

## Medication adherence and treatment retention in youth with Opioid Use Disorder

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### ABSTRACT (250/250 words)

The volatile opioid epidemic is associated with higher levels of opioid use disorder (OUD) and negative health outcomes in adolescents and young adults. Medications for opioid use disorder (MOUD) demonstrate the best evidence for treating OUD. Adherence to and retention in MOUD among adolescents and young adults, however, is incompletely understood. This systematic review examines the state of the literature regarding the association of age with adherence to and retention in MOUD using methadone, buprenorphine, or naltrexone among persons aged 10 to 24 along with related facilitators and barriers. The research team searched for all studies of MOUD that examined adherence, retention, or related concepts as an outcome variable where the sample included adolescents or young adults. Search criteria generated 10,229 records, which, after removing duplicates and conducting title/abstract screening, yielded 587 studies for full-text review. Ultimately, 52 articles met inclusion criteria for abstraction and 17 were selected for qualitative coding and analysis. This review found younger age to be consistently associated with shorter retention in the published literature, although the overall quality of included studies was low. Several factors at the individual, interpersonal, and institutional levels, such as concurrent substance use, MOUD adherence, family conflict, and MOUD dosage and flexibility, were seen as playing a role in MOUD retention among adolescents and young adults. This review highlights how MOUD providers can tailor treatment to increase retention of adolescents and young adults while pointing to the need for more research explaining MOUD adherence and retention disparities in this age group.

**KEYWORDS:** Adolescents, Young Adults, Medications for Opioid Use Disorder, Opioid Use Disorder, Methadone, Buprenorphine, Naltrexone, Retention

**ABBREVIATIONS:** low- and middle-income countries (LMIC), medications for opioid use disorder (MOUD), opioid use disorder (OUD).

### INTRODUCTION

Opioid misuse has quickly become a major public health concern globally. Most high-income countries already see epidemic rates of opioid misuse, and rates are growing in low- and middle-income countries (1). The most recent Global Burden of Disease Study (2) estimates that opioid dependence is the most common substance use disorder worldwide after alcohol use disorder and poses a considerable burden in the form of disability-adjusted life years, responsible for 86,200 deaths and 3,656,100 years of life lost.

Opioid misuse is growing among young people between the ages of 10 and 24, especially in high income countries, mainly due to increasing availability and non-medical use of prescription opioids (3, 4). This population is especially vulnerable to negative consequences of opioid

misuse, developing dependence faster than adults as a result of being in a life period critical for cognitive, emotional, and social development (5).

Medications for opioid use disorder (MOUD) are the most effective treatment for chronic opioid use disorder, and includes pharmacotherapies like methadone, buprenorphine and naltrexone, all of which work on the mu opioid receptor (6). Both methadone and buprenorphine act as opioid agonists, activating the mu opioid receptor and alleviating opioid withdrawal. Unlike methadone, which is a full agonist, buprenorphine is a partial agonist, which means it has a ceiling effect, limiting it from producing the same effects as a full agonist and resulting in a lower likelihood of producing euphoria and of causing opioid overdose and other negative effects associated with opioid consumption. Naltrexone, on the other hand, is an opioid antagonist, which means that it blocks the mu opioid receptor, preventing opioids from taking effect if used. As such, rather than alleviate opioid withdrawal, naltrexone functions to prevent relapse (7).

In both industrialized and developing countries, MOUD consistently curtail the negative health, social, and legal consequences of opioid use disorder (8, 9). More specifically, MOUD reduce opioid use and subsequent risk of HIV and hepatitis C transmission, while improving mental health and reducing drug-related and all-cause mortality (3, 9-14). Despite their remarkable success, MOUD remain either absent or inadequately scaled-to-need in most countries (1, 15, 16). Despite recommendations of optimal MOUD coverage of 40%, with minimal effective coverage as 20%, as few as an estimated 16 persons per 100 persons who inject drugs receive MOUD globally with high variability observed (1, 16).

The evidence base demonstrating the effectiveness of MOUD among adolescents and young adults is limited and mostly focuses on buprenorphine (17); that said, multiple international agencies, professional groups, and other institutions, such as the World Health Organization and the American Academy of Pediatrics (18, 19), recommend the use of MOUD for individuals in this age group. Despite these recommendations, many young people with opioid use disorder still lack access to medications for opioid use disorder (20-22). Even when they are able to access MOUD, young people still experience challenges with adherence to and retention in MOUD (23, 24). As such, there is an urgent need to identify the factors causing young people to prematurely drop out of MOUD.

Previous systematic reviews have explored the factors associated with MOUD initiation and outcome among young persons (25, 26) or have explored barriers to retention in MOUD – defined as continuous engagement in treatment – among the general population (27, 28). None, however, have examined specifically which factors are responsible for adherence to and retention in medications for opioid use disorder among young persons. In addition, a global perspective on this issue, which could highlight different approaches and their effectiveness depending on the social context, development status, and policies and procedures related to MOUD, is also lacking. Here, we review the research on the influence that age has on adherence to and retention in medications for opioid use disorder among adolescents and young adults globally.

## METHODS

The research team conducted a systematic review of all studies of medications for opioid use disorder including evidence of adherence, retention, or related concepts (e.g., compliance, dropout, attrition) as an outcome variable where individuals between the ages of 10 and 24 –

consistent with the definition of young people used by the World Health Organization and other international agencies (4) – were part of the study sample. Adherence was defined primarily by continued consumption of MOUD. Adherence (also called compliance) is sometimes measured through attendance, especially in methadone programs where consumption is observed. Other times, it is confirmed through urinalysis, which can test for metabolites of MOUD. Retention was defined by uninterrupted engagement in treatment, operationalized in a variety of ways, such as by attendance at program appointments or renewal of prescriptions. According to this definition, retention could be defined as specific time points (e.g., at three months or one year) or as the time from treatment initiation to dropout. As may be evident from the latter measurement, retention in MOUD is also sometimes defined by its opposites- treatment attrition or dropout. These definitions were used in order to broadly capture the full scope of studies examining these concepts as treatment outcomes. Standard definitions for these terms in the context of MOUD were not found in other systematic reviews on the topic.

The methods used for this review are largely summarized in the PROSPERO protocol (29). A search strategy was tested against a set of validation articles, then used in seven bibliographic databases: CINAHL, Criminal Justice Abstracts, EMBASE, Medline via Ovid, PsycINFO, Scopus, and Web of Science Core Collection. Similar search strategies were used in each database, adjusted for the subject headings available in each database's controlled vocabulary schema. The searches took place at between December 20, 2018 and January 3, 2019.

We searched for articles using title-abstract keywords and (where available) controlled vocabulary for four concepts: the population of adolescents and young adults, opioid use disorder, medications for opioid use disorder, and adherence or retention (Web Appendix). In databases with subject indexing, animal studies that did not involve human subjects were excluded. No language or date restriction was applied.

After removing as many duplicate articles as possible, title/abstract review was conducted to identify potentially relevant studies. Inclusion criteria required articles to: focus on medications for opioid use disorder; include data on adherence, retention, or related concepts as an outcome among individuals aged ten to twenty-four years (or people identified by the authors as adolescents or young adults); be an original, peer-reviewed research article; provide original data (i.e., commentaries, editorials, letters, opinions, and reviews are excluded); and have been published in a peer-reviewed journal. No publication date restriction was applied and only studies published in Bosnian, Croatian, English, Italian, Montenegrin, Russian, Serbian, or Spanish were included in the final review. These languages were selected based on the fluency of the members of the research team, which viewed including articles in as many languages as possible as important so as to include research studies from non-English-speaking countries, given the international focus of this review. Covidence was used for both title/abstract and full-text review. Disagreements around inclusion of articles in title/abstract or full-text review was resolved by a third member of the research team.

The research team systematically searched the grey literature such as relevant government websites (e.g., National Institute on Drug Abuse, Substance Abuse Mental Health Services Administration, United Nations Office of Drugs and Crime), and provider organizations (e.g., American Academy of Pediatrics, American Society of Addiction Medicine) for any documents

or data they may provide. Google Scholar was used to identify validation articles in order to ensure quality of the review.

From all relevant sources, the research team extracted data related to adherence to or retention in MOUD among young persons as defined earlier or data on the association between age and these outcomes. Information about the research study and covariates was also collected.

Two members of the research team were required to agree on study inclusion during both title/abstract review and full-text review. Members of the research team individually extracted data, which was double-checked by another member of the research team to ensure quality of data extraction. Two members of the research team conducted qualitative coding with a subset of the final articles that focused solely on adolescents and young adults; this coding was reviewed and analyzed by a third member of the research team, who developed themes based on an adapted version of the Social Ecological Model (30), a framework for organizing factors that affect behavior into nested levels. This framework was selected due to the way it represents the relationships between the individual, interpersonal, institutional, and structural factors that may influence adherence to and retention in MOUD among adolescents and young adults. Quality assessment was conducted independently by a pair of researchers using the Grading of Recommendations Assessment, Development, and Evaluation system and guidelines (31, 32). Citation analysis was conducted on 4/8/2019 on this final subset of 17 articles using Web of Science Core Collection to identify papers which cited those included articles. After deduplication of that set, 181 citations remained. Those citations were processed through title abstract review and full text screening. None of the studies identified met inclusion criteria and so no additional articles were added to the synthesis.

## RESULTS

The initial search yielded 10,229 articles, of which 5,896 were immediately identified as duplicates. The title and abstracts of a total of 4,333 articles were screened against inclusion criteria, leaving 683 articles for full-text review. A total of 52 articles were included in qualitative synthesis after full-text review as they included adolescents or young adults in the sample and examined the relationship between age and retention either continuously or in a categorical way in which the results specific to this age group could be examined. Seventeen articles focused on adolescents and/or young adults specifically; the results from these studies were coded and analyzed qualitatively. Figure 1 presents the flow of studies through the review according to PRISMA guidelines (33).

Over half of the included studies had been conducted in the United States (n=30). The majority of the other studies were conducted in other high-income countries like Australia (n=4), Ireland (n=3), Canada (n=2), France (n=2), Israel (n=1), Italy (n=1), Norway (n=1), and Switzerland (n=1). Only 7 studies were conducted in low- and middle-income countries (LMIC), including three studies in India and one each in Afghanistan, Tanzania, Turkey, and Ukraine.

Over a third of the included studies assessed adherence to or retention in buprenorphine only (n=21) or methadone only (n=16). Four studies assessed retention in treatment with naltrexone only, two with oral naltrexone and two with injectable naltrexone. Some studies assessed both methadone and buprenorphine (n=8), buprenorphine and injectable naltrexone (n=1), methadone and oral naltrexone (n=1), or all three together (n=1).

No other studies were identified through additional grey literature searches. Information about the 52 articles included in qualitative synthesis can be found in Table 1 below.

#### Relationship between age and retention

The majority of the 35 studies that examined age as a predictor of retention found that adolescents and young adults are at increased risk of dropout from MOUD treatment ( $n = 20$ , 57.1%). One study by Chaudhry and colleagues did initially find younger age to be associated with increased retention in MOUD; however, multivariate analysis determined this association to be due to confounding variables (34). The study by Cousins et al. (35) found younger age to be associated with longer retention in MOUD even after adjusting for other variables, with individuals aged 40 to 65 years having 25% greater odds of discontinuing MOUD compared with individuals aged 16 to 19 years. Almost one-third of studies ( $n = 11$ , 31.4%) found age not to be statistically significant predictors of adherence or retention in MOUD among adolescents and young adults (34, 36-45). All of these studies either were conducted in LMIC or had a low sample size (largest sample size outside of studies done in LMIC,  $n = 981$ ) (36).

#### Quality assessment

The quality of the articles exploring the association between age and retention in MOUD was low according to the guidelines outlined in the Grading of Recommendations Assessment, Development, and Evaluation system (32). This was mostly due to the fact that few of the studies in included articles were randomized controlled trials. Overall, the researchers who conducted quality assessment agreed that the studies, as a group, demonstrated low risk of overall bias and no evidence of publication bias. Indirectness was not seen as an issue in these studies. A moderate degree of inconsistency was observed across study findings, though it is notable that the studies that found no evidence of association between age and retention in MOUD were of lower quality and exhibited a greater degree of imprecision than the studies that observed a positive association between age and retention in MOUD due largely to differences in sample sizes between the two sets of articles. The articles that found older age to be associated with longer retention ( $n = 20$ ) averaged a sample size of almost 5,000 participants while the articles that observed no significant association between age and retention ( $n = 11$ ) had an average sample size that was over seven times smaller at 709 participants. As such, it is possible that some of the articles that found no association between age and retention did not have sufficient sample size to find significant results.

Only one found lower age to be correlated with increasing retention (35). Of the remaining three articles, one focused on adherence as an outcome (46), one found mixed results by gender (47), and the last found mixed results based on the time frame, identifying a positive association between age and retention at six months that was no longer significant at 12 months (48). None of these studies were included in either of the subgroups in quality assessment. The results of quality assessment are presented in Table 2 below.

#### Relationship between age and MOUD retention by MOUD type

The relationship between age and retention in MOUD was explored stratified by MOUD type (i.e., methadone, buprenorphine, naltrexone). After excluding the studies with mixed findings described earlier, a total of 20 studies examined this relationship for methadone, 15 for buprenorphine, and 2 for naltrexone. The sum of the studies listed here is greater than the total number of studies examining the relationship between age and retention in this subgroup analysis ( $n=32$ ) as six of these studies included more than one MOUD type, though the article

by D'Ippoliti and colleagues (49) only explored the relationship between age and retention for those patients on methadone and not for those on naltrexone.

Of the 20 articles that looked at the relationship between age and retention for individuals on methadone, three-quarters (75.0%) found a positive association, with older age corresponding to a greater likelihood of retention in MOUD, though one study found a negative association (5.0%). Of the 15 studies exploring this relationship among individuals on buprenorphine, two-thirds (66.7%) found a positive association between age and retention. Finally, both of the studies examining the relationship between age and retention in individuals on naltrexone found no significant association.

#### Relationship between age and MOUD retention by measurement of retention

The relationship between age and retention in MOUD was explored with relation to the length of retention measured in the study to see if studies measuring retention at longer durations of time found different results related to the association between age and retention. Of the 32 studies that did not present mixed results, one-third (34.4%, n=11) measured retention using a time frame of less than 12 months and one-quarter (25.0%, n=8) measured retention using a time frame of greater than 12 months; the remaining studies (40.6%, n=13) measured retention using a time frame of exactly 12 months or its equivalent (e.g., 52 weeks).

Similar percentages of studies that measured retention using a time frame of less than 12 months or 12 months found a positive association between age and MOUD retention (63.6% and 61.5%, respectively); the remaining studies found no significant association between age and retention in MOUD. A larger percentage of studies that measured retention using a time frame of greater than 12 months found a positive association between age and MOUD retention (75.0%); the only study to find a negative association between age and MOUD retention also used a time frame of greater than 12 months (35).

#### Relationship between age and retention by treatment of age

The relationship between age and retention was further explored to see if this relationship varied based on whether age was treated as a continuous or categorical variable. Of the 28 studies included in this analysis, over half (n=16; 57.1%) treated age as a continuous variable while the remainder treated age categorically. Four studies were excluded because it was not clear from their discussion of the analysis how age was treated; all but one of these studies found no significant association between age and retention.

Among those studies that treated age continuously, nearly two-thirds (62.5%) found a positive association between age and retention in MOUD. A larger percentage of studies that treated age categorically (83.3%) found a positive association between age and MOUD retention. The one study that found a negative association between age and MOUD retention also treated age categorically.

#### Qualitative coding and analysis

Qualitative coding and analysis were conducted with a subset of 17 articles that had data segregated by age for adolescents and young adults, either as defined by the author or based on the age range of 10 to 24 years. All of these articles explored retention in medications for opioid use disorder among adolescents and young adults, so the coding focused on factors related to retention (to the exclusion of adherence). After coding, the findings from these studies were thematically organized using Bronfenbrenner's Social Ecological Model (30). A total of sixteen codes were used, which were grouped into themes according to three levels:

individual, interpersonal, or institutional; no factors at the community or societal levels were observed. Individual-level themes included age, adherence to MOUD (as a predictor of retention), demographics other than age (i.e., gender, race/ethnicity), drug use (both past and current), physical health, psychiatric comorbidity, and treatment history for substance use disorders. Interpersonal themes encompassed relationships with others, including family members and intimate partners. Institutional themes focused on aspects of the MOUD program itself and included treatment modality, dose, structure, and timeliness (Figure 2).

At the individual level, age was not consistently associated with retention when looking only at adolescents and young adults. Two studies found age to be unrelated to retention (50, 51), one found younger age and retention to be negatively related (52), and another study found younger age and retention to be positively related (53). This contrasts with the earlier trend seen in studies with samples that included older adults, which consistently observed that age was positively related to retention. This may be due to greater homogeneity within the adolescent and young adult age group or a non-linear relationship between age and retention, though it's important to note that the article by Vo and colleagues (51) compared participants under age 24 with a separate sample of individuals ages 24 and older and found no significant association between age and retention.

Study results were similarly inconsistent when exploring the associations between race, gender, and retention. One study found no association between either race or gender and retention (53) and two other studies (51, 54) presented opposite results with respect to the association between gender and retention. It is possible that these results are attributable to differences in the age ranges of participants with participants in the study described by Vo and colleagues older than those in the other two studies; however, the type of medication used might play more of a role in the difference in results.

The research showed a consistent relationship between drug use and retention. Three studies (53-55) found that opioid use during treatment was negatively associated with retention while one of these studies (55) also found that hallucinogen use during treatment was negatively associated with retention. Two studies (54, 55) found adherence to medications for opioid use disorder to be positively related to retention. The research exploring the associations of physical health issues (50, 55) and treatment history (50, 56) with retention demonstrated mixed results, with one study finding these variables to be positively associated to retention and a second study finding a negative association between the two. Finally, psychiatric comorbidity was found in one study (50) to be positively associated with retention.

At the interpersonal level, stressful family situations, such as drug use among immediate family members (57), being raised in a single-parent household, or having a child (58) were all negatively associated with retention. On the other hand, being in an intimate relationship with someone with a history of heroin use was found to be positively associated with retention (58).

At the institutional level, three studies found the type of medication used to be unrelated to retention (51, 58, 59); however, this is contrasted by the results of two studies (20, 60) showing greater retention among individuals in methadone-based treatment compared to individuals in buprenorphine-based treatment. Results were not consistent when looking at the relationship between treatment dose and retention. One study (50) found a higher dose of buprenorphine dose to be associated with longer retention while another (57) found it to be negatively

associated with retention. Finally, timely provision of treatment was also positively associated with retention (20).

## DISCUSSION

This systematic review was conducted to assess the state of the literature on the factors associated with adherence and retention to medications for opioid use disorder among adolescents and young adults experiencing opioid use disorder, a population often identified as at heightened risk for dropout from such treatment. Many studies examining adherence or retention in MOUD that include adolescents and young adults fail to account for the possible association with age. Of the 631 articles that were excluded after full-text review, one-third (33.1%) failed to focus explicitly on adherence or retention among young persons or accounted for associations with age in their analysis while including adolescents or young adults in the total sample. Many of these studies represented age categorically in analyses, using age groups that were too broad for meaningful analysis of the relationship between adolescent or young adult status and retention in MOUD and too inconsistent for comparison of associations across studies. Other studies controlled for the possible association with age using statistical comparison of mean ages across groups. This does not, however, fully control for the possible association between age and retention, especially if the age range is skewed. Only one study – by Guillou Landreat and colleagues (46) – looked at adherence as an outcome.

This review found that adolescents and young adults with opioid use disorder demonstrate heightened risk for dropout from medications for opioid use disorder in over half of included articles. While a third of included studies did not find an association between younger age and increased risk of dropout from MOUD, the overall quality of these studies was lower. The studies in this group with higher sample sizes tended to be conducted in LMIC (37, 42, 44). This may point to the presence of potentially confounding contextual or structural factors specific to LMIC settings, such as cultural differences in attitudes towards substance use in younger age groups or different levels of acceptability or policy standards with respect to the use of medications for opioid use disorder among adolescents and/or young adults. Differences in the operationalization of retention in MOUD may also play a role in this discrepancy; the study by Armstrong et al. (42), for example, looked at departure from MOUD due specifically to relapse as an outcome rather than retention or attrition from MOUD more generally. It is also possible that these studies indicate that there are other confounding factors responsible for the observed relationship between older age and increasing retention; for example, Del Rio, Mino, and Perneger (43) found no association between age and retention after controlling for duration of opioid use. Finally, Perreault and colleagues (40), who did not find a significant association between age and retention, hypothesize that this may be due to “[d]ifferences in sampling”.

Only two of the included studies found that adolescents and young adults have longer retention in MOUD than older adults. Of these two, the one by Chaudhry and colleagues (34), while initially finding an association between younger age and longer retention, determined that this association was due to the presence of confounding variables. This was corrected by the authors’ multivariate analysis and their final results were consistent with those of most of the other papers included in our sample. The other study, by Cousins et al. (35), may have neglected to control for important confounders, such as duration of drug use history.

Stratifying by MOUD type (i.e., methadone, buprenorphine, and naltrexone) revealed that the evidence for a positive association between age and MOUD retention is fairly consistent for both methadone and buprenorphine, with a majority of studies for both medications (75.0% and 66.7%, respectively) finding such a relationship. Neither of the studies examining the relationship between age and retention for naltrexone found a significant association, which points to the need for more studies examining retention in naltrexone maintenance to explore the association with age and to include adolescents and young adults in the sample.

Exploring the relationship between age and retention in MOUD stratified by how retention was measured yielded similar results. A majority of the studies that measured retention using a time frame of less than 12 months or exactly 12 months found a positive association between age and retention in MOUD (63.6% and 61.5%, respectively). A larger percentage of studies that measured retention using a time frame greater than 12 months found a positive association between age and retention in MOUD (75.0%); however, only 8 (25%) of studies included in the subgroup analysis used a time frame greater than 12 months. This highlights the need for more studies examining retention in MOUD beyond 12 months among adolescents and young adults.

Similar percentages were observed when looking at whether the relationship between age and retention varied by whether age was treated continuously and categorically. While just under two-thirds (62.5%) of studies that treated age continuously in analysis found a positive association between age and retention, a higher percentage (83.3%) of those that treated age categorically in analysis found a positive association. This points to the possibility of a non-linear relationship between age and MOUD retention.

Few studies (n = 17; 6%) exploring retention in MOUD as an outcome focused on adolescents or young adults specifically, allowing for an analysis of the facilitators of and barriers to adherence and retention in MOUD in this population. The results of the qualitative analysis of this group of articles demonstrated that the relationship between age and retention did not stay constant when assessing the association between age and retention within adolescents and young adults, suggesting some level of homogeneity within this age group or a non-linear relationship between age and retention. Qualitative analysis revealed a number of factors at different levels that are associated with retention in MOUD among adolescents and young adults, but it is also important to note the factors that were absent from analysis and were not seen in any of the included research studies, such as individual behaviors, socioeconomic status, the role of social networks, or structural factors related to MOUD accessibility and availability. Additional research exploring the possible role of these factors in adherence to and retention in MOUD among adolescents and young adults would help to inform strategies to better engage this group in treatment.

The most consistently observed association in this review that younger age is linked to lower rates of retention was also seen in other systematic reviews on the topic of retention in MOUD (28). Of the final included articles in Brorson and colleagues' (28) 2013 systematic review of risk factors for dropout from MOUD, younger age was the most frequently cited risk factor for MOUD dropout. Unlike in the present review's final sample, Brorson, et al. did not find any articles that contradicted this relationship; indeed, of all risk factors, younger age was the only factor that consistently predicted dropout. Similarly, the observation from qualitative synthesis that youth on methadone seem to experience better retention than youth on buprenorphine or naltrexone is consistent with the findings in the reviews by Hopfer and

colleagues (26), Minozzi and colleagues (25), and Timko and colleagues (27). This paper adds to the findings of these previous reviews by exploring the factors that are possibly responsible for the shorter retention in MOUD seen among adolescents and young adults. While it is not possible to draw any definitive statements from the quantitative synthesis in this review, it does point to factors that merit more exploration in future research studies. Future research, especially qualitative and mixed methods research, should explore possible factors that explain the relationship between younger age and increased dropout from MOUD. Higher quality research studies exploring adherence to and retention in MOUD and that stratify by age groups to compare adolescents and young adults with older adults would also add to the literature significantly. These findings also point to the need for standardization in the approach to age-based analyses in quantitative research on MOUD adherence and retention where the sample includes adolescents and young adults. Finally, these findings indicate that providers of medications for opioid use disorder should consider tailored approaches to retain adolescents and young adults in treatment. At the individual and interpersonal levels, this would include screening and referral services for factors that might compromise retention, such as concurrent drug use, physical health, psychiatric comorbidity, or family stress and conflict. At the institutional level, MOUD providers should ensure that adolescents and young adults receive adequate dosing of medication and should adjust policies and procedures so that younger program participants have opportunities for more flexible dosing and pick-up schedules.

#### LIMITATIONS

This review faces the same limitation addressed by Brorson et al. (28), in that differences in the operationalization of retention, and the differences in reason for dropout, may act as a confounder of our observations. LMIC are underrepresented in our final sample of articles, while the United States is overrepresented. Studies conducted in LMIC that included adolescents and young adults and would otherwise meet our inclusion criteria did not segregate their data by age group, nor did they assess the associations between age and adherence or retention in MOUD; instead, these studies tended to focus on clinical process improvement (e.g., Hasečić) (61), demonstrating different research priorities compared to studies done in high-income countries. Few qualitative studies explore adherence and retention in MOUD in this age group. As such, the existing body of research shows an association between age and adherence/retention without exploring the specific factors responsible for lower rates of adherence and retention among adolescents and young.

The quality of the articles included for quantitative analysis and synthesis in this review were overall of low quality according to Grading of Recommendations Assessment, Development, and Evaluation standards. More high-level research studies, especially randomized controlled trials, are needed to boost the level of evidence around the association between age and retention in MOUD.

A total of 22 articles were excluded because they were in languages not spoken by any of the reviewers (Chinese, French, German, Norwegian, Persian, and Swedish). Given the international focus of this review, the review team worked to ensure that they could review articles in as many languages as possible but were unable to cover the languages of all potentially eligible articles. Additionally, EMBASE introduced indexing for adolescents late and their subsequent indexing is not as sensitive as the Medline indexing for this concept, so it is

possible that some articles where adolescents were part of the sample were overlooked in this review due to this limitation.

**CONCLUSION**

This review upholds the association seen in previous reviews that adolescents and young adults experience shorter retention in MOUD than individuals in older age groups. Studies that explore retention in MOUD as an outcome and that include adolescents or young adults in their sample should adequately stratify their findings or otherwise account for the possible difference in retention in this age group. Much of the challenge in drawing definitive conclusions in this review was due to the lack of a standardized definition of concepts such as “adolescent”, “young adult”, “adherence”, and “retention”; as such, the research community should develop and use standardized definitions for different age groups of interest as well as for the concepts of adherence and retention, in order to facilitate comparison across large groups of studies. More studies, especially randomized controlled trials and qualitative and mixed methods studies are needed that explicitly look at what mechanisms are at play that lead adolescents and young adults to drop out of MOUD earlier. Individual, interpersonal, and institutional factors, such as concurrent drug use, family conflict, and MOUD dosage and flexibility, play a key role in moderating or mediating this relationship and suggest possible avenues for better tailoring MOUD to meet the needs of this age group. It is clear that adolescents and young adults experience unique needs when it comes to continued engagement in MOUD and this review highlights the main factors that should be addressed.

Table 1. Final Articles Analyzing Adherence and/or Retention, Stratified by Age

<b>First Author, Year (Reference Number)</b>	<b>Country</b>	<b>Number of Participants</b>	<b>Study Design</b>	<b>Type of MOUD</b>	<b>Max Retention Time Frame</b>	<b>Age-related Findings</b>
Anderson 2004 (62)	Canada	5087	Program evaluation	Methadone only	12 months	Older age was associated with longer retention.
Armstrong 2010 (42)	India	2569	Operational research	Buprenorphine only	1 year	Age was not significantly associated with retention.
Babst 1971 (47)	USA	679	Secondary analysis of program data	Methadone only	2 years	Older age was associated with longer retention in men and

						with shorter retention in women.
Bartu 2002 (36)	Australia	981	Retrospective cohort study	Oral naltrexone only	87 weeks	Age was not significantly associated with retention.
Bell 2006 (60)	Australia	61	File review	Methadone, buprenorphine	185 days	All participants in the study were adolescents.  Methadone maintenance was more effective than buprenorphine at retaining adolescents in treatment.
Burns 2009 (63)	Australia	42,690	Retrospective cohort study	Methadone, buprenorphine	9 months <sup>a</sup> ; 12 months	Older age was associated with longer retention and had the largest association with retention.
Burns 2015 (64)	Australia	15,600	Retrospective cohort study	Methadone, buprenorphine	12 months	Older age was associated with longer retention.
Chaudhry 2012 (34)	USA	142	Retrospective cohort study	Oral naltrexone only	17+ weeks <sup>a</sup> ;	Older age was associated

					53-72+ weeks	with shorter retention, but this relationship did not remain so after adjusting for potential confounders .
Condelli 1993 (65)	USA	526	Secondary analysis of prospective study data	Methadone only	1 year	Older age was associated with longer retention and was the only significant predictor.
Cousins 2017 (35)	Ireland	6393	Retrospective cohort study	Methadone only	≥1 year	Older age was associated with shorter retention.
Damian 2017 (66)	USA	445	Retrospective cohort study	Buprenorphine only	90 days	Older age was associated with longer retention.
Dayal 2017 (57)	India	68	Retrospective cohort study	Buprenorphine only	1 year	All participants in the study were young adults.  Close family member substance use and buprenorphine dose were associated

						with shorter retention while recent history of injection drug use was positively associated with longer retention.
Deck 2005 (67)	USA	5308	Retrospective cohort study	Methadone only	1 year	Older age was associated with longer retention.
Del Rio 1997 (43)	Switzerland	111	Prospective cohort study	Methadone only	54 months	Older age was associated with longer retention, but only at the univariate level. Age was not significantly associated with retention in multivariate analysis.
Dhawan 2013 (37)	India	231	Intervention study	Buprenorphine only	9 months <sup>a</sup>	Age was not significantly associated with retention.
D'Ippoliti 1998 (49)	Italy	1503	Retrospective cohort study	Methadone, oral naltrexone	12 months	Older age was associated with longer retention and was the only

						demographic variable associated with retention.
Dumchev 2017 (44)	Ukraine	2916	Secondary analysis of clinical data	Methadone, buprenorphine	12 months	Age was not significantly associated with retention.
Dupouy 2013 (68)	France	1507	Retrospective cohort study	Methadone, buprenorphine	30 months	Older age was associated with longer retention.
Fishman 2010 (69)	USA	16	Retrospective chart review	Injectable naltrexone only	4 months	All participants in study were adolescents and young adults.  Factors associated with adherence or retention were not explored in study.
Gonzalez 2015 (59)	USA	80	RCT	Buprenorphine only	13 weeks	All participants in the study were young adults.  No differences in retention between group treated with memantine

						vs. group treated with buprenorphine/naloxone .
Grella 1997 (70)	USA	462	Experimental study	Methadone only	24 months	Older age was associated with longer retention.
Gryczynski 2012 (38)	USA	181	Prospective cohort study	Methadone only	12 months	Age was not significantly associated with retention.
Guillou Landreat 2014 (46)	France	67	Prospective cohort study	Buprenorphine only	10 years	Older age was associated with higher adherence.
Haddad 2013 (48)	USA	266	Retrospective cohort study	Buprenorphine only	6 months <sup>a</sup> ; 12 months <sup>a</sup>	Older age was associated with longer retention at six months, but not at 12 months.
Hadland 2018 (20)	USA	4837	Retrospective cohort study	Methadone, buprenorphine, oral or injectable naltrexone	1 year	All participants in the study were adolescents or young adults.  Timely receipt of treatment associated with longer retention; retention

						longer among group receiving methadone vs. groups receiving buprenorphine or naloxone
Hser 2014 (71)	USA	1267	RCT	Methadone, buprenorphine	24 weeks	Older age was associated with longer retention.
Joe 1975 (72)	USA	4,981	Secondary analysis of program data	Methadone only	12 months	Older age was associated with longer retention in methadone maintenance- adaptive (indefinite methadone maintenance).
Kellogg 2006 (53)	USA	147	Retrospective cohort study	Methadone only	12 months	All patients in the study were adolescents or young adults.  Age and consistent heroin use were associated with shorter retention; gender and race were

						unrelated to retention.
Kornor 2006 (56)	Norway	75	Experimental study	Buprenorphine only	9 months	All patients in the study were young adults.  Fewer previous treatment episodes was related to longer retention.
Kumar 2016 (39)	USA	113	Retrospective chart review	Buprenorphine only	90 days	Age was not significantly associated with retention.
Lambdin 2014 (73)	Tanzania	629	Retrospective cohort study	Methadone only	12 months	Older age was associated with longer retention.
Lee 2017 (74)	USA	139	Secondary analysis of RCT	Buprenorphine only	6 months	Older age was associated with longer retention.
Lo-Ciganic 2018 (75)	USA	2,361	Retrospective cohort study	Buprenorphine only	52 weeks	Older age was associated with longer retention.
Marcovitz 2016 (24)	USA	202	Retrospective chart review	Buprenorphine only	3 months	Older age was associated with longer retention.
Matson 2013 (76)	USA	185	Retrospective chart review	Buprenorphine only	≥5 months	All participants in the study

						<p>were adolescents.</p> <p>Factors associated with adherence or retention were not explored in this study.</p>
Matson 2014 (54)	USA	103	Retrospective cohort study	Buprenorphine only	1 year	<p>All participants in the study were adolescents or young adults.</p> <p>Female sex, negative urine drug screen for opioids or for marijuana, positive urine drug screen for buprenorphine/naloxone were all associated with longer retention.</p>
Mutlu 2016 (50)	Turkey	112	Retrospective cohort study	Buprenorphine only	1 year	<p>All participants in the study were adolescents.</p> <p>Buprenorphine/naloxone dose, length</p>

						of inpatient treatment, duration of program retention, and comorbid psychiatric disorder were associated with longer retention; age of admission was not associated with retention; elevated liver enzymes associated with better short-term retention but worse long-term retention.
Perreault 2015 (40)	Canada	106	Prospective cohort study	Methadone only	12 months	Age was not significantly associated with retention.
Romero-Gonzalez 2017 (77)	USA	63	Secondary analysis of RCT	Buprenorphine only	8 weeks	All participants in the study were young adults.  No difference in retention between

						heroin users vs. prescription opioid users.
Ruisenor-Escudero 2015 (78)	Afghanistan	83	Cross-sectional study	Methadone only	18 months	Older age was associated with longer retention.
Samples 2018 (79)	USA	17,329	Retrospective cohort study	Buprenorphine only	180 days	Older age was associated with longer retention.
Saxon 1996 (80)	USA	353	RCT	Methadone only	24 weeks	Older age was associated with longer retention.
Schiff 2007 (81)	Israel	2,683	Retrospective chart review	Methadone only	13 months	Older age was associated with longer retention. The interaction of age and gender was not found to be statistically significant.
Schuman-Olivier 2014 (52)	USA	294	Retrospective chart review	Buprenorphine only	3 months <sup>a</sup> ; 12 months <sup>a</sup>	All participants in the study were adolescents or young adults. Older age was associated

						with longer retention.
Smyth 2012 (82)	Ireland	100	Retrospective cohort study	Methadone, buprenorphine	12 months	All participants in the study were adolescents.  Males more likely to exit treatment because of incarceration.
Smyth 2018 (58)	Ireland	120	Retrospective cohort study	Methadone, buprenorphine	12 months	All participants in the study were adolescents.  Having children, coming from a single parent family, not being in an intimate relationship with another heroin user, and evidence of cocaine use just before treatment entry were associated with shorter retention; no difference among

						those treated with methadone vs. buprenorphine.
Soeffing 2009 (45)	USA	255	Retrospective cohort study	Buprenorphine only	12 months	Age was not significantly associated with retention.
Vo 2016 (51)	USA	56	Retrospective chart review	Buprenorphine , injectable naltrexone	24 weeks	All participants in the study were adolescents or young adults.  No difference in retention those between under age 24 and those age 24 and older or between those treated with buprenorphine vs. naltrexone; males were retained in treatment longer.
Vo 2018 (83)	USA	14	Retrospective chart review	Injectable naltrexone only	16 weeks	All participants in the study were adolescents

						<p>or young adults.</p> <p>Better adherence and retention were both associated with home-based delivery vs. clinic-based, but no statistical analysis done due to low N.</p>
Warden 2012 (55)	USA	152	RCT	Buprenorphine only	12 weeks	<p>All participants in the study were adolescents or young adults.</p> <p>Adherence, early opioid negative urines, use of any medications in the month prior to treatment entry, and lifetime non-heroin opioid use were associated with longer retention;</p>

						prior 30-day hallucinogen use was associated with shorter retention
Weinstein 2017 (23)	USA	1237	Retrospective cohort study	Buprenorphine only	≥1 year <sup>a</sup> ; ≥2 years <sup>a</sup>	Older age was associated with longer retention.
Wilder 2017 (41)	USA	189	Retrospective cohort study	Methadone only	60 days	Age was not significantly associated with retention

Abbreviations:

MOUD: medications for opioid use disorder; RCT: randomized controlled trial

<sup>a</sup>When multiple time frames are given for the length of follow-up, an (a) marks the time frame for analysis of the relationship between age and retention. In cases where multiple time frames are included but none are highlighted with an asterisk, then survival analysis (usually Cox proportional hazards regression analysis) was conducted using the length of time from treatment initiation to dropout for each study participant.

Table 2. Quality Assessment of Articles Exploring the Relationship Between Age and Retention in MOUD

Article Results	No. of Studies	No. of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Grade
Exploring relationship of age with retention	35	3	Low	Moderate	Not an issue	Some	Undetected	Low
Age was positively associated with retention	20	3	Low	None	Not an issue	Not an issue	Undetected	Low

Age was not associated with retention	11	0	Low	None	Not an issue	Very serious	Undetected	Very low
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Abbreviation: RCT, randomized controlled trial.

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