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Associations between fentanyl use and initiation, persistence, and retention on medications for opioid use disorder among people living with uncontrolled HIV disease

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Abstract

Background.—Associations between fentanyl use and initiation and retention on medications for opioid use disorder (MOUD) are poorly understood.

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Contributors

R.R. Cook and P. Todd Korthuis were responsible for study design, data analysis, data interpretation, and writing. R.R. Cook, C. King and C. Foot performed data analysis and data interpretation. R.R. Cook, P. Todd Korthuis, and R. Torralva drafted the manuscript. All authors provided critical review and approval of the manuscript.

Data Sharing

De-identified data from the study will be available to researchers free of charge at the NIDA Data Share website (http://datashare.nida.nih.gov/) within 18 months of study completion and data analysis, per CTN data sharing policy. Users must register for NIDA Data Share by providing a name and valid email address in order to download data, and agree to use that data in accordance with the NIDA Data Share Agreement detailed on the website.

Methods.—Data were from a multisite clinical trial comparing extended-release naltrexone (XRNTX) with treatment as usual (TAU; buprenorphine or methadone) to achieve HIV viral suppression among people with OUD and uncontrolled HIV disease. The exposure of interest was fentanyl use, as measured by urine drug screening. Outcomes were time to MOUD initiation, defined as date of first injection of XR-NTX, buprenorphine prescription, or methadone administration; MOUD persistence, the total number of injections, prescriptions, or administrations received over 24 weeks; and MOUD retention, having an injection, prescription, or administration during weeks 20 to 24.

Results.—Participants (N = 111) averaged 47 years old and 62% were male. Just over half (57%) were Black and 13% were Hispanic. Sixty-four percent of participants tested positive for fentanyl at baseline. Participants with baseline fentanyl positivity were 11 times less likely to initiate XR-NTX than those negative for fentanyl (aHR = 0.09, 95% CI 0.03 to 0.24, $p < .001$), but there was no evidence that fentanyl use impacted the likelihood of TAU initiation (aHR = 1.50, 0.67 to 3.36, $p = .323$). Baseline fentanyl use was not associated with persistence or retention on any MOUD.

Conclusions.—Fentanyl use was a substantial barrier to XR-NTX initiation for the treatment of OUD in persons with uncontrolled HIV infection. There was no evidence that fentanyl use impacted partial/full agonist initiation and, once initiated, retention on any MOUD.

Keywords

Fentanyl; Medications for opioid use disorder; Extended-release naltrexone; buprenorphine; opioid use disorder; HIV

INTRODUCTION

Approximately 2.1 million people in the United States have an opioid use disorder (OUD), leading to over 80,000 preventable overdose deaths in 2019–2020 (Ahmad et al., 2020). The opioid overdose crisis has evolved over time; initially, overdose deaths were largely attributable to prescription opioids and heroin, but since the mid-2010s, synthetic opioids such as fentanyl have become the primary source of opioid-related mortality (Gladden et al., 2019). While many overdoses are caused by contamination of the heroin supply, fentanyl and its various analogs have supplanted heroin as the most readily available and preferred opioid in some areas of the U.S. (Gryczynski et al., 2019). Fentanyl is 50 to 100 times more potent than morphine (Peng and Sandler, 1999), an active metabolite of heroin, allowing little tolerance for dosing errors, even among experienced people who use opioids. The highly lipophilic nature and rapid onset of fentanyl contribute to acute airway obstruction (laryngospasm) and chest wall rigidity (“wooden chest syndrome”) in addition to the respiratory depression seen with morphine derived drugs, precipitously increasing its lethality (Torralva and Janowsky, 2019). Fentanyl has slowed progress in addressing the opioid overdose crisis and created a new, more challenging, treatment environment as its availability increases and analogs with greater potency emerge (e.g. carfentanil) (Dai et al., 2019).

Medications for opioid use disorder (MOUD) are effective for treating individuals with OUD. However, the reach of MOUD remains narrow because of limited access, challenging initiations, and a complex regulatory environment governing MOUD prescribing and dispensing. Of over an estimated 2 million who may benefit from MOUD, only about 7% successfully initiate treatment, and only half of those who receive treatment are retained on MOUD after 6 months (Williams et al., 2019). Among people living with HIV, there is substantial evidence that MOUD can improve HIV outcomes, including higher rates of treatment engagement (Lucas et al., 2010), ART initiation, and viral suppression (Altice et al., 2011; Kim et al., 2021). However, rates of MOUD treatment may be lower among people living with HIV (Tsui et al., 2021), possibly because of stigma, challenging psychiatric comorbidities, high rates of homelessness, other substance use disorders, and other factors.

Standard induction protocols onto opioid partial agonist (e.g., buprenorphine) or antagonist (extended-release naltrexone; XR-NTX) therapy require a period of opioid abstinence, typically ~12 hours for buprenorphine induction, and 7–10 days for XR-NTX, in order to avoid precipitated withdrawal. Because of its high potency, short duration of effect, and lipophilicity, fentanyl use may present a significant challenge to successful MOUD initiation. Individuals using fentanyl report faster onset, greater severity, and longer duration of withdrawal symptoms compared to heroin (Gryczynski et al., 2019). Emerging pharmacokinetic research suggests that redistribution of fentanyl into adipose tissue (Peng and Sandler, 1999) and protracted clearance (Huhn et al., 2020) may contribute to precipitated withdrawal during MOUD induction among people who use fentanyl (Antoine et al., 2020; Bisaga, 2019; Silverstein et al., 2019). However, few empiric data inform the role of fentanyl use in MOUD initiation.

Following initiation, the effects of fentanyl use on MOUD retention may vary by treatment modality. One retrospective chart review found that six-month retention on buprenorphine was worse for individuals with positive fentanyl toxicology at treatment initiation (38% fentanyl-positive vs. 47% heroin-positive vs. 51% who were negative for both), although results did not meet the threshold for statistical significance (Wakeman et al., 2019). Another found that 12-month retention on methadone was slightly better for individuals who were fentanyl-positive at intake than those who were negative (53% vs. 47%) (Stone et al., 2020). To our knowledge, no studies have prospectively examined the impact of fentanyl use on initiation or retention on MOUD, including XR-NTX.

Using data from a comparative effectiveness clinical trial of MOUD treatment, we examined the impact of fentanyl use on initiating and remaining on MOUD treatment. We hypothesized that fentanyl use would reduce the likelihood of MOUD initiation, especially among participants randomized to receive XR-NTX. We also hypothesized that individuals using fentanyl at baseline would receive fewer doses of MOUD throughout the study and be less likely to remain on MOUD at 24 weeks (end of study).

METHODS

Data for this study were drawn from the Comparing Treatments for HIV-Infected Opioid Users in an Integrated Care Effectiveness Study (CHOICES) scale-up trial (National Drug Abuse Treatment Clinical Trials Network protocol number 0067). The CHOICES study was approved by the Advarra Institutional Review Board (IRB00000971) and all subjects provided written informed consent prior to participation.

Briefly, CHOICES was an open-label, non-blinded, non-inferiority trial comparing XR-NTX vs. treatment as usual (TAU) for achieving HIV viral suppression among individuals with HIV and OUD. The trial was conducted from February 2018 to November 2019 in six geographically diverse U.S. HIV clinics (Miami, FL; Washington, D.C; Baltimore, MD; Chicago, IL; Lexington, KY; Tarzana, CA). All study participants were people living with HIV and OUD. Eligibility criteria included HIV RNA PCR > 200 copies/mL, moderate to severe opioid use disorder by DSM-5 criteria without MOUD treatment in the past 4 weeks, and willingness to initiate MOUD treatment and establish HIV care. Study participants completed questionnaire, clinical, and biological assessments every four weeks for 24 weeks. Additional information about the study procedures and major results can be found on Clinicaltrials.gov, registration number NCT03275350.

Induction procedures

Participants assigned to XR-NTX underwent medically supervised withdrawal and naltrexone induction in outpatient HIV clinic or residential settings in accordance with published guidelines (Sigmon et al., 2012). Study clinicians were trained in the use of three approaches to withdrawal management, including referral to inpatient medically supervised withdrawal with injection of XR-NTX upon release, a five to seven-day protocol that allowed for buprenorphine and benzodiazepines (Bisaga et al., 2018; Sullivan et al., 2017), and a five to seven-day protocol that avoided controlled substances (Rudolf et al., 2018). Study clinicians were allowed to choose from this menu of options and adapt specific procedures to the individual participant and setting. The lead study team supported study clinicians with technical assistance regarding XR-NTX induction procedures during biweekly national study clinician calls. Participants assigned to TAU were offered the standard treatment for OUD provided at each HIV clinic. All clinics offered opioid agonist treatment services (buprenorphine or methadone), with induction procedures, the schedule of medical care, and behavioral support determined by the treating provider.

Exposure and outcome definitions

The exposure of interest, fentanyl use, was assessed via urine drug screening (UDS). UDS were collected with an FDA-approved one-step temperature-controlled test cup; a further validity check was performed using a commercially available adulterant test strip. Fentanyl is generally detectable in urine for 1–3 days after exposure (Silverstein et al., 1993), but can persist for much longer in frequent users (Huhn et al., 2020). Participants completed UDS at baseline and every four weeks for the 24-week study period, for a maximum of seven UDS per participant. Study outcomes, MOUD initiation, persistence, and retention, were determined using XR-NTX injection logs and monthly pharmacy, methadone dispensing,

and/or medical record data abstraction. For participants initiating XR-NTX, the date of first injection, the number of injections received over 24 weeks, and having an injection between weeks 20–24 were used to define initiation, persistence, and retention, respectively. For other MOUD, the initiation date was set as the first day a prescription for buprenorphine or administered dose of methadone was documented. For those who initiated MOUD, persistence was defined as the number of 4-week periods (hereafter referred to as months) where receipt of MOUD was documented at any point during the month, and retention was defined as receiving MOUD between weeks 20–24 of the study. Analyses of persistence and retention were limited to participants who initiated MOUD. No participants randomized to the TAU arm received any XR-NTX injections, but some participants assigned to XR-NTX initiated other MOUD. Analyses of "any MOUD" include these participants, but analysis of "assigned study medication" do not. To estimate the impact of fentanyl on buprenorphine initiation and retention, analyses were repeated excluding TAU participants initiating methadone. A similar analysis of methadone could not be completed because of the small number of participants receiving methadone. Participants who did not initiate any MOUD were censored on their last day of contact with study staff.

Statistical analyses.

Prior to analyses, participant demographic and clinical characteristics were summarized and compared by baseline fentanyl use using Chi-square and t-tests. Cumulative incidences of MOUD initiation by baseline fentanyl use were described using Kaplan-Meier curves. Mixed effects Cox proportional hazards models were used to estimate associations between baseline and time-varying fentanyl use and initiation on 1) any MOUD and 2) assigned study medications (XR-NTX or TAU), controlling for age, sex, race, ethnicity, severity of substance use [Addiction Severity Index summary score (Cacciola et al., 2007)], anxiety or depression [EQ5D single item screener (Herdman et al., 2011)], and stimulant (cocaine, methamphetamine, or amphetamine), benzodiazepine, and other non-fentanyl opioid use. Models were first fit without interactions between fentanyl use and treatment assignment to estimate the overall effect of fentanyl on MOUD initiation. Then, we included an interaction term and estimated fentanyl effects within each randomized treatment group. Study site was included as a random effect in Cox models. Prior to analysis, the proportional hazards assumption was verified by examining and testing for an association between scaled Schoenfeld residuals and (transformed) study time.

Among those initiating MOUD, persistence on MOUD was analyzed with Poisson regression (a negative binomial model was also considered, but there was no evidence of overdispersion). The number of months receiving MOUD was the outcome and baseline fentanyl use the exposure of interest; covariates were the same as the initiation models. Finally, logistic regression was used to examine the association between baseline fentanyl use and retention on MOUD at 24 weeks (among those who initiated), controlling for the same covariate set. To achieve model convergence, study site was included as a fixed effect in analyses of persistence and retention. All analyses were conducted using R v.3.6.1 with the 'survival', 'coxme', and 'MASS' packages at a two-tailed level of significance of .05.

RESULTS

Participant characteristics

Of 376 individuals screened for participation in the parent clinical trial, 114 were enrolled. The most common reasons for exclusion were having a suppressed HIV viral load (n = 87) or not meeting DSM-5 criteria for OUD (n = 52). For the current paper, three TAU participants who refused agonist therapy were excluded, resulting in an analytic sample of 111 participants. Participants (N = 111) were 47 years old, on average (SD = 11 years), and 62% were male. Just over half (57%) were Black, 36% were White, and 13% were Hispanic. Nearly half (43%) had less than a high school education, only five participants reported part- or full-time employment (5%), 39% had been houseless for at least one day in the past month, and 87% had a history of incarceration. Seventy-eight percent reported moderate or severe anxiety or depression. Participants had a mean baseline CD4 cell count of 411 cells/mm^3 (SD = 302) and mean viral load of 4.0 (SD = 0.97) log_{10} copies/mL. Sixty percent were hepatitis C antibody positive at baseline. At baseline, 71 (64%) participants were UDS positive for fentanyl, 49% were UDS positive for (non-fentanyl) opioids, 6% were positive for methamphetamine or amphetamines, 62% positive for cocaine, and 21% positive for benzodiazepines. Fifty-nine percent of participants reported a history of nonfatal opioid overdose. Fentanyl-positive participants were more likely have a positive UDS for other opioids and cocaine than fentanyl-negative participants (Table 1). Other demographic and clinical characteristics did not differ by baseline fentanyl positivity.

MOUD Initiation

Overall, 78/111 participants (70%) initiated MOUD during the study period, regardless of treatment assignment. Forty-four initiated buprenorphine (56% of those who initiated MOUD), 26 initiated XR-NTX (33%), and 8 initiated methadone (10%). 55/111 participants were randomized to XR-NTX; aside from the 26 receiving XR-NTX, seven people originally assigned to XR-NTX initiated buprenorphine and five methadone. Of 59 participants randomized to TAU, 37 received buprenorphine and 3 methadone (no participants randomized to TAU received XR-NTX). Among those who initiated MOUD, the median number of days between randomization and initiation was 21 (interquartile range 7 to 69) days [XR-NTX median = 11 (IQR 6–41); buprenorphine median = 25 (9–77); methadone median = 62 (5–105)]. The mean daily dose of buprenorphine was 14.6 mg, excluding 10 participants who received only one prescription (and thus may have never received more than an induction dose). The mean daily dose of methadone was 73.3 mg.

Figure 1 presents Kaplan-Meier curves of MOUD initiation by baseline fentanyl positivity. Overall, participants who tested positive for fentanyl at baseline were half as likely to initiate MOUD as compared to those who were negative for fentanyl (adjusted HR [aHR] = 0.47, 95% CI 0.27 to 0.83, $p = .009$). When analyzing initiation on assigned study medication, participants with baseline fentanyl positivity were 11 times less likely to initiate XR-NTX than those negative for fentanyl (aHR = 0.09, 95% CI 0.03 to 0.24, $p < .001$). There was no evidence that fentanyl use impacted TAU initiation (aHR = 1.50, 0.67 to 3.36, $p = .323$) or initiation of buprenorphine specifically (aHR = 1.35, 0.59 to 3.11, $p = .477$). All p values for

interactions between fentanyl use and treatment assignment were <.001. Effect sizes were slightly larger when fentanyl use was treated as a time-varying covariate (Table 2).

Of the 10 participants who never received more than one prescription for buprenorphine, 5 were UDS positive for fentanyl at baseline. Although we cannot confirm whether those participants were successfully inducted on buprenorphine or not, we performed a sensitivity analysis assuming all were induction failures and thus did not successfully initiate MOUD. Results of this analysis still showed no evidence that fentanyl adversely affected buprenorphine initiation (aHR = 1.55, 0.58 to 4.14, $p = .378$)

MOUD Persistence

Analyses of MOUD persistence included 76 of 78 participants initiating MOUD, as duration data was not available for two XR-NTX participants initiating buprenorphine. Among those initiating buprenorphine, the mean number of months with a prescription was 2.6 (SD = 1.5); only two participants (5%) had a prescription for all six months. The mean number of XR-NTX injections received was 3.3 (SD = 2.1) and seven of 26 participants (27%) got all six possible injections. Finally, the mean number of months on methadone was 4.5 (SD = 2) and four of eight participants (50%) were administered methadone in all six months. Baseline fentanyl use had little impact on MOUD persistence overall (adjusted IRR [aIRR] = 0.99, 95% CI 0.69 to 1.42, $p = .953$) or by assigned medication (XR-NTX aIRR = 0.97, 95% CI 0.48 to 1.95, $p = .927$; TAU aIRR = 1.27, 0.78 to 2.07, $p = .338$; buprenorphine aIRR = 1.17, 0.71 to 1.94, $p = .537$; Table 3).

Retention on MOUD

Overall, 37/78 participants were retained on MOUD at 6 months (47%); 18/44 on buprenorphine (41%), 8/8 on methadone (100%), and 11/26 on XR-NTX (42%). There was no evidence that baseline fentanyl use impacted retention on any MOUD (adjusted OR [aOR] = 1.37, 95% CI 0.36 to 5.28, $p = .640$) or assigned medication (XR-NTX aOR = 0.82, 95% CI 0.04 to 16.01, $p = .896$; TAU aOR = 0.87, 0.12 to 5.95, $p = .884$; buprenorphine aOR = 0.58, 0.08 to 4.21, $p = .591$; Table 4).

DISCUSSION

In a clinical trial of treatment-seeking participants with uncontrolled HIV disease and untreated OUD, fentanyl use was the most frequently detected opioid and substantially decreased XR-NTX initiation, but not initiation of buprenorphine or methadone. Among participants that initiated MOUD, there was little evidence that fentanyl use impacted retention on MOUD. As fentanyl and other highly potent synthetic opioids increasingly become the leading contributors to overdose deaths, this study provides important data suggesting that fentanyl use may not adversely affect buprenorphine initiation nor retention and persistence on any MOUD.

Even prior to widespread fentanyl use, induction onto opioid antagonist therapy (i.e., XR-NTX) proved challenging. The largest U.S. comparative effectiveness study to date initiated treatment in medically supervised withdrawal inpatient facilities; still, only 72% of participants randomized to XR-NTX initiated treatment as compared to 94% of those

randomized to buprenorphine (Lee et al., 2018). The pilot for the current study, CTN-0055, noted 68% induction success in the XR-NTX group compared to 96% among TAU participants (Korthuis et al., 2017). Widespread use of fentanyl and its analogues is likely to exacerbate this disparity. Fentanyl is highly lipophilic, and an injected dose will rapidly redistribute from the bloodstream into adipose tissue where it releases back into plasma over a period of 8–12 hours. This long elimination half-life causes repeated doses to accumulate, leading to much slower clearance of fentanyl compared to morphine (Peng and Sandler, 1999). Consequently, individuals who frequently use fentanyl may experience prolonged and intensified withdrawal, making initiation onto XR-NTX extremely challenging. Our data provide important clinical evidence that underscores this challenge, and suggest that intensive induction protocols including inpatient medically supervised withdrawal management may be required for successful XR-NTX treatment initiation for persons using fentanyl.

In contrast to XR-NTX, we found no evidence that fentanyl use affected the likelihood of initiating partial or full opioid agonist therapy (buprenorphine or methadone). Although observational evidence and clinical experience describe challenges with buprenorphine induction among people who use fentanyl, including concerns about higher rates of precipitated withdrawal (Antoine et al., 2020; Bisaga, 2019; Silverstein et al., 2019), novel cross-taper induction strategies that have emerged since our study was initially designed may be successful in this population (Ahmed et al., 2020). Buprenorphine induction procedures in our study were determined by treating providers who were trained in early naltrexone cross-tapering strategies and aggressive withdrawal symptom management (Rudolf et al., 2018; Sibai et al., 2020). Unfortunately, we were not able to examine the impact of fentanyl on methadone initiation specifically, as only a few participants initiated methadone. However, our data encouragingly supports the feasibility of initiating buprenorphine among people using fentanyl, and we have little reason to believe results would be different for methadone, which does not produce precipitated withdrawal.

Also encouraging is the lack of evidence showing that, among those who started treatment, fentanyl use decreased persistence and retention on MOUD, including XR-NTX. Although not conclusive, our data add to the very limited clinical evidence suggesting that, once initiated, MOUD treatment continuation is not impeded by baseline fentanyl use in a treatment-seeking population (Stone et al., 2020; Wakeman et al., 2019). However, analyses to date (including ours) have only been able to examine fentanyl use as a binary exposure. Several studies demonstrate reduced retention on buprenorphine or methadone with increasing frequency of heroin/opioid use (O'Connor et al., 2020); frequency of fentanyl use may similarly decrease retention. Another limitation to our findings was that, for analyses of persistence and retention, only participants' baseline fentanyl use was considered. To better understand the impact of fentanyl on treatment retention, future studies should utilize time-varying models to reflect the dynamic relationship between fentanyl use and MOUD treatment over time (Daniel et al., 2011; Robins et al., 2000).

In this study, we were unable to determine whether individuals were using fentanyl intentionally or unintentionally testing positive for fentanyl-contaminated drugs. Anecdotal reports from site investigators suggested that intentional use was ubiquitous in East

coast sites (including the study's largest recruiting sites), while unintentional use was more common in Midwestern and Western states, consistent with differences in regional prevalence of fentanyl use during the study period (Hedegaard et al., 2019). As such, fentanyl 'exposure' may be a more accurate description than fentanyl 'use' for some participants, but we are reasonably confident that the majority were knowingly using fentanyl. Although all analyses accounted for study site, intentional and possibly more frequent fentanyl use may explain some of the observed variability in MOUD induction success. With new data showing rapid expansion of fentanyl, its analogues, and other highly potent synthetic opioids (e.g., U47700) into Western states, intentional fentanyl use is quickly becoming the norm nationwide (Shover et al., 2020).

Our results should be considered in light of some additional limitations. First, several commonly available fentanyl analogs are not detected by urine drug screens, and the true prevalence of fentanyl analogues may be higher than indicated by our data. Second, this study was conducted exclusively among individuals living with uncontrolled HIV infection, and may not be generalizable to others living with OUD. MOUD was delivered in HIV care clinics, and participants received supplementary services related to their HIV care (e.g., primary care, peer support, and social services) that may have affected MOUD outcomes as well. Also, participants may have provided additional, potentially random drug screenings as part of their OUD treatment, which were not recorded in the study database. Finally, this study was conducted in a relatively small sample and null findings may be susceptible to type II error, especially treatment assignment-stratified results. However, encouragingly, most effect sizes of fentanyl on TAU initiation, persistence, and retention were small or even positive.

As rates of fentanyl use and overdose rapidly increase nationwide (Gladden et al., 2019), increased understanding of the effects of fentanyl and its analogs on MOUD treatment initiation and retention are urgently needed. Our study highlights the distinct challenge that fentanyl use presents to XR-NTX initiation and provides some assurance that buprenorphine initiation is feasible even in people using fentanyl. The unique pharmacology of fentanyl is likely to make withdrawal management prior to induction even more difficult. Yet, once this hurdle is overcome, baseline fentanyl use did not appear to negatively impact retention on MOUD, although more research is needed. Clearly, efforts to increase treatment initiation, improve treatment retention and reduce overdose must identify and address the unique challenges that fentanyl use presents to all persons with OUD.

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Conflict of Interest

Dr. Korthuis reports grants from NIH National Institute on Drug Abuse and serves as principal investigator for NIH-funded studies that accept donated study medication from Indivior (buprenorphine) and Alkermes (extended-release naltrexone). Alkermes donated XR-NTX for CHOICES study participants. Dr. Tookes reports grants from Gilead Sciences. Other authors report no conflicts of interest.

References

Ahmad FB, Rossen LM, Sutton P, 2020. Provisional drug overdose death counts. National Center for Health Statistics.

Ahmed S, Bhivandkar S, Lonergan BB, Suzuki J, 2020. Microinduction of Buprenorphine/Naloxone: A Review of the Literature. Am J Addict.

Altice FL, Bruce RD, Lucas GM, Lum PJ, Korthuis PT, Flanigan TP, Cunningham CO, Sullivan LE, Vergara-Rodriguez P, Fiellin DA, Cajina A, Botsko M, Nandi V, Gourevitch MN, Finkelstein R, 2011. HIV treatment outcomes among HIV-infected, opioid-dependent patients receiving buprenorphine/naloxone treatment within HIV clinical care settings: results from a multisite study. J Acquir Immune Defic Syndr 56 Suppl 1(Suppl 1), S22–32.

Antoine D, Huhn AS, Strain EC, Turner G, Jardot J, Hammond AS, Dunn KE, 2020. Method for Successfully Inducting Individuals Who Use Illicit Fentanyl Onto Buprenorphine/Naloxone. Am J Addict.

Bisaga A, 2019. What should clinicians do as fentanyl replaces heroin? Addiction 114(5), 782–783. [PubMed: 30661265]

Bisaga A, Mannelli P, Yu M, Nangia N, Graham CE, Tompkins DA, Kosten TR, Akerman SC, Silverman BL, Sullivan MA, 2018. Outpatient transition to extended-release injectable naltrexone for patients with opioid use disorder: A phase 3 randomized trial. Drug Alcohol Depend 187, 171–178. [PubMed: 29674251]

Cacciola JS, Alterman AI, McLellan AT, Lin YT, Lynch KG, 2007. Initial evidence for the reliability and validity of a “Lite” version of the Addiction Severity Index. Drug Alcohol Depend 87(2–3), 297–302. [PubMed: 17045423]

Dai Z, Abate MA, Smith GS, Kraner JC, Mock AR, 2019. Fentanyl and fentanyl-analog involvement in drug-related deaths. Drug Alcohol Depend 196, 1–8. [PubMed: 30658219]

Daniel RM, De Stavola BL, Cousens SN, 2011. Gformula: Estimating Causal Effects in the Presence of Time-Varying Confounding or Mediation using the G-Computation Formula. The Stata Journal 11(4), 479–517.

Gladden RM, O’Donnell J, Mattson CL, Seth P, 2019. Changes in Opioid-Involved Overdose Deaths by Opioid Type and Presence of Benzodiazepines, Cocaine, and Methamphetamine - 25 States, July-December 2017 to January-June 2018. MMWR Morb Mortal Wkly Rep 68(34), 737–744.

Gryczynski J, Nichols H, Schwartz RP, Mitchell SG, Hill P, Wireman K, 2019. Fentanyl exposure and preferences among individuals starting treatment for opioid use disorder. Drug Alcohol Depend 204, 107515. [PubMed: 31525569]

Hedegaard H, Bastian BA, Trinidad JP, Spencer MR, Warner M, 2019. Regional Differences in the Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2017. Natl Vital Stat Rep 68(12), 1–16.

Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X, 2011. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 20(10), 1727–1736. [PubMed: 21479777]

Huhn AS, Hobelmann JG, Oyler GA, Strain EC, 2020. Protracted renal clearance of fentanyl in persons with opioid use disorder. Drug Alcohol Depend 214, 108147. [PubMed: 32650192]

Kim J, Lesko CR, Fojo AT, Keruly JC, Moore RD, Chander G, Lau B, 2021. The Effect Of Buprenorphine On HIV Viral Suppression. Clin Infect Dis.

Korthuis PT, Lum PJ, Vergara-Rodriguez P, Ahamad K, Wood E, Kunkel LE, Oden NL, Lindblad R, Sorensen JL, Arenas V, Ha D, Mandler RN, McCarty D, 2017. Feasibility and safety of extended-release naltrexone treatment of opioid and alcohol use disorder in HIV clinics: a pilot/feasibility randomized trial. Addiction 112(6), 1036–1044. [PubMed: 28061017]

Lee JD, Nunes EV Jr., Novo P, Bachrach K, Bailey GL, Bhatt S, Farkas S, Fishman M, Gauthier P, Hodgkins CC, King J, Lindblad R, Liu D, Matthews AG, May J, Peavy KM, Ross S, Salazar D, Schkolnik P, Shmueli-Blumberg D, Stablein D, Subramaniam G, Rotrosen J, 2018. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet 391(10118), 309–318. [PubMed: 29150198]

Lucas GM, Chaudhry A, Hsu J, Woodson T, Lau B, Olsen Y, Keruly JC, Fiellin DA, Finkelstein R, Barditch-Crovo P, Cook K, Moore RD, 2010. Clinic-based treatment of opioid-dependent HIV-infected patients versus referral to an opioid treatment program: A randomized trial. Ann Intern Med 152(11), 704–711. [PubMed: 20513828]

O'Connor AM, Cousins G, Durand L, Barry J, Boland F, 2020. Retention of patients in opioid substitution treatment: A systematic review. PLOS ONE 15(5), e0232086. [PubMed: 32407321]

Peng Philip W.H., Sandler Alan N., 1999. A Review of the Use of Fentanyl Analgesia in the Management of Acute Pain in Adults Anesthesiology 90(2), 576–599. [PubMed: 9952166]

Robins JM, Hernán MA, Brumback B, 2000. Marginal structural models and causal inference in epidemiology. Epidemiology 11(5), 550–560. [PubMed: 10955408]

Rudolf G, Walsh J, Plawman A, Gianutsos P, Alto W, Mancl L, Rudolf V, 2018. A novel non-opioid protocol for medically supervised opioid withdrawal and transition to antagonist treatment. Am J Drug Alcohol Abuse 44(3), 302–309. [PubMed: 28795846]

Shover CL, Falasinnu TO, Dwyer CL, Santos NB, Cunningham NJ, Freedman RB, Vest NA, Humphreys K, 2020. Steep increases in fentanyl-related mortality west of the Mississippi River: Recent evidence from county and state surveillance. Drug and alcohol dependence 216, 108314–108314. [PubMed: 33038637]

Sibai M, Mishlen K, Nunes EV, Levin FR, Mariani JJ, Bisaga A, 2020. A week-long outpatient induction onto XR-naltrexone in patients with opioid use disorder. Am J Drug Alcohol Abuse 46(3), 289–296. [PubMed: 31860366]

Sigmon SC, Bisaga A, Nunes EV, O'Connor PG, Kosten T, Woody G, 2012. Opioid detoxification and naltrexone induction strategies: recommendations for clinical practice. Am. J. Drug Alcohol Abuse 38(3), 187–199. [PubMed: 22404717]

Silverstein JH, Rieders MF, McMullin M, Schulman S, Zahl K, 1993. An analysis of the duration of fentanyl and its metabolites in urine and saliva. Anesth Analg 76(3), 618–621. [PubMed: 8452277]

Silverstein SM, Daniulaityte R, Martins SS, Miller SC, Carlson RG, 2019. "Everything is not right anymore": Buprenorphine experiences in an era of illicit fentanyl. Int J Drug Policy 74, 76–83. [PubMed: 31563098]

Stone AC, Carroll JJ, Rich JD, Green TC, 2020. One year of methadone maintenance treatment in a fentanyl endemic area: Safety, repeated exposure, retention, and remission. J Subst Abuse Treat 115, 108031. [PubMed: 32600619]

Sullivan M, Bisaga A, Pavlicova M, Choi CJ, Mishlen K, Carpenter KM, Levin FR, Dakwar E, Mariani JJ, Nunes EV, 2017. Long-Acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine. Am J Psychiatry 174(5), 459–467. [PubMed: 28068780]

Torralva R, Janowsky A, 2019. Noradrenergic Mechanisms in Fentanyl-Mediated Rapid Death Explain Failure of Naloxone in the Opioid Crisis. J Pharmacol Exp Ther 371(2), 453–475. [PubMed: 31492824]

Tsui JI, Akosile MA, Lapham GT, Boudreau DM, Johnson EA, Bobb JF, Binswanger IA, Yarborough BJH, Glass JE, Rossom RC, Murphy MT, Cunningham CO, Arnsten JH, Thakral M, Saxon AJ, Merrill JO, Samet JH, Bart GB, Campbell CI, Loree AM, Silva A, Stotts AL, Ahmedani B, Braciszewski JM, Hechter RC, Northrup TF, Horigian VE, Bradley KA, 2021. Prevalence and Medication Treatment of Opioid Use Disorder Among Primary Care Patients with Hepatitis C and HIV. J Gen Intern Med 36(4), 930–937. [PubMed: 33569735]

Wakeman SE, Chang Y, Regan S, Yu L, Flood J, Metlay J, Rigotti N, 2019. Impact of Fentanyl Use on Buprenorphine Treatment Retention and Opioid Abstinence. J Addict Med 13(4), 253–257. [PubMed: 30550392]

Williams AR, Nunes EV, Bisaga A, Levin FR, Olfson M, 2019. Development of a Cascade of Care for responding to the opioid epidemic. Am J Drug Alcohol Abuse 45(1), 1–10. [PubMed: 30675818]

Highlight

- Fentanyl use decreases extended-release naltrexone initiation
- Fentanyl use may not affect buprenorphine or methadone initiation
- Fentanyl use may not affect retention on medication for opioid use disorder

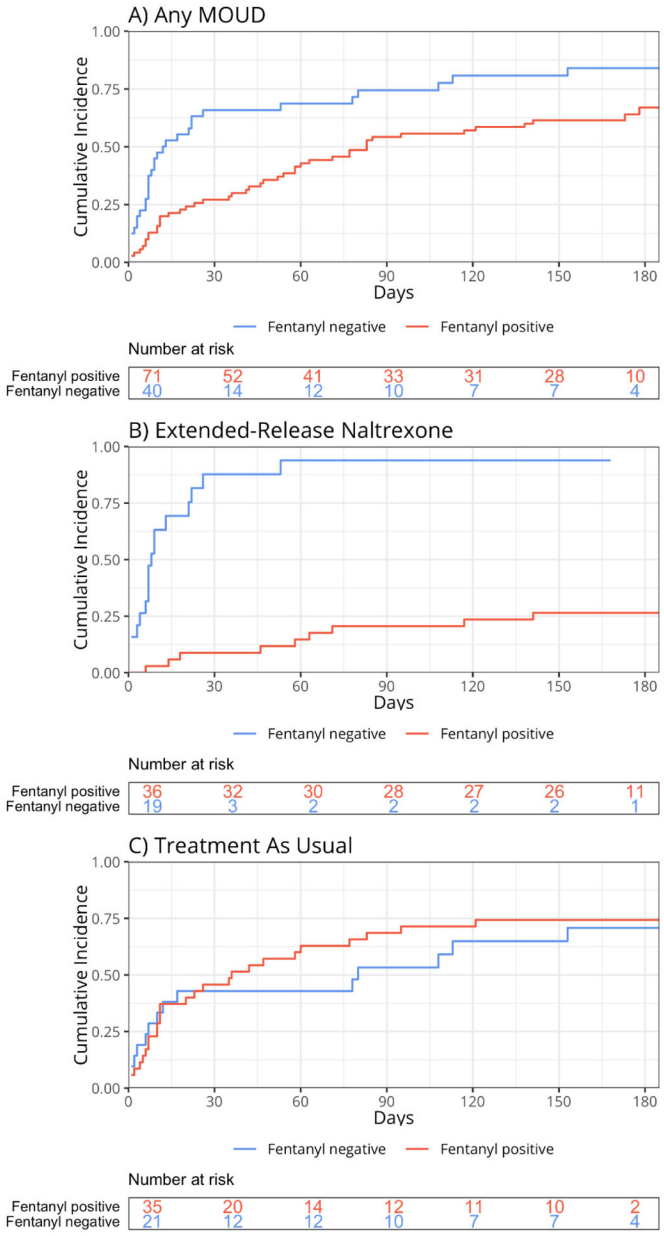

Figure 1.

Kaplan-Meier cumulative incidence of A) initiation on any medication for opioid use disorder (MOUD), B) initiation on extended-release naltrexone, and C) initiation on treatment as usual (buprenorphine or methadone).

Table 1.

Participant characteristics by baseline fentanyl positivity, N = 111 CHOICES participants

Characteristic	Overall	Fentanyl positive n=71	Fentanyl negative n=40	*p*
Mean Age (SD)	47 (11.1)	46 (10.8)	48 (11.8)	.53
Male	69 (62.2%)	41 (57.8%)	28 (70%)	.23
Race/Ethnicity				.71
Black	63 (56.8%)	41 (57.7%)	22 (55%)	
White	40 (36%)	26 (36.6%)	14 (35%)	
Other	8 (7.2%)	4 (5.6%)	4 (10%)	
Hispanic	14 (12.6%)	9 (12.7%)	5 (12.5%)	.99
< High School Education	48 (43.2%)	32 (45.1%)	16 (40%)	.69
Employed	5 (4.5%)	3 (4.2%)	2 (5%)	.99
Anxiety or depression				.33
None	31 (27.9%)	17 (23.9%)	14 (35%)	
Moderate	63 (56.8%)	44 (62%)	19 (47.5%)	
Severe	17 (15.3%)	10 (14.1%)	7 (17.5%)	
Houseless in past 30 days	43 (38.7%)	29 (40.8%)	14 (35%)	.69
History of incarceration	96 (86.5%)	62 (87.3%)	34 (85%)	.78
Mean CD4 cells/mm^3 (SD)	411.1 (302.1)	383.9 (276.8)	459.8 (341.4)	.24
HIV viral load (log_{10} copies/mL) (SD)	4.0 (0.97)	4.0 (1.0)	4.1 (1.0)	.52
HCV antibody positive	66 (60%)	44 (62.9%)	22 (55%)	.43
UDS				
Opioids	54 (48.6%)	47 (66.2%)	7 (17.5%)	<.001
Methamphetamine/Amphetamines	7 (6.3%)	4 (5.6%)	3 (7.5%)	.7
Cocaine	69 (62.2%)	54 (76.1%)	15 (37.5%)	<.001
Benzodiazepines	23 (20.7%)	15 (21.1%)	8 (20%)	.99
History of opioid overdose	65 (58.6%)	42 (59.2%)	23 (57.5%)	.99

Table 2.

Associations between baseline and time-varying fentanyl use and medications for opioid use disorder (MOUD) initiation, N = 111 CTN 0067 CHOICES participants.

	N initiating	HR[a] (95% CI); *p*	Adjusted HR[b] (95% CI); *p*
Baseline fentanyl use			
Any MOUD			
Fentanyl positive	46	0.51 (0.31, 0.83); .007	0.47 (0.27, 0.83); .009
Fentanyl negative	32	Ref	Ref
Assigned study medication *			
XR-NTX			
Fentanyl positive	9	0.08 (0.03, 0.20); <.001	0.09 (0.03, 0.24); <.001
Fentanyl negative	17	Ref	Ref
TAU[c]			
Fentanyl positive	26	1.32 (0.66, 2.63); .437	1.50 (0.67, 3.36); .323
Fentanyl negative	14	Ref	Ref
Buprenorphine			
Fentanyl positive	23	1.21 (0.60, 2.45); .595	1.35 (0.59, 3.11); .477
Fentanyl negative	14	Ref	Ref
Time-varying fentanyl use			
Any MOUD			
Fentanyl positive	54	0.38 (0.24, 0.63); <.001	0.54 (0.30, 0.98); .041
Fentanyl negative	24	Ref	Ref
Assigned study medication *			
XR-NTX			
Fentanyl positive	11	0.04 (0.02, 0.12); <.001	0.06 (0.02, 0.17); <.001
Fentanyl negative	15	Ref	Ref
TAU			
Fentanyl positive	32	1.28 (0.63, 2.61); .490	1.58 (0.71, 3.54); .261
Fentanyl negative	8	Ref	Ref
Buprenorphine			
Fentanyl positive	29	1.19 (0.57, 2.45); .644	1.41 (0.62, 3.21); .418
Fentanyl negative	8	Ref	Ref

[a] Adjusted for study site only

[b] Adjusted for study site, age, sex, race, ethnicity, severity of substance use, anxiety or depression, and stimulant, benzodiazepine, and other opioid use

[c] Treatment as usual includes buprenorphine or methadone

* *p* for interaction between fentanyl use and treatment assignment <.001

Table 3.

Associations between baseline fentanyl use and persistence on 1) any medications for opioid use disorder (MOUD) and 2) assigned study MOUD (N = 76 participants initiating MOUD with duration data).

	Mean (sd), Median	**IRR[a] (95% CI); *p***	**Adjusted IRR[b] (95% CI); *p***
Any MOUD			
Fentanyl positive	3.07 (1.73), 3	0.94 (0.70, 1.27); .689	0.99 (0.69, 1.42); .953
Fentanyl negative	3.19 (1.99), 3	Ref	Ref
Assigned study medication			
XR-NTX			
Fentanyl positive	2.78 (1.86), 2	0.82 (0.49, 1.35); .426	0.97 (0.48, 1.95); .927
Fentanyl negative	3.64 (2.21), 4	Ref	Ref
TAU[c]			
Fentanyl positive	3.13 (1.75), 3	1.23 (0.79, 1.94); .362	1.27 (0.78, 2.07); .338
Fentanyl negative	2.50 (1.56), 2.5	Ref	Ref
Buprenorphine			
Fentanyl positive	2.71 (1.45), 3	1.09 (0.69, 1.75); .702	1.17 (0.71, 1.94); .537
Fentanyl negative	2.50 (1.56), 2.5	Ref	Ref

[a] Adjusted for study site only

[b] Adjusted for study site, age, sex, race, ethnicity, severity of substance use, anxiety or depression, and stimulant, benzodiazepine, and other opioid use

[c] Treatment as usual includes buprenorphine or methadone

Table 4.

Associations between baseline fentanyl use and retention on 1) any medication for opioid use disorder (MOUD) and 2) assigned study MOUD (N = 78 participants initiating MOUD with retention data).

	N (%)	OR[a] (95% CI); *p*	Adjusted OR[b] (95% CI); *p*
Any MOUD			
Fentanyl positive	23/46 (50%)	1.15 (0.40, 3.31); .793	1.37 (0.36, 5.28); .640
Fentanyl negative	14/32 (44%)	Ref	Ref
Assigned study medication			
XR-NTX			
Fentanyl positive	4/9 (44%)	0.84 (0.20, 3.55); .809	0.82 (0.04, 16.01); .896
Fentanyl negative	7/17 (41%)	Ref	Ref
TAU[c]			
Fentanyl positive	10/26 (38%)	0.94 (0.16, 5.39); .946	0.87 (0.12, 5.95); .884
Fentanyl negative	6/17 (35%)	Ref	Ref
Buprenorphine			
Fentanyl positive	7/23 (30%)	0.62 (0.14, 2.75); .531	0.58 (0.08, 4.21); .591
Fentanyl negative	6/14 (43%)	Ref	Ref

[a] Adjusted for study site only

[b] Adjusted for study site, age, sex, race, ethnicity, severity of substance use, anxiety or depression, and stimulant, benzodiazepine, and other opioid use

[c] Treatment as usual includes buprenorphine or methadone