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# Associations Between Buprenorphine \Naloxone and Methadone Treatment and non-Opioid Substance Use in Prescription-Type Opioid Use Disorder: Secondary Analyses From the OPTIMA Study

## Associations entre le traitement avec la buprénorphine/naloxone et avec la méthadone et l'utilisation de substances non opioïdes dans le trouble lié à l'usage d'opioïdes de type sur ordonnance : analyses secondaires de l'étude OPTIMA

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**Abstract**

**Objectives:** There is limited evidence on how opioid agonist treatment (OAT) may affect psychoactive non-opioid substance use in prescription-type opioid use disorder (POUD) and whether this effect might explain OAT outcomes. We aimed to assess the effect of methadone on non-opioid substance use compared to buprenorphine/naloxone (BUP/NX), to explore whether non-opioid substance use is associated with opioid use and retention in treatment, and to test non-opioid use as a moderator of associations between methadone with retention in OAT and opioid use compared to BUP/NX.

**Methods:** This is a secondary analysis of data from the OPTIMA trial, an open-label, pragmatic, parallel, two-arm, pan-Canadian, multicentre, randomized-controlled trial to compare standard methadone model of care and flexible take-home

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dosing BUP/NX for POUD treatment. We studied the effect of methadone and BUP/NX on non-opioid substance use evaluated by urine drug screen (UDS) and by classes of non-opioid substances (i.e., tetrahydrocannabinol [THC], benzodiazepines, stimulants) (weeks 2–24) using adjusted generalized estimation equation (GEE). We studied the association between non-opioid substance-positive UDS and opioid-positive UDS and retention in treatment, using adjusted GEE and logistic regressions.

**Results:** Overall, methadone was not associated with non-opioid substance-positive UDS compared to BUP/NX (OR: 0.78; 95%CI, 0.41 to 1.48). When non-opioid substances were studied separately, methadone was associated with lower odds of benzodiazepine-positive UDS (OR: 0.63; 95% CI: 0.40 to 0.98) and THC-positive UDS (OR: 0.47; 95% CI: 0.28 to 0.77), but not with different odds of stimulant-positive UDS (OR: 1.29; 95% CI: 0.78 to 2.16) compared to BUP/NX. Substance-positive UDS, overall and separate classes, were not associated with opioid-positive UDS or retention in treatment.

**Conclusion:** Methadone did not show a significant effect on overall non-opioid substance use in POUD compared to BUP/NX treatment but was associated with lower odds of benzodiazepine and THC use in particular. Non-opioid substance use did not predict OAT outcomes. Further research is needed to ascertain whether specific patterns of polysubstance use (quantity and frequency) may affect treatment outcomes.

**Abrégé**

**Objectifs:** Les données probantes sont limitées en ce qui concerne la façon dont le traitement agoniste opioïde (TAO) peut influencer l'utilisation de substances psychoactives non opioïdes dans le trouble lié à l'usage d'opioïdes de type sur ordonnance (TUOO) et si cet effet pourrait avoir un impact sur les résultats du TAO. Nous visions à évaluer l'effet de la méthadone sur l'utilisation de substances non-opioïdes comparé à la buprénorphine/naloxone (BUP/NX) et à explorer si l'utilisation de substances non-opioïdes est associée à l'utilisation d'opioïdes et à la rétention en traitement. Nous cherchions à tester l'utilisation de non-opioïdes comme modérateur des associations de la méthadone avec la rétenton et l'usage d'opioïdes comparativement à la BUP/NX.

**Méthodes:** C'est une analyse secondaire des données de l'essai OPTIMA, un essai ouvert, pragmatique, parallèle, à deux volets, pancanadien, multicentrique, randomisé et contrôlé pour comparer le modèle de soins standard à la méthadone avec le dosage flexible à emporter de BUP/NX pour le traitement du TUOO. Nous avons étudié l'effet de la méthadone et de la BUP/NX sur l'utilisation de substance non-opioïde évaluée par dépistage de drogues dans l'urine (DDU) et par des classes de substances non-opioïdes (c.-à-d., tétrahydrocannabinol [THC], benzodiazépines, stimulants) (semaines 2–24) en utilisant l'équation d'estimation généralisée ajustée (EEGA). Nous avons étudié l'association entre le DDU de substances positives non-opioïdes et le DDU opioïde positif et la rétention en traitement, à l'aide de l'EEGA ajustée et des régressions logistiques.

**Résultats:** En général, la méthadone n'était pas associée à un DDU de substances non-opioïdes positives comparativement à la BUP/NX (RC : 0,78; IC à 95% 0,41 à 1,48). Quand des substances non-opioïdes ont été étudiées séparément, la méthadone était associée à des probabilités plus faibles de DDU de benzodiazépine positif (RC 0,63; IC à 95% 0,40 à −0,98) et de DDU de THC positif (RC 0.47; IC à 95% 0,28 à 0,77), mais pas avec des probabilités différentes de DDU de stimulants positif, (RC 1,29; IC à 95% 0,78 à 2,16) comparativement à la BUP/NX. Les DDU de substances positifs, en général et les classes séparées n'étaient pas associés au DDU d'opioïde positif ou à la rétention en traitement.

**Conclusion:** La méthadone n'a pas montré un effet significatif sur l'utilisation générale de substances non opioïdes dans le TAO comparativement au traitement de BUP/NX, mais elle était associée avec des probabilités plus faibles d'utilisation de benzodiazépine et de THC en particulier. L'utilisation de substances non-opioïdes ne prédisait pas les résultats du TAO. Il faut plus de recherche pour confirmer si les profils spécifiques d'utilisation de polysubstances (quantité et fréquence) peuvent affecter les résultats du traitement.

**Keywords**

opioid use disorder, opioid replacement therapy, buprenorphine, methadone, retention

**Mots clés**

trouble d'utilisation d'opioïde, thérapie de remplacement d'opioïdes, buprénorphine, méthadone, rétention

## Introduction

The global burden of drug use disorders is an increasing concern, with a high prevalence of opioid use disorder (OUD) (26.8 million cases) and non-opioid substance use disorder (36.8 million cases) in 2016 worldwide.[1] The contribution of prescription opioids (PO) to disease burden of OUD increased in recent years. In 2018, among the 3.7 million Canadians who used POs in past 12 months, 9.6% had engaged in problematic PO use, which may be harmful to health.[2] Further, in the last few years, there was a rapid increase in unregulated supply of highly potent opioids, including fentanyl and fentanyl analog-type substances,[3] which was associated with a majority (76%) of accidental apparent opioid toxicity deaths.[4] With the ongoing opioid crisis, there is an urgent need for effective nationwide actions to improve access to opioid agonist therapy (OAT).[5]

OAT is recommended in Canada for the management of OUD related to prescription-type opioids (e.g., unregulated or prescription fentanyl). Opioid agonists such as methadone and buprenorphine exert their effect by binding to opioid receptors as complete and partial μ receptor agonists.[6] Buprenorphine is formulated with naloxone as buprenorphine/naloxone (BUP/NX), which has a better safety profile than methadone and is offered as a first-line treatment due to its greater flexibility than methadone with the option for at-home unsupervised treatment. Methadone is recommended as a second-line treatment.[7] A recent randomized clinical trial in prescription-type opioid use disorder (POUD) showed that flexible take-home dosing BUP/NX is non-inferior to standard supervised methadone treatment in reducing opioid use during treatment, while methadone was associated with better retention in assigned OAT.[8]

Compared to available medications for the treatment of OUD,[9] there is still little to no pharmacological treatments approved for non-opioid drug use disorders other than alcohol and nicotine, such as stimulants (i.e., cocaine, amphetamine, methamphetamine) and cannabis.[10,11] Further, the potential effect of opioid agonists on concurrent non-opioid substance use still needs further investigation in context of POUD. There may be some beneficial effects of OAT in reducing non-opioid substance use or some potential detrimental effect in increasing non-opioid substance use as a compensatory mechanism following OAT in individuals with polysubstance use. Some qualitative evidence suggested that patients may initiate methamphetamine when they decrease their use of opioids due to the emergence of a compensatory craving for euphoric experiences.[3,12] Cannabis, including tetrahydrocannabinol (THC), is also used by some persons as an opioid sparing agent for pain management or hoping to offset opioid-related withdrawal symptoms.[13–15] Other earlier longitudinal studies in adults with OUD receiving OAT maintenance showed that lower heroin use frequency was associated with reduced use of other opioids, cocaine, amphetamine, and benzodiazepines.[16] Moreover, Dong et al. (2020) reported reduced unregulated prescription opioid use following OAT initiation with a decreased benzodiazepine use but with no effect of OAT on stimulant and cannabis use.[17]

Mechanisms and potential effects of OAT on drug use may thus vary according to classes of substances, for example, depressants versus stimulants. Further, there is a concern about the reduced effectiveness and benefits of OAT related to use of other substances; for example, Bunting et al. (2022) found that sedative use during first 4 weeks of OAT initiation caused an increase in opioid craving.[18] Overall, evidence is unclear on how OAT (i.e., methadone compared to BUP/NX) may affect non-opioid psychoactive substance use; this evidence is further limited among population with POUD. Moreover, the impact of use of these substances on OAT outcomes is unknown. Looking at mediation and moderation by unregulated substance use in these associations may be useful to guide clinical practice.

Given these critical gaps in knowledge, the present study aims to (1) explore relative effect of methadone compared to BUP/NX treatment on non-opioid substance use (e.g., benzodiazepines, stimulants, and cannabis) in adults with POUD; (2) verify whether non-opioid substance use during OAT may predict opioid use and retention in OAT; and (3) verify whether non-opioid substance use is a moderator of associations of methadone with retention in OAT and opioid use compared to BUP/NX.

## Methods

### Study Design

This study is a secondary exploratory analysis using data from the Optimizing Patient Centered Care (OPTIMA) trial, an open-label, pragmatic, parallel two-arm, pan-Canadian, multicentre, randomized-controlled trial that compared two models of care (standard supervised methadone model of care vs. flexible, early take-home dosing BUP/NX) for treatment of POUD. The study was approved by local Canadian research ethics committees and was registered in the clinicaltrial.gov registry (NCT03033732).[19]

### Participants

The study included participants who were recruited (from 2017 to 2020) and randomized in OPTIMA trial ($n = 271$ total, methadone $n = 133$, and BUP/NX $n = 138$). Briefly, participants were non-pregnant adults (18–64 years) who met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for moderate to severe OUD primarily attributable to PO (i.e., prescription opioids, fentanyl) at the time of recruitment. Additionally, those who had heroin as the main substance used in the month preceding screening were excluded, as the study

was aimed at POs. Finally, individuals who were on OAT during 4 weeks before screening, or with concurrent chronic pain necessitating ongoing opioid therapy, were excluded. The inclusion and exclusion criteria are detailed elsewhere.[8,19]

## Procedures

Eligible participants who provided informed consent were randomized using computer-generated randomization according to a 1:1 ratio and using stratified permuted blocks by site and lifetime heroin use. Both participants and clinicians were aware of the assigned intervention (methadone vs. BUP/NX). The OPTIMA trial had a 24-week duration where each participant was randomized to either methadone or BUP/NX arm and had regular biweekly visits with targeted health questionnaires and urine drug tests.

Opioid agonist treatment dosing followed Health Canada guidelines.[7] The pragmatic trial design allowed physicians to modify dosing according to participants' needs. Opioid agonist treatment was initiated within 14 days of randomization. Methadone was provided via daily supervised ingestion, and after 2–3 months of treatment initiation, take-home doses were then allowed for clinically stable participants according to clinicians' discretion. The methadone starting dose was 20–30 mg/day on average, which was titrated by an average of 5–10 mg increments every few days to 1–2 weeks until a stable dose, as determined by the clinical evaluation, was reached (e.g., usually between 60 and 120 mg/day with some participants going beyond this dose). BUP/NX was offered as take-home doses to participants, with 1-week carries of BUP/NX within 2 weeks and 2-week carries within 4 weeks after treatment initiation, on condition of clinical stability. BUP/NX was prescribed with an average initial dose of 4 mg/1 mg with the possibility of reaching up to 12 mg/3 mg on the first day. Doses were titrated until a stable dose was reached (e.g., up to 24–32 mg/6–8 mg/day in some participants).

## Study Variables

*Independent Variable.* The main independent variable for this study was assignment to the OPTIMA trial's OAT group (i.e., methadone vs. BUP/NX at randomization).

*Other Variables and Outcomes.* Urine drug screen (UDS) was measured every 2 weeks using Health Canada-approved Rapid Response™ Multi-Drug one-step Screen Test panel. They were measured at each visit (positive/negative) (weeks 2–24) and averaged as a proportion of substance-positive UDS out of 12 collected samples (weeks 2–24) during OAT. We included 2 variables: non-opioid substance-positive UDS and opioid-positive UDS.

*Non-opioid substance-positive UDS* were measured by substance-positive UDS and were grouped for each class of substance, that is, central nervous system depressants (benzodiazepines), stimulants (cocaine and amphetamine-type stimulants), and cannabis (THC). A binary UDS variable (positive: yes/no) and proportions of positive screening for non-opioid substances (overall and as separate classes) were created.

*Opioid-positive UDS* was measured at each visit (yes/no) and then averaged as proportion of opioid-positive UDS during study visits (i.e., any detected opioid was considered positive UDS except for assigned OAT).

*Retention in treatment* was measured by presence of both an active prescription and a UDS positive for assigned OAT at study end.

*Tested moderators* included UDS positive for non-opioid substance used during the trial and were tested as moderators of potential associations between OAT assignment at randomization and unregulated opioid use and retention in treatment (i.e., as repeated measure and as overall proportion of non-opioid substance-positive UDS, respectively).

*Other variables, covariates, and potential confounders* included time defined as a continuous variable (0–11), reflecting number of study visits (i.e., first follow-up visit coded as 0 and last visit coded as 11). Other covariables included age, biological sex, housing (yes/no), education (elementary up to high school vs. college/university), ethnicity (Caucasian vs. others), prescription coverage (yes/no), self-reported lifetime heroin status at baseline (yes/no), non-opioid substance-positive UDS at baseline (yes/no), and study site (7).

## Statistical Analyses

*Main Analyses.* Descriptive analyses of study variables at baseline and follow-up including non-opioid substance-positive UDS were reported by OAT group at randomization.

We included all participants who were randomized to OAT in first objective of study, using an intention-to-treat approach (data were analyzed based on treatment allocated at randomization). Missing UDS were imputed conservatively as positive UDS for tested substances in main analyses. This imputation was supported by the fact that almost all of study samples (94.8%) had opioid-positive UDS and non-opioid substance-positive UDS (87.5%) at baseline.

Adjusted generalized estimation equations (GEE) were used to study non-opioid substance-positive UDS (yes/no) as repeated measures in the first objective as a function of OAT at randomization. Adjusted GEE were used to study longitudinal data of opioid-positive UDS (yes/no) as a function of non-opioid substance-positive UDS in the second objective of the study. The analyses for the second study objective excluded participants who did not initiate OAT and excluded all missing UDS at each study visit (without UDS imputation). GEE models used exchangeable correlational matrix. Logistic regression was used to study retention in treatment at study end (yes/no) as a function of proportion

of non-opioid substance-positive UDS in second objective (i.e., UDS proportion was calculated including participants having at least one available UDS). Interactions between OAT and non-opioid substance-positive UDS in predicting opioid-positive UDS and retention were assessed for the third objective.

All analyses were adjusted for stratification factors including study site and lifetime heroin use, and other relevant characteristics such as baseline non-opioid substance-positive UDS and covariates that showed significant associations with outcomes in bivariate analyses. We also reported (standardized) mean differences for the main results.

*Sensitivity Analyses.* Additional analyses were conducted for first study objective by including participants who were randomized, initiated OAT, and provided valid UDS, without imputing missing UDS. We also imputed missing data on non-opioid substances by baseline values of UDS for the first and second study objectives.

The significance level was set using a type I error rate ($\alpha = .05$; two-sided) for all analyses. Analyses and data preparation were carried out using R-Studio (PBC, version 4.1.2) and SPSS (IBM, version 26) statistical packages.

## Results

### Characteristics of Participants at Baseline and Follow-up

The study sample included 271 participants with a mean (SD) age of 39.04 (10.50) years. Most participants were male (65.68%), Caucasian (67.16%), and without stable housing (63.10%). Among study participants, 80.07% had opioid prescriptions, and 68.63% had reported lifetime heroin use at baseline. Results of baseline UDS showed that 94.83% had positive results for opioid use and 87.45% for non-opioid substance use. Sample descriptive analyses are summarized in Table 1. Non-imputed positive UDS for non-opioid substances are summarized in Supplemental Table 1.

### Primary Analysis

*Effect of methadone versus BUP/NX treatment on non-opioid substance use (adjusted GEE models):* Methadone compared to BUP/NX was not associated with non-opioid substance-positive UDS (OR: 0.78; 95%CI, 0.41 to 1.48). When non-opioid substances were studied separately, methadone compared to BUP/NX was associated with lower odds of benzodiazepine-positive UDS (OR: 0.63; 95%CI, 0.40 to 0.98) and lower odds of THC-positive UDS (OR: 0.47; 95%CI, 0.28 to 0.77) but not of stimulant-positive UDS (OR: 1.29; 95%CI, 0.78 to 2.16) (Supplemental Figure 1; Table 2).

*Associations between non-opioid substance-positive UDS use during OAT treatment and opioid-positive UDS in participants with available UDS (adjusted GEE models):* Non-opioid substance-positive UDS during study were not associated with opioid-positive UDS, both overall (OR: 1.21; 95%CI, 0.64 to 2.31) and as separate classes—that is, THC (OR: 0.92; 95%CI, 0.48 to 1.74), benzodiazepine (OR: 1.29; 95%CI, 0.54 to 3.08), and stimulants (OR: 1.80; 95%CI, 0.99 to 3.28) (Table 3). There was no interaction between OAT and non-opioid substance-positive UDS in predicting opioid-positive UDS (OR: 1.42; 95%CI, 0.46 to 4.42).

*Associations between non-opioid substance-positive UDS during OAT treatment and retention in treatment in participants with available UDS (adjusted logistic regression models):* The proportions of non-opioid substance use during the study (OR: 0.37; 95%CI, 0.11 to 1.24) and as separate classes—that is, THC (OR: 0.58; 95%CI, 0.37 to 1.39), benzodiazepine (OR: 1.01; 95%CI, 0.24 to 4.53), and stimulants (OR: 0.63; 95%CI, 0.21 to 1.81)—were not associated with retention in treatment (Table 4). There was no interaction between OAT and proportions of non-opioid substance-positive UDS in predicting retention (OR:1.34; 95%CI, 0.13 to 13.83).

### Sensitivity Analyses in Participants ($n = 193$) who Initiated OAT and Provided at Least 1 Valid UDS Without Imputation (First Objective)

Associations between OAT and non-opioid substance-positive UDS overall and as separate classes (i.e., THC, benzodiazepines, stimulants) (Table 5) were in the same direction as the main analyses but not statistically significant.

### Sensitivity Analyses of Non-Opioid Substance Use With Baseline Observation Carried Forward Imputation of UDS

Sensitivity analyses showed that methadone versus BUP-NX had a significant association with THC-positive UDS (OR: 0.60; 95%CI, 0.38 to 0.95); the association with benzodiazepine-positive UDS was similar to the primary analysis (OR: 0.54; 95%CI, 0.28 to 1.02), but did not reach statistical significance (Supplemental Table 2).

Non-opioid substance-positive UDS in those who initiated OAT ($N = 193$) was associated with opioid use (OR: 1.87; 95%CI, 1.06 to 3.27) (missing data were imputed as opioid-positive), and this was specifically with stimulant use (OR: 2.85; 95%CI, 1.65 to 4.94) with interaction by time in treatment (OR: 1.08; 95%CI, 1.01 to 1.16) (Supplemental Table 3).

## Discussion

This study, which consists of secondary analyses of a pragmatic real-world clinical trial, showed that type of OAT

**Table 1.** Descriptive Analyses of Study Variables at Baseline and Follow-up[¥].

| Variables | | Total ($n = 271$) | Methadone ($n = 133$) | BUP-NX ($n = 138$) | *P*-value[+] |
|---|---|---|---|---|---|
| | Categories | | | | |
| At Baseline | | | | | |
| Age | | 39.04 ± 10.50 | 39.37 ± 10.39 | 38.72 ± 10.63 | 0.609 |
| Sex | Male | 178(65.68%) | 83(62.41%) | 95(68.84%) | 0.323 |
| | Female | 93(34.32%) | 50(37.59%) | 43(31.16%) | |
| Ethnicity | Caucasian/White | 182(67.16%) | 89(66.92%) | 93(67.39%) | 0.440 |
| | South Asian | 2(0.74%) | 0(0%) | 2(1.45%) | |
| | Other Asian | 2(0.74%) | 1(0.75%) | 1(0.72%) | |
| | Latin American /Hispanic | 1(0.37%) | 0(0%) | 1(0.72%) | |
| | Middle Eastern | 2(0.74%) | 1(0.75%) | 1(0.72%) | |
| | Black African | 2(0.74%) | 2(1.50%) | 0(0.50%) | |
| | Black Caribbean | 2(0.74%) | 0(0%) | 2(1.45%) | |
| | First Nations | 46(16.97%) | 21(15.79%) | 25(18.12%) | |
| | Métis | 13(4.80%) | 6(4.51%) | 7(5.07%) | |
| | Other | 16(5.90%) | 11(8.27%) | 5(3.62%) | |
| | Choose not to answer | 3(1.11%) | 2(1.50%) | 1(0.72%) | |
| Education | Elementary | 6(2.21%) | 4(3.01%) | 2(1.45%) | 0.267 |
| | Middle school | 43(15.87%) | 27(20.30%) | 16(11.59%) | |
| | High school | 118(43.54%) | 50(37.59%) | 68(49.28%) | |
| | Technical/trade school | 25(9.23%) | 11(8.27%) | 14(10.14%) | |
| | Some college/university | 32(11.81%) | 17(12.78%) | 15(10.87%) | |
| | College/university | 46(16.97%) | 23(17.29%) | 23(16.67%) | |
| | Choose not to answer | 1(0.37%) | 1(0.75%) | 1(0.37%) | |
| Housing | Yes | 171(63.10%) | 84(63.16%) | 87(63.04%) | 0.999 |
| | No | 100(36.90%) | 49(36.84%) | 51(36.96%) | |
| Site | CAMH | 49(18.08%) | 23(17.29%) | 26(18.84%) | 0.973 |
| | CHUM | 65(23.99%) | 33(24.81%) | 32(23.19%) | |
| | CRAN | 7(2.58%) | 3(2.26%) | 4(2.90%) | |
| | OATC | 3(1.11%) | 1(0.75%) | 2(1.45%) | |
| | ODPC | 79(29.15%) | 39(29.32%) | 40(28.99%) | |
| | PHSC | 9 (3.32%) | 6(4.51%) | 3(2.17%) | |
| | RAAC | 59(21.77%) | 28(21.05%) | 31(22.46%) | |
| Prescription coverage | Yes | 217(80.07%) | 107(80.45%) | 110(79.71%) | 0.622 |
| | No | 48(17.71%) | 22(16.54%) | 26(18.84%) | |
| | Don't Know | 6 (2.21%) | 4(3.01%) | 2(1.45%) | |
| Heroin use status at baseline | Yes | 186(68.63%) | 91(68.42%) | 95(68.84%) | 0.999 |
| | No | 85(31.37%) | 42(31.58%) | 43(31.16%) | |
| Opioid-positive UDS at baseline | Yes | 257(94.83%) | 128(96.24%) | 129(93.48%) | 0.460 |
| | No | 14(5.17%) | 5(3.76%) | 9(6.52%) | |
| Non-opioid substances-positive UDS at baseline | Yes | 237(87.45%) | 118(88.72%) | 119(86.23%) | 0.680 |
| | No | 34(12.55%) | 15(11.28%) | 19(13.77%) | |
| At follow-up | | | | | |
| Proportion of benzodiazepine-positive UDS | | 0.61 ± 0.39 | 0.55 ± 0.40 | 0.67 ± 0.37 | 0.014* |
| Proportion of THC-positive UDS | | 0.78 ± 0.33 | 0.72 ± 0.36 | 0.84 ± 0.29 | 0.002* |
| Proportion of stimulants-positive UDS | | 0.79 ± 0.33 | 0.79 ± 0.33 | 0.78 ± 0.32 | 0.869 |
| Proportion of opioid-positive UDS | | 0.79 ± 0.33 | 0.82 ± 0.31 | 0.76 ± 0.35 | 0.154 |
| Proportion of non-opioid substances-positive UDS | | 0.92 ± 0.21 | 0.91 ± 0.22 | 0.93 ± 0.20 | 0.399 |
| Retention in treatment at study end | | 77(28.52%) | 45(33.83%) | 32(23.36%) | 0.076 |

*Note.* BUP-NX = buprenorphine-naloxone; British Columbia: RAAC = The Rapid Access Addiction Clinic; PHSC: the Portland Hotel Society Medical Clinic; ODPC = the Opioid Dependency Program Clinic; CAMH = the Centre for Addictions and Mental Health; OATC: the Ontario Addiction Treatment Centre; CHUM = the Centre Hospitalier de l'Université de Montréal; CRAN = the Centre de Recherche et d'Aide pour Narcomane; THC = tetrahydrocannabinol; UDS = urine drug screen.

[¥]Values are expressed as No.(%) or mean ± standard deviation.

[+] *P*-value of comparisons between methadone and BUP-NX groups (T-test for continuous variables and chi-square test for categorical variables).

*Statistically significant at *P*-value < 0.05.

**Table 2.** Associations Between OAT (Methadone vs. BUP-NX) Treatment and Non-Opioid Substance Use.

| Variables | Category | OR = exp(B) | 95%CI | *P*-value | MD | SMD |
|---|---|---|---|---|---|---|
| | Dependent variable: non-opioid substance-positive UDS | | | | | |
| Time | | 1.07 | 1.01–1.32 | 0.015* | — | — |
| OAT | Methadone | 0.78 | 0.41–1.48 | 0.451 | −0.02 | −0.038 |
| | BUP-NX | REF | REF | | — | |
| OAT*time interaction | Methadone*time interaction | 0.99 | 0.921.08 | 0.918 | — | — |
| | BUP-NX*time interaction | REF | REF | | | |
| | Dependent variable: stimulant-positive UDS | | | | | |
| Time | | 1.08 | 1.04–1.13 | <0.001* | — | — |
| OAT | Methadone | 1.29 | 0.78–2.16 | 0.326 | 0.01 | 0.026 |
| | BUP-NX | REF | REF | | — | |
| OAT*time interaction | Methadone*time interaction | 0.97 | 0.91–1.03 | 0.249 | — | — |
| | BUP-NX*time interaction | REF | REF | | | |
| | Dependent variable: benzodiazepine-positive UDS | | | | | |
| Time | | 1.11 | 1.08–1.16 | <0.001* | — | — |
| OAT | Methadone | 0.63 | 0.40–0.98 | 0.043* | −0.13 | −0.27 |
| | BUP-NX | REF | REF | | — | |
| OAT*time interaction | Methadone*time interaction | 0.99 | 0.94–1.03 | 0.569 | — | — |
| | BUP-NX*time interaction | REF | REF | | | |
| | Dependent variable: THC-positive UDS | | | | | |
| Time | | 1.08 | 1.04–1.13 | <0.001* | — | — |
| OAT | Methadone | 0.47 | 0.28–0.77 | 0.003* | −0.13 | −0.32 |
| | BUP-NX | REF | REF | | — | |
| OAT*time interaction | Methadone*time interaction | 1.0 | 0.95–1.05 | 0.836 | — | — |
| | BUP-NX*time interaction | REF | REF | | | |

*Note.* BUP-NX = buprenorphine-naloxone; OR = odds ratio; OAT = opioid agonist treatment; REF = reference; UDS = urine drug screen; THC = tetrahydrocannabinol; MD = mean difference of between-group proportions; SMD = standardized mean difference.
*Statistically significant at *P*-value < 0.05; analyses were adjusted for stratification factors: study site, lifetime heroin use; included covariables had no missing values.

(methadone vs. BUP/NX) was not associated with non-opioid substance-positive UDS overall or with stimulant-positive UDS. However, methadone was associated with lower odds of benzodiazepine-positive UDS and THC-positive UDS compared to BUP/NX. Non-opioid substance-positive UDS overall and as classes were not associated with opioid-positive UDS or retention in treatment in this sample of people using potent prescription-type opioids.

Investigating the effect of methadone compared to BUP/NX on non-opioid substance use showed that participants assigned to methadone may be less likely to have THC- and benzodiazepine-positive UDS (but not stimulant). These associations can be explained in part by the fact that BUP is a partial agonist and may therefore be insufficient in alleviating residual withdrawal and craving symptoms in POUD. This may result in individuals with POUD using substances such as THC and benzodiazepine, but not stimulants, to compensate for residual symptoms, and such a potential beneficial effect of using THC during OUD treatment warrants further study.[13,14] It may be also that the reported positive results are related to substances that can be detected for an extended period of time (e.g., THC, long-acting or chronic benzodiazepine use), which may not apply to stimulant use, explaining in part the absence of robust associations with stimulants in our study. However, previous research reported a reduction in benzodiazepine use but not stimulant use in persons treated with OAT including methadone and BUP/NX treatment.[17] The latter study by Dong et al. did not focus on individuals with POUD and instead included individuals with a diverse profile of opioid use, including heroin. It is possible that compensatory use of benzodiazepine and THC is only necessary in context of use of highly potent opioids and within BUP/NX treatment, as shown in our study. Further, other studies showed that participants retained in OAT and not using unregulated opioids had lower stimulant use, while higher stimulant use was reported in those initiating OAT and actively using unregulated opioids.[20,21] Therefore, the potential moderating effect of continuous unregulated opioid use on stimulant use during OAT may warrant further studies.[20] More research is also needed on effective treatments for reducing stimulant use in the context of concomitant OUD treatment.[22]

Other mechanisms may be involved in our findings that show less potential increase or a decrease in benzodiazepine use when using methadone compared to BUP/NX in POUD. While participants assigned to methadone and BUP/NX in our study received similar interventions from pharmacists, safety-related pharmacy policies that prevent professionals from serving methadone to patients who are intoxicated may have deterred some patients from co-using other

**Table 3.** Associations Between Non-Opioid Substance Use and Opioid Use (Opioid-Positive UDS) in Those Who Initiated OAT With at Least One Available UDS ($N = 193$).

| Variables | Category | OR = exp(B) | 95%CI | *P*-value | MD | SMD |
|---|---|---|---|---|---|---|
| | Model 1 | | | | | |
| Time | | 0.96 | 0.88–1.05 | 0.394 | — | — |
| OAT | BUP-NX | 0.41 | 0.24–0.70 | 0.001* | −0.22 | −0.454 |
| | Methadone | REF | REF | | — | |
| Non-opioid substance-positive UDS | Yes | 1.21 | 0.64–2.31 | 0.557 | 0.05 | 0.101 |
| | No | REF | REF | | | |
| Non-opioid substance-positive UDS*time interaction | Positive UDS*time interaction | 1.0 | 0.90–1.103 | 0.939 | — | — |
| | Negative UDS*time interaction | REF | REF | | | |
| | Model 2 | | | | | |
| Time | | 0.96 | 0.89–1.03 | 0.261 | — | — |
| OAT | BUP-NX | 0.43 | 0.25–0.74 | 0.002* | −0.20 | 0.412 |
| | Methadone | REF | REF | | — | |
| THC use | Yes | 0.92 | 0.48–1.74 | 0.789 | −0.03 | 0.015 |
| | No | REF | REF | | — | |
| Benzodiazepine use | Yes | 1.29 | 0.54–3.08 | 0.569 | 0.01 | 0.020 |
| | No | REF | REF | | — | |
| Stimulant use | Yes | 1.80 | 0.99–3.28 | 0.056 | 0.18 | 0.392 |
| | No | REF | REF | | — | |
| THC use*time interaction | Positive UDS *time interaction | 0.99 | 0.91–1.08 | 0.797 | — | — |
| | Negative UDS*time interaction | REF | REF | | | |
| Benzodiazepine use*time interaction | Positive UDS *time interaction | 0.96 | 0.83–1.10 | 0.554 | — | — |
| | Negative UDS*time interaction | REF | REF | | | |
| Stimulant use*time interaction | Positive UDS *time interaction | 1.04 | 0.96–1.12 | 0.383 | — | — |
| | Negative UDS*time interaction | REF | REF | | | |

*Note.* BUP-NX = buprenorphine-naloxone; OR = odds ratio; OAT = opioid agonist treatment; REF = reference; UDS = urine drug screen; THC = tetrahydrocannabinol; MD = mean difference of between-group proportions; SMD = standardized mean difference.
*Statistically significant at *P*-value < 0.05; models were adjusted for statistically significant covariables in binary analyses: age, housing, education, ethnicity, study site, lifetime heroin use, baseline non-opioid substance-positive UDS, baseline other substance-positive UDS; included covariables had no missing values.

**Table 4.** Associations Between Non-Opioid Substance Use and Retention in OAT Treatment at the Study End in Those Who Initiated OAT With a Least One Available UDS Including Available 1–12 UDS ($N = 193$).

| Variables | Category | OR = exp(B) | 95%CI | *P*-value | MD | SMD |
|---|---|---|---|---|---|---|
| | Model 1 | | | | | |
| OAT | Methadone | 2.92 | 1.41; 6.32 | 0.005* | 0.11 | 0.299 |
| | BUP-NX | REF | REF | | — | |
| Proportion of non-opioid substance use during the study | | 0.37 | 0.11; 1.24 | 0.108 | — | — |
| | Model 2 | | | | | |
| OAT | Methadone | 2.92 | 1.40; 6.39 | 0.005* | 0.05 | 0.191 |
| | BUP-NX | REF | REF | | — | |
| Proportion of stimulants use during the study | | 0.63 | 2.21; 1.81 | 0.387 | — | — |
| Proportion of THC use during the study | | 0.58 | 2.37; 1.39 | 0.227 | — | — |
| Proportion of benzodiazepine use during the study | | 1.013 | 0.24; 4.53 | 0.986 | — | — |

*Note.* BUP-NX = buprenorphine-naloxone; OR = odds ratio; OAT = opioid agonist treatment; REF = reference; UDS = urine drug screen; THC = tetrahydrocannabinol; MD = mean difference of between-group proportions; SMD = standardized mean difference.
*Statistically significant at *P*-value < 0.05; models were adjusted for statistically significant covariables in binary analyses; analyses were adjusted for: sex, ethnicity, OAT, study site, lifetime heroin use, housing, prescription drug coverage, proportion of other substance use during the study; included covariables had no missing values.

substances like benzodiazepines. The observed associations between methadone compared to BUP/NX and lower THC and benzodiazepine use in our study may be complex, and need further research, including qualitative studies to discern any underlying explanatory mechanisms.

Exploring the association of non-opioid substance use with outcomes of methadone and BUP/NX treatment showed that non-opioid substance use as measured by UDS, overall and as separate classes, was not consistently associated with outcomes, including opioid use and retention

**Table 5.** Associations Between OAT (Methadone vs. BUP-NX) Treatment and Non-Opioid Substance Use (e.g., other CNS Depressants (Benzodiazepines), Stimulants (Cocaine and ATS), and Cannabis) in Those Who Initiated OAT With at Least One Available UDS ($N = 193$).

| Variables | Category | OR = exp(B) | 95%CI | *P*-value |
|---|---|---|---|---|
| | Dependent variable: non-opioid substance-positive UDS | | | |
| Time | | 1.03 | 0.98–1.09 | 0.241 |
| OAT | Methadone | 0.93 | 0.49–1.75 | 0.819 |
| | BUP-NX | REF | REF | |
| OAT*time interaction | Methadone*time interaction | 0.89 | 0.921.05 | 0.577 |
| | BUP-NX*time interaction | REF | REF | |
| | Dependent variable: stimulant-positive UDS | | | |
| Time | | 1.0 | 0.95–1.04 | 0.813 |
| OAT | Methadone | 1.78 | 0.99–3.18 | 0.052 |
| | BUP-NX | REF | REF | |
| OAT*time interaction | Methadone*time interaction | 0.98 | 0.93–1.04 | 0.492 |
| | BUP-NX*time interaction | REF | REF | |
| | Dependent variable: benzodiazepine-positive UDS | | | |
| Time | | 0.99 | 0.92–1.06 | 0.772 |
| OAT | Methadone | 0.65 | 0.32–1.34 | 0.245 |
| | BUP-NX | REF | REF | |
| OAT*time interaction | Methadone*time interaction | 1.02 | 0.93–1.12 | 0.649 |
| | BUP-NX*time interaction | REF | REF | |
| | Dependent variable: THC-positive UDS | | | |
| Time | | 1.0 | 0.98–1.03 | 0.802 |
| OAT | Methadone | 0.70 | 0.41–1.17 | 0.170 |
| | BUP-NX | REF | REF | |
| OAT*time interaction | Methadone*time interaction | 0.99 | 0.95–1.03 | 0.598 |
| | BUP-NX*time interaction | REF | REF | |

*Note.* BUP-NX = buprenorphine-naloxone; OR = odds ratio; OAT = opioid agonist treatment; REF = reference; UDS = urine drug screen; THC = tetrahydrocannabinol.

*Statistically significant at *P*-value < 0.05; analyses were adjusted for stratification factors: study site, lifetime heroin use; included covariables had no missing values.

in treatment in main analyses (only with significant associations with opioid use in sensitivity analyses). This absence of associations may be explained in part by the heterogeneity of POUD populations treated with OAT in terms of contributing factors and motives for use of each substance and for polysubstance use. For example, the use of non-opioid substances in certain subgroups of our sample may have helped them reduce their opioid use, while in other participants, it may have triggered opioid use, so that, as a whole, there was no effect of non-opioid substance use. Another retrospective study similarly reported no associations between non-opioid substance use (e.g., unregulated benzodiazepine) with opioid use and retention in OAT.[23] However, other studies reported lower retention rates in OAT among those using stimulants.[24,25] It has also been noted that there may be interactions between different substance classes in patterns of use. For example, a prospective cohort study conducted in persons using unregulated drugs[26] showed that in the absence of treatment, the use of stimulants was associated with higher heroin use, while THC use was associated with less heroin use. Further, some authors have suggested testing potential beneficial effect of medical THC use in reducing unregulated opioid use in OUD.[27] However, there is still conflicting evidence on the associations between THC use and OUD treatment outcomes.[28–30] Overall, our binary UDS results may not support any effect of the tested non-opioid substances, including THC, on OAT outcomes (i.e., retention in treatment in particular); specific combinations and profiles of polysubstance use (i.e., frequency and potency) may warrant further investigation.

The absence of associations between the use of stimulants and OAT outcomes (i.e., opioid use and retention) in our main analyses, but with significant associations of stimulant use with opioid use in sensitivity analyses (i.e., with stronger associations when stimulants were used later during the final period of study), may also be explained in part by different populations enrolled in OPTIMA and other trials. Other studies showing that non-opioid substance use, such as the use of stimulants, may negatively affect treatment outcomes for OUD were conducted mainly in persons who use heroin. For example, co-use of stimulants in persons who use heroin receiving treatment was associated with lower retention in treatment and higher heroin use and relapse rates.[31,32] Our study had a population with POUD, including those using highly potent opioids. It is plausible that potential harms related to POUD outweighed potential detrimental effects of stimulant use on OAT outcomes, masking any potential associations.

Testing potential interactions between treatment by OAT and non-opioid substance use showed that non-opioid substance use was not a significant moderator in associations between types of OAT and treatment outcomes (both unregulated opioid use and retention in treatment) in our study. This may also be explained in part by frequent use of highly potent opioids among persons with POUD. The potential differential effect of methadone versus BUP/NX on outcomes may therefore be mainly dependent on reducing potent opioid use, and this difference may not be affected by co-use of non-opioid substances. There was also no significant interaction between non-opioid substance use and time since OAT initiation in predicting unregulated opioid use in our study. However, a previous study by Wang et al. (2017)[26] showed that the use of non-opioid substances may diminish the beneficial effect of OAT in terms of opioid use reduction with time. Again, this moderation effect was detected among individuals who use heroin and does not seem to apply in POUD population.[26] The differential effect of OAT used in OPTIMA in terms of reduced opioid use may also be explained in part by reduced opioid craving,[33] which may not be affected by non-opioid substance use when related to highly potent opioid exposure. Overall, non-opioid substance use seemed to play a limited role in treatment-related outcomes in POUD in our study.

### *Strengths and Limitations*

The present study included OUD populations mainly using opioids other than heroin (including prescription-type opioids, such as fentanyl) in a real-world context of OAT. The study covered a variety of settings, harm reduction strategies, and contexts of opioid and non-opioid substance accessibility in Canadian provinces. The use of real-world context helped to increase generalizability of our study results to actual OUD populations frequently using highly potent synthetic opioids. However, our study had several limitations. First, we had missing UDS (i.e., about 24% of UDS were missing) mainly due to loss to follow-up, and this may underlie some potential selection bias for non-imputed data on missing UDS and result in potential overestimation of substance use when imputing missing UDS as positive. However, this last bias effect is likely limited as missed visits and UDS were simultaneously applicable to our main variables of interest, that is, non-opioid substance-positive UDS and opioid-positive UDS and in both OAT arms. Also, additionaly imputing missing UDS by baseline values helped in clarifying any potential associations. Second, we did not explore potential effect of frequency and quantity of non-opioid substance use or presence of polysubstance use disorders, as well as their interaction with OAT type on associations with treatment outcomes. Such potential associations and interactions may need further study. Third, alcohol use as a central nervous system suppressor was not included among the non-opioid substances explored in our study, and alcohol use may have different associations with OAT and treatment outcomes in POUD. Fourth, our sample excluded those who used opioids for concurrent pain treatment, and study results may not be extrapolated to this population. Fifth, UDS does not distinguish between voluntary and involuntary use of non-opioid substances. Sixth, the study site was only included as a fixed-effect adjustment factor in the analyses, and the potential variation between sites in the reported associations may need further study. Finally, our study was exploratory in nature with no a priori statistical power calculation. Therefore, non-significant tested interactions should be considered with caution. For example, sensitivity analyses showed that our sample size could only detect moderate between-group differences in retention of more than 20% (and with 80% statistical power) (G*power v.3.1.9.6, Germany, 2020).

## Conclusion

Methadone did not show any overall differential effect on non-opioid substance use in adults with POUD compared to BUP/NX. However, methadone was associated with lower odds of benzodiazepine and THC use. While the full agonist properties of methadone may explain such findings, exact mechanisms may require further investigation. The implications of such effect on OAT outcomes remains poorly understood; while non-opioid substance use was not associated with OAT outcomes in our study, more refined approaches, such as qualitive or mixed studies, may be needed to fully understand the interplay between OAT, non-opioid substance use, and treatment outcomes. The integration of polysubstance use assessment and related interventions (e.g., education, psychotherapy, frequent follow-ups) should be a mainstay in therapeutic plans for adults with POUD treated with OAT.[7,20,25]

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session of a National Advisory Board Meeting (Emerging Trends BUP-XR) for Indivior Canada and has been consultant for Shinogi. MES has received partial support from Indivior's Investigator Initiated Study programme for work outside this study. SM has participated in a session of a national advisory board meeting for Indivior Canada as well as for Abbvie Canada.The OPTIMA clinical trial was registered on clinicaltrials.gov before the enrollment of the first participant (NCT03033732).

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## Supplemental Material

Supplemental material for this article is available online.

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