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REVIEW ARTICLE

The impact of benzodiazepine use on treatment retention in opioid agonist treatment: A literature review

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Abstract

It is well established that there is an elevated overdose risk with benzodiazepine (BZD) use during opioid agonist treatment (OAT). However, further studies regarding other aspects of how BZDs influence OAT are necessary. This review summarizes the literature on concurrent BZD use with medications for opioid use disorder (MOUD) and how they affect treatment retention in OAT. EMBASE (Ovid), PubMed, and Google Scholar database search tools were used to search for studies that examined the effect of concurrent BZD and MOUD on treatment retention in OAT. Studies published up to January 30th, 2024, were included with no restriction applied other than English language. The criteria for included literature were the presence of both BZD and at least one MOUD as a variable and treatment retention or MOUD adherence as an outcome. Fourteen articles met the criteria for review: eleven retrospective studies and three observational studies. Methadone was utilized in seven studies, buprenorphine in five, naltrexone in one, and suboxone (buprenorphine + naloxone) in one study. The included studies indicated that when BZDs are taken as prescribed and for shorter periods in conjunction with OAT, subjects are retained in their MOUD programs just as well as patients who do not take BZDs. Any potential benefits of increased treatment retention must be balanced against potential harmful effects of BZD use, such as drug overdose and addiction. Further studies must be performed to validate the results of treatment retention and to evaluate other factors that might affect OAT.

Keywords: Benzodiazepine; Opioid agonist therapy; Treatment retention

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1. Introduction

North America and many other parts of the word are currently in an opioid crisis,[1-3] which is compounded by comorbid conditions for many opioid users.[4-8] For patients with opioid use disorder (OUD), the standard of care includes opioid agonist treatment/therapy (OAT),[9] where medications for opioid use disorder (MOUD), such as methadone, buprenorphine and naltrexone are substituted in place of more potent and harmful opioids.[10-13] The use of MOUD can help alleviate withdrawal symptoms and/or cravings that can be experienced as a result of discontinuing opioid usage.[10,14,15] Furthermore,

OAT has demonstrated effectiveness in supporting long-term abstinence, aiding in rehabilitation, and lowering the risk of overdosing and relapse.[10,16,17]

Polysubstance use, both prescription and illicit, is extremely common during OAT.[18-21] The concurrent use of MOUD with benzodiazepines (BZDs) has raised concerns due to its high potential for abuse and dependence.[18] BZDs are a class of anticonvulsant/anxiolytic drugs that are prescribed to treat insomnia, anxiety, depression, muscle spasms, panic attacks and seizure disorders, many of which are common opioid withdrawal symptoms.[22,23] When BZDs are taken alone, overdose risk is minimal.[24] However, when taken alongside MOUD, both drugs act synergistically to enhance GABA receptor function, significantly increasing the risk of respiratory depression, opioid-related overdose and other substance-related overdose, hospitalization and death.[24-27] It has been reported that the mortality rate for concurrent administration of both medications is ten times higher than those taking only opioids.[28] The risk of respiratory depression, overdose and death can be exacerbated due to the prevalence of illicit BZDs laced with synthetic opioids.[29] As such, BZD use is often present in opioid overdoses, with one recent study identifying BZD use in 80% of fatal opioid overdoses.[30] Despite the increased overdose risk with BZD, they are often prescribed alongside OAT.[31] Current recommendations are for short-term BZD use, however, many patients consume BZDs illicitly, where the dose, frequency, and duration of BZD use are not defined or regulated.[31] In the face of increasing concerns over BZD use in OAT, the US Food and Drug Administration has stated that patients should not be turned away from OAT if they have a history of BZD use or are currently using BZD.[32]

Currently, the association between concurrent BZD and MOUD use and increased overdose risk is well established.[14,15,26] However, the association between BZD use and retention in OAT programs remains less well known. This literature review therefore aims to evaluate how the concurrent use of BZD and MOUD specifically influences treatment retention in OAT programs, which is an important part of recovery. In this review, we explore the impact of important variables in BZD use, including the prevalence of BZD use in the MOUD-using population, as well as BZD use at intake into the treatment program, licit versus illicit BZD use, frequency of BZD use, and where BZD prescribed use was considered as a variable in treatment outcomes.

We note however, *a priori*, that it is important to consider that any such benefits from improved treatment retention must be balanced against a possible greater risk of drug poisoning from BZDs when combined with MOUD and potential concurrent use of either licit or illicit opioids.

2. Methods

2.1. Search strategy

When selecting the articles for this review, the authors started by making a comprehensive selection of terms that could be used to describe opioids, OAT, BZDs, and treatment retention. These terms were chosen with the help of a university librarian and by looking through articles in PubMed and Google Scholar to see what terms were commonly used. For the final analysis, studies were searched for that reported the effect of concurrent BZD and MOUD on treatment retention in OAT. EMBASE, PubMed, and Google Scholar (Ovid) were searched for studies from inception until January 30, 2024. The search strategy used keywords that described opioids, BZDs, OATs, and treatment retention (Table 1).

Keywords included plural options whenever possible and were adapted to the requirements of the database. Additional studies were identified by searching the reference list of relevant publications and by using EMBASE, PubMed, and Google Scholar, as previously.[33,34] There were no limitations placed on language, year, age, sex, ethnicity, research location, or trial length during the literature search, but only studies in English were included. A study was included if it: involved both BZD and one of the MOUDs (methadone, buprenorphine, or naltrexone adherence) and treatment retention as one of the primary or secondary outcomes. All literature must have been published in a peer-reviewed journal. It is worth noting that in the title and abstract search, many of the articles lacked the treatment retention aspect of our search criteria. This was in part because the database matched a part of the terms that we included: "drug" in "drug adherence" or

Table 1. Search terms for literature review

Major category	Search terms
Benzodiazepine	Benzodiazepine(s), benzodiazepine dependence
Opioids	Opioid(s), opioid/opiate agonist, medication for opioid use disorder(s), MOUD(s), buprenorphine(s), buprenorphine plus naloxone, methadone(s), naltrexone(s)
Opioid agonist treatment	Treatment for opioid use disorder, opioid agonist treatment(s), buprenorphine treatment(s), methadone treatment(s), methadone maintenance treatment(s), medication assisted treatment(s), OAT(s), MAT(s), MMT(s)
Treatment retention	Treatment retention, treatment response(s), program retention(s), drug adherence(s), medication compliance(s)

"treatment" in "treatment retention" as two examples. As such, many of the selected articles were not included after the initial abstract reading.

2.2. Data extraction and analysis

Information taken from the studies included: author information, date of publication, journal of publication, location of study, study design, trial duration, sample size, subject demographics (age, sex, polysubstance use, and psychiatric comorbidities), MOUD used for treatment (and dose if available), definition of treatment retention, percentage of BZD users in each cohort, and methods for evaluating opioid and BZD use. We followed the definition of treatment retention provided in each study. Due to the large variability of each study's design and OAT program, we did not perform a meta-analysis of the study results. Instead, we provided a narrative summary of the key findings according to similarities in study design and methodology, as previously.[35-37]

3. Results

3.1. Search results and characteristics of studies

The search identified 141 publications and 136 articles were screened after removing duplicates (Figure 1).

Twenty-seven full-text articles were evaluated for eligibility. Fourteen papers were selected for analysis: eleven retrospective cohort studies and three observational studies. Table 2 outlines the main study design of each study, while Table 3 provides study characteristics about the subjects and the study location.

Methadone was used in seven studies, buprenorphine in five, naltrexone in one, and suboxone in one study. All studies utilized urine drug testing (UDT) to evaluate the presence of opioids, BZDs, and other substances at intake and/or during OAT. Some studies performed immunoassays to distinguish between different opioids, including whether they were illicit or prescribed. Statistical methods utilized to compare BZD's effect on OAT retention included Cox regression analyses, adjusted hazard-ratios, adjusted odds-ratios, and Z-scores.

3.2. BZD use within each study

Thirteen of the included studies reported on the percentage of BZD-positive patients within their cohort. The study by Ray-Griffith *et al.*[38] was the only included study that did not include this outcome. In the retrospective study by Morford *et al.*,[39] 18% of patients tested positive at intake. The retrospective cohort study by Brands *et al.*,[40] found that 70.9% of patients used BZD in the past year and 33% had consumed BZD for 30 out of the 90 days before treatment initiation. Similarly, the observational study by Durand *et al.*,[41] found that 65.5% of patients possessed a BZD prescription 90 days before treatment. In the retrospective cohort study by Franklyn *et al.*,[42] 15% of patients were BZD-positive at intake. The observational cohort study by Dayal *et al.*[43] noted that 16% of study patients used BZD. In the retrospective cohort study conducted by Hallowell *et al.*,[44] 18% of subjects were found to have overlapping BZD and buprenorphine prescriptions during a 12-month treatment period. In the retrospective study conducted by Schuman-Olivier *et al.*,[45] 48% of participants were found to

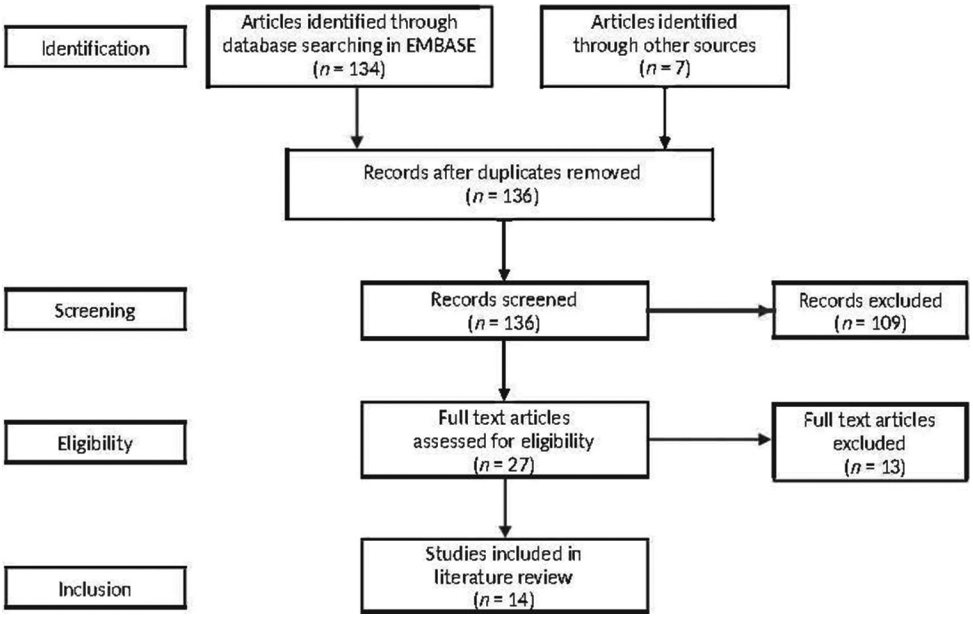


Figure 1. Flow design

Table 2. Study design

Study	Publication Year	Journal	Study Design and Methodology
Raffa *et al.*[47]	2007	*Drug Alcohol Dependence*	The primary outcome was methadone adherence. Methadone adherence was monitored through urine toxicology testing for methadone in addition to other opioids, BZDs, amphetamines, and cocaine. The schedule of urinalysis testing was not included. A patient was considered to have discontinued treatment if the records indicated no methadone doses between two scheduled urinalysis tests. Multiple linear regression analysis and two-term interactions were performed for each illicit drug class and any additional cofounders.
Brands *et al.*[40]	2008	*Journal of Addictive Diseases*	Patients were divided into 3 groups based on the nature of their BZD use: non-users, occasional users (<30 days of use during the 90 days before intake), and regular/problem users (more than 30 days). During intake, patients were surveyed and their demographics (age, sex, marital status, employment status, and education), opioid use history, and other drug history were recorded. For the first 3 months of treatment urine toxicology was performed twice a week. The frequency of drug screening following 3 months was left to the physician's discretion. Treatment retention of MMT was the primary outcome. Secondary outcomes consisted of BZD's effect on psychiatric morbidity, opioid reduction, and cocaine reduction. Univariate and Multiple regression analyses were used to examine the difference in treatment retention between the three groups at different MMT durations (1 – 3 months, 4 – 6 months, and 7 – 12 months).
Schuman-Olivier *et al.*[45]	2013	*Drug Alcohol Dependence*	Through urine toxicology screening, BZD misuse history, and whether they possessed a BZD prescription, patients were classified into four consorts: BZD misuse history with BZD prescription, BZD misuse history with no prescription, no BZD misuse history with a BZD prescription, and no BZD misuse history and no prescription. BZD misuse was defined as having evidence of inappropriate use of a BZD prescription. Urine toxicology was conducted at intake, then twice a week for a month. Frequency decreased to once a week until month 6 when patients considered clinically stable were transitioned to once a month for the remainder of treatment. Primary Outcomes included 12-month treatment retention, urine toxicology for illicit opioids, total emergency department (ED) visits, and odds of an ED visit related to an opioid overdose or accidental injury during treatment. Their definition of treatment retention was not provided.
White *et al.*[48]	2014	*Journal of Psychoactive Drugs*	The authors compared patients' treatment retention with drug usage. Drug testing frequency varied but ranged from weekly to monthly random urine toxicology screens. Patients were included in the study if three or more drug screenings were performed. A distinction was made between prescription and illicit drug use during analysis. The primary outcome was treatment retention; however, they did not define the term.
Peles *et al.*[50]	2014	*Israel Journal of Psychiatry and Related Sciences*	The primary outcome of interest is the prevalence among MMT patients, BZD's effect on long-term treatment retention, and evaluate how possible it is to discontinue MMT treatment following a year. Patients performed urine toxicology at intake, then at random throughout MMT treatment (range 1 – 11 a month). A patient was defined as if one of the samples was positive. Kaplan Meier with log-rank was used to calculate treatment retention for the cohort.
Dayal *et al.*[43]	2016	*Journal of Substance Use*	The outcomes of interest in this study are uptake rate, retention, and compliance with naltrexone therapy. Retention was defined as the duration of time in therapy from initiation to discontinuation. Compliance is defined by the extent a patient adheres to naltrexone dosage and schedule. Logistic regression was used to evaluate the predictors of naltrexone therapy compliance and retention.
Franklyn *et al.*[42]	2017	*Harm Reduction Journal*	Two different comparisons were performed: (1) Patients were separated into the BZD group if they had a BZD-positive urine sample in their 1st month of treatment; (2) Patients were separated into 4 groups based on the frequency of BZD-positive urine samples: 0 – 25, 25 – 50, 50 – 75, and 75 – 100%. Urine toxicology screening was conducted one to two times a week. One-year retention was characterized by the Cox proportional hazard model. The primary outcome was methadone or Suboxone (buprenorphine+naloxone) retention. Patients were considered to be retained in treatment based on seeing evidence of a dose of medication within 30 days.
Eibl *et al.*[49]	2019	*Journal of Addiction Medicine*	Patients were separated into four groups depending on whether they processed a BZD prescription and the frequency of BZD-positive urine samples (UDS+was indicated if the frequency was over 0.3). Patients were screened for BZD bi-weekly. Methadone treatment retention was the primary outcome. Treatment retention was defined as a prescription refill within 30 days of the previous prescription.

(Cont'd...)

Table 2. ***(Continued)***

Study	Publication Year	Journal	Study Design and Methodology
Montalvo *et al.*[51]	2019	*The American Journal of Addictions*	The primary outcome of the study was adherence to buprenorphine treatment≥1 year. Secondary outcomes included 2-year buprenorphine treatment retention. Among patients kept on continuous buprenorphine treatment, Bivariate analysis was performed to see if there was a significant difference in buprenorphine adherence between those who were and weren't co-prescribed BZDs.
Park *et al.*[46]	2020	*Addiction*	Authors compared characteristics between individuals with at least one BZD prescription filled during the study to those with no BZD prescription. They performed outcome event rates and Kaplan-Meier curves for four outcomes: Fatal opioid overdose, non-fatal overdose, all-cause mortality, and buprenorphine discontinuation. The primary outcome was time for fatal opioid overdose. Secondary outcomes included: time to non-fatal overdose, all-cause mortality, and buprenorphine discontinuation. Buprenorphine discontinuation was defined as a patient going more than 30 consecutive days without a prescription filled.
Durand *et al.*[41]	2021	*Drug Alcohol Dependence*	By following methadone prescription records, authors were able to follow a patient's engagement in the MMT program. A patient was considered to be retained in treatment in their methadone prescriptions coverage was maintained with no interruptions longer than 7 days. The primary outcome was the time of dropout of MMT at 3 months and 1 year. Determinants include sex, age, median methadone dose, history of co-prescription (BZDs, antidepressants, antipsychotics), and incarceration. The author examined prescription records for BZDs during MMT and up to 90 days before initiating treatment,
Ray-Griffith *et al.*[38]	2021	*The American Journal on Addictions*	Participants were split into two groups: postpartum treatment retention and postpartum treatment dropout. A bivariate analysis was performed on both groups to identify factors affecting treatment retention at 12 weeks postpartum. Treatment retention was defined as attending an appointment 10 – 14 weeks postpartum. In this article, treatment retention was not dependent on a prescription for buprenorphine. The presence of other substances (including BZD) was evaluated using urine drug toxicology results.
Morford *et al.*[39]	2022	*Drug Alcohol Dependence*	Based on a urine toxicology screening at intake, they separated patients into BZD and no-BZD groups for comparison. Kaplan-Meyer analysis was used to characterize treatment retention. The primary outcome of methadone discontinuation was defined as a patient going more than 30 consecutive days without a methadone dose shown in their electronic medical records.
Hallowell *et al.*[44]	2022	*Drug Alcohol Dependence*	The primary outcome was buprenorphine retention over a 12-month OAT period. Treatment retention was defined as having a medication possession ratio (total days supply of a medication/number of days in the period) during the patient's follow-up period. Multivariable logistic regression models were used to characterize treatment retention and buprenorphine prescription.

have a history of BZD misuse, with 17% of the BZD misuse group possessing a BZD prescription and 83% not having a prescription. Conversely, 52% had no BZD misuse history, with 19% of the no BZD misuse group possessing a BZD prescription and 83% not having a prescription.

In the retrospective cohort study conducted by Park *et al.*,[46] 24% of participants filled at least one prescription for BZDs while receiving buprenorphine therapy. In the study by Raffa *et al.*,[47] 61.7% of participants tested positive for BZDs. In the retrospective cohort study conducted by White *et al.*,[48] 20% of participants were found to have illicit baseline BZD use. From the BZD-positive group, 62% had prescriptions. In the retrospective study by Eibl *et al.*,[49] 75% of subjects had no BZD prescription and tested below the 30% BZD urine screen threshold. Six percent of subjects had no BZD prescription and tested above the 30% BZD urine screen threshold. Thirteen percent of subjects had no BZD prescription and tested below the 30% BZD urine screen threshold. Finally, 6% of subjects had no BZD prescription and tested above the 30% BZD urine screen threshold. In the study conducted by Peles *et al.*,[50] BZD prevalence fluctuated from year to year, with a peak of 61% and a low of 25.4%.

3.3. Studies that distinguish between BZD-positive and BZD-negative at treatment intake

Three retrospective and one observational cohort studies were conducted on treatment retention in OAT where the authors separated subjects into BZD-positive and BZD-negative groups based on UDT during treatment intake.

Table 3. Study characteristics

Study	Number of Subjects	Age (±SD)	Sex (%)	MOUD dose (±SD)	Setting	Polysubstance use	Psychiatric Comorbidity	Methodology and Location
Raffa *et al.*[47]	60	39.2 (6.4)	35% M; 65% F	Methadone 88.5 (56.8) mg/day	Community health center	Amphetamine 47% Cocaine 90%	ND	Retrospective cohort study of patients in methadone maintenance treatment in Vancouver, Canada.
Brands *et al.*[40]	172	31.9 (1.1) – 38.2 (1.2)	26 – 48% F	ND	Outpatient hospital clinic	Alcohol 60 – 84% Cannabis 52 – 68% Cocaine 48 – 63%	Depression 42 – 68% Anxiety 18 – 52%	Retrospective chart review of patients in methadone maintenance treatment in Toronto, Canada.
Schuman-Olivier *et al.*[45]	386	35.6 (10.5) – 37.7 (11.6)	35 – 64% F	ND	Academic community healthcare system	Cocaine 10 – 25% Cannabis 22 – 33% Amphetamine 4 – 8%	ND	Sequential-admission retrospective study in buprenorphine treatment programs in Boston, USA
White *et al.*[48]	604	53 (range 20 – 79)	61% M	ND	Private, non-profit addiction treatment center	Cocaine 29% Cannabis 27% Amphetamine 43%	ND	Retrospective chart review on patients in methadone maintenance treatment in Washington, DC, USA
Peles *et al.*[50]	787	ND	ND	ND	MMT clinic	ND	ND	Retrospective cohort study that investigated the prevalence of BZD usage in Tel Aviv, Israel.
Dayal *et al.*[43]	140	30.4 (10.1)	99% M	ND	Tertiary care drug dependence treatment center	Alcohol 21% Cannabis 26%	Excluded Ss with DSM Axis 1 disorder	Retrospective chart review of patients who were prescribed naltrexone treatment in Northern India.
Franklyn *et al.*[42]	3850	30.8 (10.2) – 34.3 (10.9)	56 – 60% M: 40 – 44% F	Methadone 75 – 85 (33 – 36) mg/day Suboxone 8 – 12 (7 – 8) mg/day	58 addiction treatment centers	ND	ND	Retrospective cohort study for patients initiating OAT in Ontario, Canada
Eibl *et al.*[49]	3692	31.3 (9.7) – 37.5 (10.8)	50 – 57% M: 43 – 50% F	Methadone 64 (30) – 69 (31) mg/day	52 addiction treatment centers	ND	Dx of mood/anxiety disorder 36-81%	Retrospective cohort analysis using urine drug screening data and prescription information in Ontario, Canada.

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Table 3. ***(Continued)***

Study	Number of Subjects	Age (±SD)	Sex (%)	MOUD dose (±SD)	Setting	Polysubstance use	Psychiatric Comorbidity	Methodology and Location
Montalvo *et al.*[51]	321	38 (10)	62% M: 38% F	ND	Behavioral Health Clinic	Other substance use disorder 60%	Depression 85% Anxiety 70% Other mood disorder 61%	Retrospective chart analysis of patients who received at least one buprenorphine prescription in Boston, USA.
Park *et al.*[46]	63345	38 (11)	38% F	Buprenorphine 0>16 mg/day	Multiple	ND	Depression 27% Anxiety 22% Bipolar/psychosis 7%	Retrospective cohort analysis linking five collections of data sets from Massachusetts, USA of buprenorphine users.
Durand *et al.*[41]	2035	34.4	68% M	Methadone range<60 – >120 mg/day	Primary care and specialist addiction services	ND	Antidepressants 48% Antipsychotics 24%	Observational cohort study in Ireland
Ray-Griffith *et al.*[38]	64	28.1 (4.4)	100% F	Buprenorphine 17.8 (6.1) mg/day	Women's Mental Health Program at university hospital	Nicotine use 80% Other substance use disorder 77%	DSM Axis 1 disorder 84% Depression 57% PTSD 48%	Retrospective chart review of postpartum women with OUD treated with buprenorphine at Women's Mental Health Program in Arkansas, USA
Morford *et al.*[39]	2968	37 (11)	63% M: 37% F	ND	Not-for-profit, community-based opioid treatment program	Cannabis 29% Cocaine 34%	ND	Retrospective cohort study of patients in an open-methadone program in Connecticut, USA
Hallowell *et al.*[44]	4898	18 – 65+	61% M 37% F	Buprenorphine dose range 0 to 24+mg/day	Multiple	ND	ND	Retrospective cohort study of Rhode Island, USA residents who initiated buprenorphine use.

Abbreviations: BZT: Benzodiazepine; DSM: Diagnostic and Statistical Manual of Mental Disorders; F: Female; M: Male; MMT; Methadone maintenance treatment; ND: Not determined; OAT: Opioid agonist treatment; OUD: Opioid use disorder; PTSD: Post-traumatic stress disorder; Ss: Subjects.

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In the retrospective study by Mortford *et al.*,[39] 31% of participants in both BZD and non-BZD groups remained in OAT after 12 months. Multivariable Cox regression showed no significant difference in treatment duration between the two groups. Similarly, Cox regression analysis by Brands *et al.*[40] indicated that BZD was not a predictor of 1-year treatment retention. Treatment retention was found to be 60% within the cohort.

Conversely, in the retrospective cohort study by Franklyn *et al.*,[42] BZD use was found to be a negative predictor of treatment retention, with a lower median retention of 215 days, compared to 265 days compared to non-users. BZD-positive subjects were found to be more likely to drop out from treatment compared to non-users using baseline urine toxicology, with an adjusted hazard ratio of 1.15. The observational study by Dayal *et al.*[43] reported a significant increase in treatment retention among patients who did not report concurrent BZD use at intake.

3.4. Studies that did not distinguish between illicit and prescription BZD use

Five retrospective and two observational studies were conducted on treatment retention in OAT where the authors did not distinguish between illicit and prescription BZD use. All four studies separated subjects into groups based on intake UDTs[39,40,42,43] and did not include BZD prescription as an independent variable. In the retrospective study by Peles *et al.*,[50] subjects who were BZD-negative upon admission were found to stay in treatment significantly longer compared to their BZD-positive counterparts, respectively. The observational study by Durand *et al.*[41] reported an increased risk of treatment dropout at 12 months associated with BZD use, with a hazard ratio of 1.22. In contrast, the retrospective study by Raffa *et al.*[47] noted a small (3.25%) but significant increase in methadone adherence associated with BZD use.

3.5. Studies that include BZD prescription as a variable

Seven articles included BZD prescription as an independent variable when comparing BZD's effect on OAT treatment. A retrospective study by Eibl *et al.*[49] reported that subjects with a BZD prescription had a statistically similar likelihood of treatment retention, regardless of the frequency of the BZD use. In the retrospective study by Park *et al.*,[46] a BZD prescription during buprenorphine treatment was associated with significantly decreased risk of treatment discontinuation (HR=0.78). In the study by White *et al.*,[48] 42% of patients who used illicit BZDs left the program during the follow-up period, compared to only 10% of subjects with no drug use. The retrospective study by Montalvo *et al.*[51] reported that a BZD prescription was a statistically significant predictor of treatment retention at 1 year, with an adjusted multivariate-OR=2.44. However, at 2 years, a BZD prescription was no longer a significant predictor of treatment retention. Buprenorphine adherence as a secondary outcome was high in both 1-year (95.8%) and 2-year (97.3%) treatment retention groups, with no difference in buprenorphine adherence between the BZD prescription group and no-BZD prescription.

A retrospective study conducted by Hallowell *et al.*[44] showed that individuals who were dispensed overlapping BZD and buprenorphine prescriptions (30 days or more supply) had higher odds of successful treatment retention than those who were prescribed supplies of 7 days or less (adjusted OR = 1.99). It is important to note, though, that in clinical practice, patients given larger drug prescriptions of drugs with potentially harmful side-effects are more likely to be medically stable,[49] thus providing a possible cofound. Conversely, in this study, it is possible that those given the shorter-duration prescriptions may have been less medically stable. The observational study by Durand *et al.*[41] reported that a BZD prescription within 90 days before OAT initiation showed no significant effect on treatment retention. In the retrospective study by Schuman-Olivier,[45] the 12-month treatment retention was 40% among all participants. The study found that retention in treatment or the use of illicit opioids was not linked to either prescription or past abuse of BDZs.

3.6. Studies that consider the frequency of BZD use

Two studies included a comparison of BZD's effect on OAT treatment retention by grouping patients by the frequency of BZD UDT screens. In the study by Franklyn *et al.*[42] subjects had an increased risk of treatment discontinuation with higher frequency of BZD use. Compared to subjects with a BZD frequency of <25%, subjects who were 25–50% BZD-positive were 26.6% more likely to discontinue treatment. Patients who had 50 – 75% BZD-positive frequency were 37.4% more likely to terminate treatment. Strikingly, patients with a BZD frequency >75% were 174.4% more likely to terminate treatment. Similarly, the study by Eibl *et al.*[49] showed a two-fold greater likelihood of treatment discontinuation of patients without a BZD prescription but were heavily using BZD. Comparing the BZD-/UDS+ group to the reference group (BZD-/UDS-) had an adjusted OR=0.38. Other BZD use groups were not statistically different than the BZD-/UDS- group concerning treatment retention.

3.7. OAT program for postpartum women

A retrospective study by Ray-Griffith *et al.*[38] investigated factors affecting treatment retention in an OAT program

for pregnant women. Seventy-three percent of subjects were retained in treatment and 26% dropped out of treatment by 12 weeks postpartum. The percent positive UDT BDZ tests were significantly greater for the drop-out group (30%) than the retained group (9%). A BDZ positive UDT did not differ significantly between the groups at enrollment (29% versus 17.0%) or proximate to delivery (24% versus 13%), but a positive UDT for BDZ any time during the third trimester was significantly more likely in the dropout group (47% versus 16%).

4. Discussion

4.1. Interpretation of results

The increased overdose risk with concurrent BZD and MOUD use is well established,[26,52,53] but further exploration is necessary to understand other aspects of OAT that are affected by concurrent BZD and MOUD use. This review included studies that examined how concurrent BZD and MOUD use in OAT influences treatment retention. Our review encompasses 11 retrospective cohort studies[38-40,42,44-47,49-51,54] and three observational studies.[41,43,48]

The reviewed studies are consistent with previous reports of high polysubstance use among subjects in OAT.[19,55-58] BZD-positive subjects ranged from a frequency of 15% at intake[42] to a high of 61.7% at intake,[47] similar to the range of BZD use (18 – 50%) reported by Lintzeris *et al.*[59] in OATs. Furthermore, evidence of high BZD and opioid co-use before the initiation of OAT[40] has been documented. Overall, these findings underscore the relevance of our review, as BZDs are commonly consumed alongside opioid agonists in OAT programs.

Disparate results were observed in studies that separated subjects into BZD and no-BZD groups, based on intake toxicology results. Two studies[42,43] indicated that BZD use is a predictor of treatment discontinuation whereas two other studies[39,40] found no association between BZD use at intake and treatment retention. A similar relationship is seen with the seven studies that separated the participants into BZD-positive and BZD-negative groups without distinguishing between prescription and illicit BZD use39 – 43,47,50. Four studies showed that BZD use is a predictor of treatment discontinuation,[40,42,43,50] while two studies[42,43] indicated no relationship between BZD use and treatment retention. Finally, Raffa *et al.*[47] showed increased treatment retention with concurrent BZD and MOUD use. These inconsistent findings may suggest the relationship between concurrent BZD and MOUD use on treatment retention is complex and varies based on additional variables that do not remain constant between studies and require further evaluation.

Studies that examined the impact of having a BZD prescription on treatment retention found no significant difference in treatment retention between individuals who were BZD-negative and those with a BZD prescription.[41,45,49] However, there was a substantial increase in treatment retention in individuals with a BZD prescription compared to participants who used illicit BZD.[44,46,48,51] These findings highlight potential importance of prescriptions for individuals in OAT programs who are known to use illicit BZD, as BZDs are regulated substances of known purity and concentration monitored and adjusted by medical professionals. In contrast, illicit BZD use is self-regulated by participants, potentially resulting in increased dosage and side-effects, especially if impure drugs are consumed.[60] Overall, these findings trend to suggest that retention may be greater in OAT programs where BZDs – if used - are under the management of a clinical expert. However, the evidence is far from conclusive, and any modest increases in OAT program retention must be considered in balance with other risks associated with concurrent MOUD and BZD use. Further studies will be required to address this balance in more depth.

When analyzing whether the frequency of concurrent BZD use affects treatment retention, studies indicated an increased risk of treatment discontinuation with prolonged BZD use.[42,49] The increased risk of treatment discontinuation may stem from the appearance of withdrawal effects from continued BZD use, subsequently resulting in more OAT discontinuation. In addition, comparing the effects of a BZD prescription and the frequency of BZD use, Eibl *et al.*[49] noted that subjects with a BZD prescription had a statistically similar likelihood of treatment retention regardless of their frequency of BZD use. This suggests that a BZD prescription may be a stronger predictor of treatment retention than the frequency of BZD use. However, it is worth noting that the study grouped participants into high BZD frequency and low BZD frequency using a fraction of positive urine drug screening for BZD of 30%, a threshold they believe denoted a high versus low frequency of BZD use. Future studies in this area would benefit from considering alternate possible thresholds, based on clinically relevant criteria. For instance, implementing a similar grouping to Frankyn *et al.*,[42] where subjects were divided into four groups based on the percentage of BZD-positive urine samples would allow for a more complex analysis, if sufficiently well statistically powered.

In addition to the primary outcome of 1-year treatment retention, Montalvo *et al.*[51] included secondary outcomes of 2-year treatment retention and buprenorphine adherence. The study indicated that a BZD prescription

increases the likelihood of 1-year treatment retention but was not statistically significant at 2 years. This suggests that BZD's effect on treatment retention may be more impactful at the start of OAT. This relationship could be present for two reasons: (1) BZD use is helpful with alleviating opioid withdrawal symptoms[15] which are much more prevalent at the start of OAT (2) BZDs are typically intended for short-term use, and if used for longer periods it may be prescribed at lower doses or tolerance may develop,[61,62] diminishing their positive impact on treatment retention. Montalvo *et al.*[51] did not report the BZD doses, thus further experiments are required to test our hypotheses. Another conclusion by the authors is that the increase in treatment retention seen with a BZD prescription was not a result of a change in MOUD adherence.[51] This finding is consistent with prior reports that BZD use, specifically under a prescription, is to alleviate comorbidities caused by opioid withdrawal.

The study by Ray-Griffith *et al.*[38] addressed the complex issue of BZD use in OAT programs by pregnant and postpartum women. To our knowledge, this is the only study of its kind, and so comparison is not possible. Nonetheless, this study provides an important investigation, specifically for the effects of illicit BZD use history on treatment retention during pregnancy. Two participants within the cohort had a BZD prescription. Following the removal of the two participants from the statistical analysis, the treatment dropout group had a relatively high rate of BZD use compared to the treatment retained group. The treatment dropout group was statistically more likely to be BZD-positive during the first trimester. The correlation between BZD use in the third trimester and postpartum treatment retention suggests that BZD use history is a predictor of treatment retention. Thus, BZD use might be only beneficial to OAT during the treatment itself, where regulation and monitoring are present. Further analysis is required to evaluate if the increased treatment dropout is solely due to having a history of BZD use, or if having BZD use specifically in the third trimester is significant to OAT retention.

5. Limitations

It is important to note that this literature review was conducted using data from 14 different studies. Some methodologies and primary outcomes were frequently used to provide additional opportunities for comparison, while others were limited to one or two articles on the topic. Thus, more studies must be conducted to validate present experimental results. In addition, while our included studies have investigated the effects of concurrent BZD use in OAT on treatment retention, there is a gap in how specific aspects of individual OAT programs might influence treatment retention. There was also a significant lack of information in the studies about the patterns of illicit BZD use among subjects, and the psychological reasons for its use. Concurrent BZD use with opioids can occur for diverse reasons, including self-medication of opioid withdrawal symptoms, concomitant mental health issues such as underlying anxiety, to increase the euphoric effects of each drug, and as a broader pattern of polysubstance abuse.[24,63] More detailed information about motives for BZD use with opioids would be clinically informative for healthcare providers and could help guide clinical management. In addition to more detailed information about patterns of drug use, it would be informative for studies to include more granular details about the patients and treatment characteristics, as these are critical factors in treatment retention. Patient characteristics including age, sex, psychiatric comorbidities, and substance use all heavily influence treatment adherence,[64-66] while treatment characteristics including MOUD dose, dosing flexibility, and treatment setting similarly influence adherence.[67-69] From Table 3, it was evident that these details are frequently not included in relevant publications.

It must also be noted that the studies we evaluated were conducted across many different regions and countries, where drug protocols and laws for BZD, MOUD, and OAT programs differ, although approximately half of the studies were completed in the North East US (Table 3). Given the widespread use of opioids throughout North America (and increasingly elsewhere) studies in more diverse regions would be a welcome addition to the literature. The included studies also had slightly varying definitions of treatment retention (Table 2). Standardizing the definition of treatment retention may help prevent the presence of biases within the data.

6. Conclusion

The existing literature on this topic consists of diverse studies of substantially different methodologies and outcome measures. Due to the intrinsic complexity and variability of many of the outcome measures, in a typically polysubstance-using population, and a lack of standardized instruments with which to measure these outcome variables, drawing firm conclusions that can be generalized to this field as a whole is not yet possible. Future studies should include a more comprehensive and precise methodology in the evaluation of BZD use during OAT programs, using more rigorous methodological evaluations if possible. Thus, until there are interventional, randomized clinical trials with head-to-head comparisons of treatment interventions, the benefits of different approaches to BZD management can only be indirectly inferred from the existing literature. It may be helpful for

clinicians to identify which studies most closely resemble their own patients and healthcare practices in trying to better consider which approaches may have clinical utility. Furthermore, any potential benefits from greater retention in OAT programs must be considered as part of the "big picture" where other factors, such as the risk of BZD toxicity and addiction represent significant health challenges to those enrolled in OAT programs. Finally, further research needs to be conducted to continue expanding the scope of BZDs' other effects on OAT. This should include evaluating polysubstance tapering or how transitioning patients from illicit BZD use to prescription might impact treatment retention.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

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