White, individuals are significantly less likely to be prescribed an opioid for medical purposes or must present with higher pain levels before being given a prescription (Haq et al., 2021; Johnson-Jennings et al., 2020). While it is possible that more diverse individuals were included in the studies reviewed, the authors of included articles did not indicate clearly whether certain groups are well represented in their clinical trials as made evident in their manuscripts. Therefore, prescribers seeking information about efficacy of a certain medication for OUD would be unable to determine whether specific medications would be useful for specific patients that they were seeing and likely would not have the time to contact authors to determine whether the sample included populations similar to their patient. Similarly, patients looking to access more information about treatment options they are considering would not be able to tell whether individuals whose identities are similar to their own were represented in clinical trials testing the different types of medications. As suggested by others, to address such problems, researchers should strive to carefully collect demographic information and report findings, and journal reviewers and editors should require that the articles they publish include full descriptive information of the relevant demographics of their samples (Schick et al., 2020).

Furthermore, an important weakness in the reviewed literature is that article's participants were, on average, 36.2 years old; this finding is notable given that OUDs are most prevalent among young adults between ages 18–25 years old (SAMHSA, 2019). With the exception of three trials looking at youth/young adults, the average ages for all articles were between 30 and 47 years old, likely representing an older population than those for whom OUD prevalence rates are especially high. Moreover, the finding that only 16.0% of articles

conducted subgroup analyses by any demographic factor and 10.0% indicated that a lack of subgroup analyses or diverse samples was a limitation to their articles is problematic given that there have been multiple calls for more inclusive research (Clark et al., 2019; Gatzke-Kopp, 2016). Given that efficacy may be different among diverse demographic groups (Crist et al., 2013; Pro et al., 2020), it is important that research samples are representative of the diversity that exists in the population most adversely effected by OUDs. It is also noteworthy that many samples were small in size and the average sample size was only 148 participants; therefore, many articles may have been underpowered for subgroup analyses. It may also be that in articles with large samples, authors conducted subgroup analyses by demographic group but found null results and may have decided not to pursue publication, given that nonsignificant results are less likely to be accepted for publication (Dwan et al., 2008).

In terms of articles for specific medications for OUD, there are a few notable differences by medication. First, there were meaningful differences in racial composition by medication type. For example, Black participants made up 49.6% of the samples for the methadone articles, 16.0% for buprenorphine articles, and 61.4% for naltrexone articles. While there is no evidence to suggest how or why samples are chosen for these articles, it is worth noting that buprenorphine has been found to potentially be safer than methadone because it is less susceptible to misuse and overdose (Johnson et al., 1992; Ling et al., 1994), and it is often more accessible than methadone because of its ability to be prescribed with monthly (versus daily) visits (SAMHSA, 2020). By contrast, naltrexone has low adherence rates and is not preferred due to its negative side effects (e.g., dysphoria and severe withdrawl symptoms; Rothenberg et al., 2002). This discrepancy in racial enrollment is problematic given that Black individuals are underrepresented in the medication for OUD with the most RCTs and that is thought to be the safest and more accessible with relatively good adherence (buprenorphine). At the same time, Black individuals are well represented in RCTs for medications with worse adherence (naltrexone) or potentially less safety and accessibility (methadone). This finding is in contrast to young adult and adolescent trials, which were all conducted with buprenorphine. These findings may suggest that there is bias in researcher's sample selection process or in grants that are being funded for Black individuals who are best represented in trials with a less-preferred medication for OUD (i.e., naltrexone). Overall, it is abundantly evident that more equitable diversity representation is necessary across medications for OUD in RCTs.

Limitations and Future Directions

While the present study provides important information in regard to diverse demographic inclusion in RCTs for pharmacological treatment of OUDs, the results should be considered in the context of their limitations. First, articles included in the present study were limited to those within the U.S. and written in English, which may have omitted articles conducted elsewhere that were more inclusive of particular demographic groups. Second, although the present study covered the medications for OUD currently approved by the FDA, there may be other medications that could be used for OUD treatment that are not included in the present study. Third, while not a limitation of the present review but rather a limitation of the literature and scientific publishing practices, articles that include more diverse groups may not have been accepted for publication, especially if they had small sample sizes.

Fourth, it is possible that authors of articles that contained more diverse samples did not perceive the need to report on issues related to inclusion and diversity as a limitation to their study. Thus, the 90.0% percent in the present review that did not include a lack of diverse representation in their limitations may be inflated, although there were few articles that reportedly had diverse representation across all demographics. Finally, articles reviewed herein were located through only one database (PubMed), and while this database should contain all NIH-funded research, it is possible that our review missed some relevant literature; future reviews should also search ClinicalTrials.gov and other relevant databases.

Future research should examine ways to enhance motivation or create more guidelines for necessary inclusion of diverse samples. It may be necessary and important to over-sample for groups not well represented in current research. Journal reviewers and editors should also be encouraged to consider the representation of articles they publish and request diverse samples. Furthermore, grant reviewers (especially for NIH funded research) should ensure proposed articles include samples representative of OUD prevalence (and perhaps focus on groups disproportionately affected by related health disparities). It may be that diverse sample are difficult to obtain due to a mistrust by groups historically treated unethically in research (Harris et al., 1996; Pacheco et al., 2013; Schick et al., 2020). Moreover, as Schick at colleagues (2020) suggest, the lack of diverse representation in RCTs may reflect the lack of diverse researchers and individuals holding graduate degrees; therefore, investing resources to support the careers of researchers from marginalized backgrounds is warranted as it may increase representative research. While programs such as certain T-32 NRSA Diversity Supplement Awards, the LEADership, Education and Development (LEAD) program, the McNair Scholars program, and others target these aims, there is still a lack of diverse representation in science and higher education, suggesting the need to continue with such efforts. As the present study attests, there are meaningful gaps in the existing literature on OUD pharmacological treatment, and these steps are important and necessary to ensure diverse groups are represented in RCTs. For instance, despite high prevalence rates of opioid-related overdoses in rural communities (Paulozzi & Xi, 2008), none of the included articles specifically noted or focused on studying populations in rural communities. Therefore, future studies should aim to recruit rural samples, report on community and neighborhood information, and compare the efficacy of medications for OUD in rural versus urban samples. Including such variables will be helpful to contextualize the findings.

Finally, a notable finding, while not a focal point of the present study, was that over half of the naltrexone articles ($n = 5$) were specifically conducted with populations involved with the criminal justice system, while only one of the methadone articles and none of the buprenorphine articles were conducted specifically with people involved in the criminal justice system. As we noted previously with respect to Black individuals, because naltrexone is a less preferred medication for the treatment of OUDs, this may represent bias in sample selection. It is worth examining in future studies the extent to which, and how equitably, people involved in the criminal justice system are included in pharmacological trials for OUD.

Conclusions

The present study reviewed the inclusion of diverse demographic groups among 50 RCTs examining the efficacy of methadone, buprenorphine, and naltrexone for OUDs. Results demonstrated that some aspects of sex/gender and racial/ethnic information was typically provided in RCTs and people of low SES were generally well represented; however, several groups were not included (e.g., NH/OPI or multiracial individuals) or minimally included (AI/AN or Asian individuals). Furthermore, certain groups (e.g., Black individuals) were better represented in methadone and naltrexone articles than they were in buprenorphine articles. It is important that all people receive efficacious pharmacological care for OUDs in the midst of the current opioid epidemic, particularly participants from diverse or marginalized backgrounds who may already be at increased risk for disparities related to OUDs.

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Public Significance Statement:

Opioid use disorders are prevalent in the U.S. and disproportionality affect people from marginalized backgrounds; yet, the present systematic review finds that most trials of pharmacological treatment are conducted with majority White and male participants. Participants from diverse or marginalized backgrounds that may be at increased risk for disparities related to OUDs are currently underrepresented in treatment trials

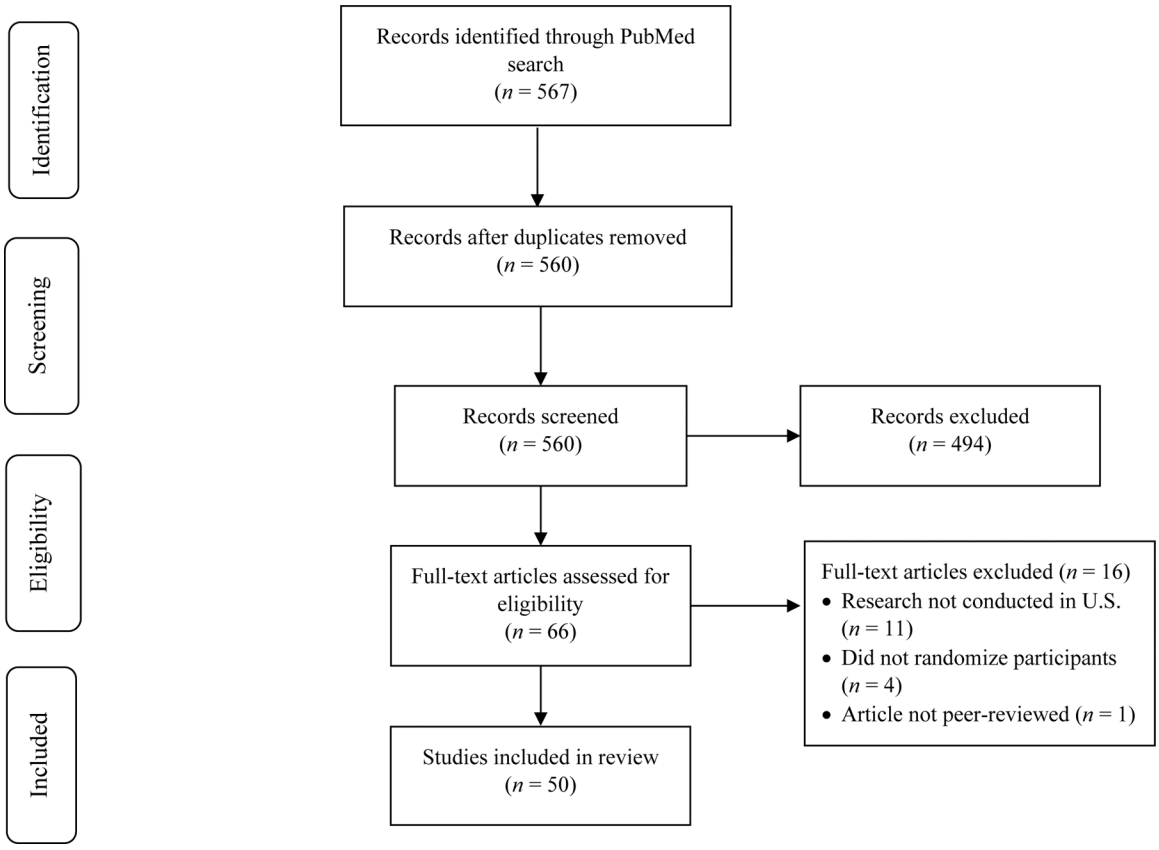

Figure 1.
Flow Diagram for PRISMA Systematic Review Procedure

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Table 1

Summary of Included Articles

Citation	Sample Size	Mean Age (Years)	Sex/Gender Reporting	Sex/Gender Inclusion	Race/ Ethnicity Reporting	Racial/Ethnic Inclusion	SES Inclusion	Subgroup Analyses	Discussed Diversity in Limitations
Methadone									
Fiellin et al., 2001	46	41	Partial	65% men	Partial	78% White	67% employed full-time Monthly income, *M* = $1541	No	None
Gruber et al., 2008	111	42	Full	61% male 39% female	Full	41% White 30% Black 5% Asian 4% AI/AN 20% Hispanic/Latinx	Monthly income, *M* = $1398	No	None
Masson et al., 2004	91	Not reported	None		None		None	No	Yes: SES
Schwartz et al., 2017	295	43	Partial	59% male	Full	41% White 58% Black 1% Hispanic/Latinx	37% employed	No	Yes: race, SES
Schwartz et al., 2020	225	38	Partial	80% male	Full	25% White 62% Black 13% other 3% Hispanic/Latinx	44% employed	Yes: sex	None
Sees et al., 2000	179	39	Partial	59% men	Full	51% White 30% Black 13% Hispanic/Latinx 6% other	47% employed full-time 9% no stable living arrangement Monthly income, *M* = $855	No	None
Strain et al., 1999	192	38	Partial	65% men	Partial	49% White	25% employed	Yes: sex	None
Strain et al., 1993	95	35	Partial	68% male	Partial	52% Black	60% unemployed	No	None
Buprenorphine									
Collins et al., 2005	106	36	Partial	72% male	Full	53% White 12% Black 29% Hispanic/Latinx 6% other	56% employed	No	None
Cushman et al., 2016	113	40	Partial	69% male	Full	49% White 23% Black 20% Hispanic/Latinx 8% other	35% homeless	No	None
D'Onofrio et al., 2015	329	31	Partial	76% men	Full	75% White 7% Black 16% Hispanic/Latinx 1% other	52% employed full-time 26% employed part-time 9% no stable living arrangement	No	None

Citation	Sample Size	Mean Age (Years)	Sex/Gender Reporting	Sex/Gender Inclusion	Race/ Ethnicity Reporting	Racial/Ethnic Inclusion	SES Inclusion	Subgroup Analyses	Discussed Diversity in Limitations
Fiellin et al., 2006	166	36	Partial	78% male	Partial	77% White	48% employed full-time Monthly income, *m* = $1368	No	None
Fiellin et al., 2014	113	30	Partial	58% male	Partial	96% White 7% Hispanic/Latinx	44% employed full-time	No	None
Gunderson et al., 2010	20	45	Partial	90% male	Full	45% White 20% Black 35% Hispanic/Latinx	25% employed	No	None
Haight et al., 2019	489	40	Full	66% male	Full	71% White 27% Black/AA 2% other	None	No	Full
Hopper et al. 2005	20	47	Partial	65% male	Partial	85% Black/AA	20% employed	No	None
Johnson et al., 1995a	99	34	Partial	29% female	Partial	50% non-White	36% employed	No	None
Johnson et al., 1995b	150	33	Partial	38% female	Partial	47% non-White	23% employed	Yes: gender	None
Ling et al., 2010	163	37	Partial	47% male	Full	75% White 12% Black 13% other 15% Hispanic/Latinx	None	No	None
Ling et al., 1998	736	36	Partial	33% female	Full	49% White 22% Black 28% Hispanic/Latinx	33% unemployed	No	None
Ling et al., 2009	516	36	Partial	33% female	Partial	76% White 12% Black 6% Hispanic/Latinx	35% unemployed	No	None
Lofwall et al., 2018	428	38	Full	61% men 39% women	Partial	75% White	35% employed	No	None
Lucas et al., 2010	93	46	Partial	28% female	Partial	98% Black/AA	30% employed 48% own/rent home 39% staying with others 4% group home 9% homeless	No	None
Marsch et al., 2005a	134	33	Partial	63% male	Partial	98% White	46% employed full-time Monthly income, *m* = $871	Yes: SES, gender	None
Marsch et al., 2005b	36	17	Partial	39% male	Partial	97% White	None	No	None
Marsch et al., 2016	53	21	Full	58% male 42% female	Partial	76% White	9% homeless	No	None
Potter et al., 2015	252	33	Partial	43% female	Partial	89% White	67% employed full-time	Yes: SES, gender, race, age	None

Citation	Sample Size	Mean Age (Years)	Sex/Gender Reporting	Sex/Gender Inclusion	Race/ Ethnicity Reporting	Racial/Ethnic Inclusion	SES Inclusion	Subgroup Analyses	Discussed Diversity in Limitations
Rosenthal et al., 2013	287	36	Partial	61% male	Full	83% White 13% Black 5% other 18% Hispanic/Latinx	None	No	None
Rosenthal et al., 2016	177	39	Full	59% male 41% female	Full	95% White 3% Black 1% Asian 1% AI/AN 1% other 3% Hispanic/Latinx 97% non-Hispanic/Latinx	55% employed full-time 10% employed part-time 18% unemployed 7% retired/disability	No	Yes: race, SES
Sigmon et al., 2016	50	35	Partial	58% male	Partial	88% White	52% employed	No	None
Stein et al., 2020	110	32	Partial	68% male	Partial	79% White 11% Black 12% other 10% Hispanic/Latinx	15% employed	Yes: gender, race	None
Woody et al., 2008	152	19	Partial	59% male	Partial	74% White 2% Black 1% Filipino 25% Hispanic/Latinx	N/A *	No	Yes: race
Naltrexone									
Comer et al., 2006	60	41	Full	77% male 24% female	Full	37% White 35% Black 3% Asian 18% Hispanic/Latinx 7% other	None	No	None
Coviello et al., 2010	111	34	Partial	82% male	Full	47% White 26% Black 27% Hispanic/Latinx	23% employed	No	None
Friedmann et al., 2018a	15	37	Partial	93% male	Partial	83% White	20% employed	No	None
Friedmann et al., 2018b	308	44	Partial	85% male	Partial	20% White 50% Black 27% Hispanic/Latinx	18% employed	Yes: sex, SES, race	None
Jarvis et al., 2019	84	43	Partial	71% men	Partial	80% Black	53% unemployed	No	None
Lee et al., 2016	308	44	Partial	85% male	Partial	20% White 50% Black 27% Hispanic/Latinx	18% employed	No	None
Lee et al., 2015	33	44	Full	100% male	None		18% employed 33% homeless	No	Yes: sex
Mannelli et al., 2009	96	33	Partial	61% male	Full	71% White 29% Black	53% unemployed	No	None

Citation	Sample Size	Mean Age (Years)	Sex/Gender Reporting	Sex/Gender Inclusion	Race/ Ethnicity Reporting	Racial/Ethnic Inclusion	SES Inclusion	Subgroup Analyses	Discussed Diversity in Limitations
Sullivan et al., 2013	57	41	Partial	77% men	Partial	37% White 35% Black 18% Hispanic/Latinx	None	No	None
Methadone and Buprenorphine									
Johnson et al., 2000	220	36	Partial	34% female	Partial	60% non-White	30% employed	Yes: sex, age, race	None
Johnson et al., 1992	162	33	Full	70% men 30% women	Full	58% White 40% Black 2% other	None	No	None
Kosten et al., 1993	125	32	Partial	73% male	Partial	69% White	55% employed full-time	No	None
Ling et al., 1996	225	41	Full	80% male 20% female	Full	14% White 20% Black 65% Hispanic/Latinx 1% other	None	No	None
Schottenfeld et al., 2005	162	36	Partial	66% male	Full	52% White 36% Black 11% Hispanic/Latinx	42% employed	No	None
Schottenfeld et al., 1997	116	33	Partial	69% male	Partial	78% White	71% employed	No	None
Strain et al., 1994	164	32	Partial	71% male	Full	49% White 51% Black/AA	35% employed	No	None
Buprenorphine and Naltrexone									
Bisaga et al., 2018	378	36	Full	66% male 34% female	Full	74% White 20% Black/AA 6% other	None	No	other
Lee et al., 2018	474	34	Full	70% male 30% female	Partial	76% White 10% Black 17% Hispanic/Latinx	18% employed 63% unemployed	No	None

Note. SES = socioeconomic status; AI/AN = American Indian/Alaska Native; AA = African American.

*Years of education and employment were assessed but are not strong indicators of SES among youth.

Table 2

Summary of Reporting and Inclusion of Diverse Demographic Groups, Subgroup Analyses, and Limitations

	Total Sample* (articles, *n* = 50) (participants, *n* = 9,124)	Methadone only (articles, *n* = 8) (participants, *n* = 1,234)	Buprenorphine only (articles, *n* = 24) (participants, *n* = 4,792)	Naltrexone only (articles, *n* = 9) (participants, *n* = 1,072)
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Sex Reporting				
Full	11 (22.0%)	1 (12.5%)	4 (16.7%)	2 (22.2%)
Partial	38 (76.0%)	6 (75.0%)	20 (83.3%)	7 (77.8%)
None	1 (2.0%)	1 (12.5%)	0	0
Sex Inclusion				
Reported on inclusion of female/women participants	17 (34.0%)	1 (12.5%)	10 (41.7%)	1 (11.1%)
Females/women included[a]	1,380 (22.3%)	43 (5.4%)	883 (31.8%)	12 (1.3%)
Race/Ethnicity Reporting				
Full	21 (42.0%)	4 (50.0%)	9 (37.5%)	3 (33.3%)
Partial	27 (54.0%)	3 (37.5%)	15 (62.5%)	5 (55.6%)
None	2 (4.0%)	1 (12.5%)	0	1 (11.1%)
Racial/Ethnic Inclusion				
Reported on inclusion of Black participants	32 (64.0%)	5 (62.5%)	14 (58.3%)	7 (77.8%)
Black participants included[b]	1,909 (27.3%)	446 (49.6%)	614 (16.0%)	475 (61.4%)
Reported on inclusion of Asian participants	3 (6.0%)	1 (12.5%)	1 (4.2%)	1 (11.1%)
Asian participants included[b]	8 (0.1%)	5 (0.6%)	1 (0.03%)	2 (0.3%)
Reported on inclusion of AI/AN participants	2 (4.0%)	1 (12.5%)	1 (4.2%)	0
AI/AN participants included[b]	6 (0.1%)	4 (0.4%)	2 (0.1%)	0
Reported on inclusion of Hispanic/Latinx participants	24 (48.0%)	4 (50.0%)	12 (50.0%)	5 (55.6%)
SES Inclusion				
Reported on employment	36 (72.0%)	6 (75.0%)	17 (70.8%)	7 (77.8%)
Reported on income	5 (10.0%)	3 (37.5%)	2 (8.3%)	0
Reported on living arrangement or homelessness	6 (12.0%)	1 (12.5%)	4 (16.7%)	1 (11.1%)
None	10 (20.0%)	1 (12.5%)	4 (16.7%)	2 (22.2%)
Other Inclusion				

	Total Sample* (articles, *n* = 50) (participants, *n* = 9,124)	Methadone only (articles, *n* = 8) (participants, *n* = 1,234)	Buprenorphine only (articles, *n* = 24) (participants, *n* = 4,792)	Naltrexone only (articles, *n* = 9) (participants, *n* = 1,072)
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Reported on HIV status	3 (6.0%)	1 (12.5%)	2 (8.3%)	0
Reported on Hepatitis C status	5 (10.0%)	0	5 (20.8%)	0
Reported on people on parole/probation or incarcerated/in court ordered treatment	7 (14.0%)	1 (12.5%)	0	5 (55.6%)
Subgroup Analyses Conducted				
Race/Ethnicity	4 (8.0%)	0	2 (8.3%)	1 (11.1%)
Sex/Gender	8 (16.0%)	2 (25.0%)	4 (16.7%)	1 (11.1%)
SES	3 (6.0%)	0	2 (8.3%)	1 (11.1%)
Included as Limitations				
Race/Ethnicity	3 (6.0%)	1 (12.5%)	2 (8.3%)	0
Sex/Gender	1 (2.0%)	0	0	1 (11.1%)
SES	3 (6.0%)	2 (25.0%)	1 (4.2%)	0

Note. The numbers presented in this table do not necessarily reflect the full counts and percentages of individuals included but reflect representation based on information given in the articles. Percentages may not total 100 due to partial reporting; SES = socioeconomic status; AI/AN = American Indian/Alaska Native.

*The total sample sizes and percentages are based off all articles including those for methadone, buprenorphine, naltrexone, and articles including two medications of interest.

[a]The percentage of females/women included is based on the combined sample size of articles reporting any sex/gender information (*n* = 6,192; 790; 2,779; and 915 participants for the total sample, methadone, buprenorphine, and naltrexone, respectively).

[b]The percentage of individuals included is based on the combined sample size of articles reporting any racial/ethnic information (*n* = 6,994; 900; 3,843; and 774 participants for the total sample, methadone, buprenorphine, and naltrexone, respectively).