A CHANGING EPIDEMIC AND THE RISE OF OPIOID AND STIMULANT CO-USE

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A CHANGING EPIDEMIC AND THE RISE OF OPIOID AND STIMULANT CO-USE

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EDITORIAL
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Editorial: A Changing Epidemic and the Rise of Opioid-Stimulant Co-Use

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Editorial on the Research topic

A Changing Epidemic and the Rise of Opioid-Stimulant Co-Use

BACKGROUND

The current opioid crisis in the United States has been escalating for the past two decades, and it has only worsened since the emergence of coronavirus disease in 2019 (COVID-19) (1, 2). The COVID-19 pandemic brought up unprecedented challenges in dealing with the opioid crisis, including those falling under the (i) public policy level: disruptions in addiction treatment recovery services, delivery of mental health/harm reduction services; (ii) individual level: loss of work and worsening of pre-existing psychiatric conditions; and (iii) interpersonal level: a lack of peer support, all of which may lead to increased opioid use, relapse risk, and overdoses (1, 3). The opioid epidemic and overdose deaths have been described as a "triple wave epidemic," with the first wave involving prescription opioids, followed by heroin-related overdoses, and the current wave involving illicit fentanyl and fentanyl analogs (4). The triple wave crisis has been amplified by a "fourth wave," which has been dominated by fentanyl but also includes cocaine and methamphetamine-related deaths (5). Although there has been a decline in overdose deaths involving prescription opioids, the opioid crisis has worsened overall (5). The growing use of synthetic opioids [such as illicitly-manufactured fentanyl (IMF)] in combination with cocaine and methamphetamine has resulted in significant increases in co-use-related overdose deaths (5).

The driving factors for stimulant use in recent years include the increasing availability of methamphetamine in the markets with the relative absence of certain opioids making the former more attractive pills (6). To some extent, restricting access to prescription opioids may be linked to an increase in methamphetamine use (6). One of the possible explanations for the rise in methamphetamine usage, according to user experience, is that it served as an opioid substitute, offered a synergistic high, and balanced out the effects of opioids in order to regain "normalcy" (6).

Although the link between opioid and stimulant concurrent use (e.g., speed-ball or goof-ball) is not novel, attention has been drawn due to an increase in the number of stimulant-related overdose deaths, most likely due to fentanyl being increasingly mixed into cocaine and methamphetamine. Concurrent use of stimulants and opioids is becoming more common, and polydrug use (e.g., co-use of a stimulant along with an opioid) has been linked to drug overdose deaths (6). Sedatives, particularly benzodiazepines or alcohol, are known to interact with opioids and are frequently implicated in opioid overdose deaths due to their respiratory depressant effect. The combination of heroin, cocaine, and injected speedballs is also a known predictor of overdose (7). Although the pharmacodynamics of stimulants in combination with opioids are not fully understood, one

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possible explanation for speedball-related mortality is that cocaine causes severe vasoconstriction, causing the body to use more oxygen, whereas heroin's depressant effects slow breathing rates, leading to respiratory failure. It's unclear if the link between these drugs and overdose mortality is due to drug interactions or if drug users overdose on heroin to reduce their stimulated "highs" (7). Our personal experience at a methadone clinic in rural Vermont, as well as current literature suggests that individuals who use concurrent opioids and stimulants believe stimulants are safer, combining stimulants and opioids to offset the negative effects of opioids, such as withdrawal symptoms, limiting opioid use, finding cheaper substitutes for heroin, relieving fatigue, lethargy, and some combining to enhance a "high" (6, 8). However, in many cases, fentanyl is mixed with cocaine or methamphetamine without the user's knowledge, and a person with no tolerance to opioids may suffer a fatal overdose (9, 10). The United States reported the greatest ever overdose fatalities ever recorded—totaling 93,000 deaths due to OUD (11) (Ellis et al.). Along with research efforts, recently published literature reports also underline polydrug use, which is more prevalent among individuals with OUD (Ellis et al.). As a result, the federal and state level agencies have made an effort to promote preclinical and clinical research on the effects of co-use of stimulants and opioids, as well as the development and implementation of evidence-based interventions to prevent drug overdose.

SHIFTING TRENDS OF DRUG USE AND PREVALENCE

According to the CDC, during 2015–2018, an estimated 1.6 million US adults, on average, reported past-year methamphetamine use; 52.9% of persons using methamphetamine in the past year met diagnostic criteria for methamphetamine use disorder, and nearly 25% reported injecting methamphetamine within the past year (12). The National Survey on Drug Use and Health (NSDUH) estimated that in 2019, 2 million individuals aged 12 or older used methamphetamine, up from 1.4 million in 2016 (13). Acknowledging the dearth of data on co-use, and to improve our understanding of polysubstance use among individuals with OUD, a retrospective analysis conducted from 1991 to 2020 was assessed (Ellis et al.); the authors found an 82.4% exposure to stimulants among people with OUD, whereas crack/cocaine (68.6%), prescription stimulants (50.6%), and methamphetamine (63.1%) were commonly reported. Among 7,109 individuals, the mean age of first exposure to either substance was 22.3 years. Using a national opioid surveillance system and analyzing data from 124 OUD treatment centers between 2017 and 2020, Ellis et al. report that that the average age for "initial exposure" to any stimulant or opioid has increased from 10 years to 23.5 years since the 1990s. These large shifts in populations may be linked to healthcare practitioners and systems' efforts to raise public awareness about the consequences of the medications (Ellis et al.). Therapeutic and preventive efforts should consider the newest wave's key demographics (i.e., shifting ages, rurality), poly drug use (i.e., a mixture of methamphetamine and cocaine with fentanyl), and counterfeit prescription pills.

Aside from synthetic opioids and stimulants, there has been a dramatic increase in the number of prescription and over-the-counter (OTC) drugs owing to their abuse potential at high doses or idiosyncratic methods of self-administration (14). Schifano et al. investigated the rising popularity and availability of prescription drugs (pregabalin, bupropion, venlafaxine, olanzapine, clenbuterol, and loperamide) (15). In line with this, pregabalin and gabapentin abuse appears to have increased dramatically in recent years among people with SUD, particularly those abusing opioids. Gabapentin was the tenth most commonly prescribed medication in the United States in 2016, while pregabalin ranked eighth in invoice drug spending with $4.4 billion in sales. According to the Canadian study, concomitant gabapentin and opioid exposure was associated with a 49% increased risk of dying from an opioid overdose (16), and due to such alarming rates, gabapentin is now considered an emerging threat in today's opioid epidemic. Identifying some potential gaps and challenges related to the emerging crisis of novel psychoactive substances, Schifano et al. identify the potential factors influencing this rapidly shifting drug scenario (15). For example, web-based pro-drug information to vulnerable subjects such as children and adolescents and psychiatric patients, failure to identify abuse or misuse potential during pre-marketing processes, and a lack of post-marketing substance abuse surveillance. Pharmacovigilance measures should be considered in cases of prescription and OTC drug abuse in order to detect, assess, understand, and prevent adverse effects or other drug-related problems.

OPIOIDS AND STIMULANTS TRENDS IN GENERAL AND DURING COVID-19

Experiments involving human and animal subjects provide some evidence that stimulants such as amphetamine potentiate the analgesic effects of morphine (17). Psychostimulant drugs in animal studies present with intrinsic analgesic properties and also enhance the analgesic properties of opioids, which may explain the user groups' reasoning. Deaths involving cocaine and psychostimulants have increased in recent years, particularly among opioid users. In 2017, opioids were involved in nearly three-fourths of cocaine-related deaths and nearly half of psychostimulant-related deaths (18). Ellis et al. reported an increase in past-month methamphetamine use among opioid-dependent individuals, from 18.8% in 2011 to 34.2% (6). A recent study analyzing data from the 2015–2019 National Surveys on Drug Use and Health (NSDUH) reported that among those reporting past month heroin usage, methamphetamine use increased nearly 5-fold (from 9 to 44%). Similarly, those who used heroin in the past year used methamphetamine twice as much (22.5 to 46.7%). Rurality, past year injection drug use, and serious mental illness have all been linked to methamphetamine use among individuals who use heroin (19). The use of stimulants alone or in combination with other drugs has been linked to several social, mental, and physical health problems

such as homelessness, drug-related crime, overdoses, suicide, cardiovascular diseases, and infectious disease transmission (e.g., Hepatitis C and HIV) (20).

The global prevalence of stimulants has drastically risen since 2010. Over 5 million Americans reported current cocaine use in 2020, while over 2.5 million Americans aged 12 and older reported using methamphetamine in the previous year. According to recent estimates, there are ∼18 million cocaine users worldwide, with the highest rates in the US (2.1%). A recent study identified that areas dense in black and Hispanic racial/ethnic groups had a 575% increase in cocaine and opioid mortality rate compared to a 184% increase across white groups (8). From 2015 until 2019, psychostimulants' overdose among US adults, largely methamphetamine, increased by 180% (from 5526 to 15,489 overdosage estimates) (20). A rise in psychostimulant-related mortality could be attributed to increased availability and market expansion in areas and user groups traditionally associated with methamphetamine use (10). According to reports by US federal agencies, methamphetamine availability in the United States continues to be widespread, its purity and potency remain high, and its price remains relatively low (10). In our observation working with patients, patients report an increase in stimulant use due to the growing fear of fentanyl adulteration of heroin and the risk of overdose.

The COVID-19 pandemic has had an impact on the network of cocaine trafficking supply lines, but it has not significantly reduced overall supply to the United States. Despite the rising crisis, there are no FDA-approved pharmacological treatments to treat amphetamine or cocaine addiction, and unfortunately no antidotes to treat stimulant overdoses. During the COVID-19 era, the US, saw a rise in overdose deaths caused by illicit fentanyl, fentanyl analogs, methamphetamine, and cocaine, often in combination or mixed with other drugs, evidenced by the alarming 100,306 drug overdose deaths in the US, during the 12 months ending in April 2021, a 28.5% increase from the 78,056 deaths during the same period the year before (21). The main drivers were synthetic opioids (i.e., fentanyl), but stimulants like cocaine and methamphetamine were also increased. During the pandemic, drug use increased in both quantity and frequency, leading to an increase in drug overdose deaths. A plausible explanation for the increase in substance use during the pandemic included coping with emotional stress, social isolation, economic stress related to COVID-19, and increased general anxiety and depression. The rising number of overdose deaths involving synthetic opioids could be attributed to heroin shortages and the economic downturn during the pandemic, which led to users switching to substances such as low-cost fentanyl and its derivatives.

The disruption in heroin supply has also exacerbated harmful drug use, such as the use of home-produced injectable opioids like "krokodil," also known as "Russian Magic," a cheap but extremely dangerous substitute for heroin. During the peak of the pandemic, we saw two cases at our clinic who reported using krokodil in the absence of heroin. Contrary to the majority of reports indicating a significant increase in drug use and overdose deaths around the world, an Italian study assessed the psychopathological burden in people with substance use disorders, more specifically craving changes in daily habits, which only showed modest change during the COVID-19 pandemic (22). The Italian cohort posits that craving for drugs is considered as a significant therapeutic target for lowering the risk of relapse and improving patients' quality of life (22). Low levels of craving during a pandemic like COVID-19 may be attributable to a perceived lack of availability of the drugs and reduced societal pressure on people using drugs. The study found that craving was lower in inpatients than in outpatients, highlighting the importance of residential treatment in substance use disorders (22). The findings of this study could be put into practice as one of many options for dealing with the 4th wave crisis.

RECOMMENDATIONS AND FUTURE DIRECTIONS

In light of the many risks and consequences of stimulant and opioid use, some interventions can reduce the rate of fatal opioid overdoses. For example, (i) the scalability of rapid fentanyl test strips to detect fentanyl in illicit drugs may be useful in harm reduction interventions (23). (ii) Initiating or continuing medications for opioid use disorder. (iii) Due to the rise in polydrug overdoses, treatment providers must assess for concurrent substance use disorders and offer evidence-based treatments. (iv) Distribution of naloxone through cost-effective, pharmacy- and community-based programs; expanding the locations of naloxone distribution centers, particularly in minority populations, rural communities, and homeless shelters. (v) Naloxone is not effective against stimulant overdose, but it should be offered due to the rise of concurrent opioid use. (vi) Educating individuals not to use drugs alone, ensuring that naloxone is available and that people who use drugs and their loved ones know how to use it. (vii) Educating individuals that they may require repeated doses of naloxone to reverse an overdose due to the potency of IMF and fentanyl analogs (24). (viii) On a personal level, individuals exposed to opioids and stimulants together ought to be aware of symptoms, pulse rate, heart rate, and rhythm for prevention (25). (ix) Although there are no FDA-approved medications to treat stimulant use disorders, treatment providers offer evidence-based treatment approaches such as community reinforcement, motivational interviewing, and cognitive-behavioral therapy combined with contingency management (12). (x) identifying jurisdictions and vulnerable groups (e.g., IV drug users) who are at higher risk of infectious disease, and expanding harm reduction approaches for those groups, e.g., syringe exchange programs (SEPs). (xi) With the growing COVID-19 and opioid epidemic, wearable monitors with inbuilt artificial intelligence-powered sensors linked to medical devices can become key in attaining urgent medical attention (26). This growing problem of stimulant-opioid co-use requires an emphasis on access to evidence-based treatment.

This paper serves as a call to action for the high prevalence of substance and opioid co-use, albeit with a paucity of data (Ware et al.). Polydrug use develops due to various reasons such as accessibility, motivation, and awareness. The fourth wave of the opioid crisis has been on the rise since the

late 20th century, however, with the COVID-19 pandemic in the mix, demographic shifts from the adults to the pediatric population may reemerge with shifting behaviors (27). The recent opioid epidemic surge provides an opportunity to understand the conducive factors to polydrug use and OUD amplified by the COVID pandemic. In the broader sphere of addiction medicine and public health, educational and preventive efforts are required to reduce harmful outcomes and promote treatment to reduce morbidity and mortality trends, paralleled with narcotics regulations and monitoring; an understanding of the social narrative and socioeconomic influences on substance consumption is essential to effectively address the "fourth wave of the opioid crisis."

AUTHOR CONTRIBUTIONS

SA, ZS, and AS contributed to the conceptualization, planning and implementation, writing—original draft, and review—of the research. SA supervised this article, conducted analysis and interpretation of literature review, and critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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The Effects of Low Dose Naltrexone on Opioid Induced Hyperalgesia and Fibromyalgia

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Objectives: While opioids temporarily alleviate pain, the overshoot of balancing pain drivers may increase pain, leading to opioid induced hyperalgesia (OIH). Our goal was to find out what chronic opioid treatment does to pain tolerance as measured by the cold pressor test (CPT), an objective measure of pain tolerance, and to find an alternative effective treatment for chronic pain and FM.

Materials and Methods: The setting was an academic addiction medicine service that has an embedded pain service. Patients had routine clinical care starting with an evaluation that included assessment of medical and psychiatric conditions. Participants were 55 patients with OIH and 21 patients with fibromyalgia; all had at least two CPTs. Treatment included a single dose of buprenorphine for detoxification. In this open-label case series, patients were treated with low dose naltrexone (LDN), a pure opioid receptor antagonist that, we hypothesize, treats OIH and FM by restoring endogenous opioid tone.

Results: Comparing initial and last CPT times, those with OIH more than quadrupled their pain tolerance, and those with FM doubled theirs. This improved pain tolerance for OIH and FM was statistically significant ($p < 0.0001$ and $p = 0.003$, respectively) and had a large effect size ($r = 0.82$ and $r = 0.63$, respectively).

Discussion: Results suggest that patients on chronic opioid therapy should have pain tolerance measured by CPT with detoxification and LDN provided to correct opioid induced hyperalgesia if found. FM may also be treated with LDN. The main limitation of the findings was lack of a randomized control group treated with placebo.

Keywords: opioid induced hyperalgesia, chronic pain, fibromyalgia, opioid use disorder, low dose naltrexone

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INTRODUCTION

The opioid epidemic has long entered the public consciousness. Three hundred eighty-three thousand and ninety-one deaths from overdose in the US during 2001 to 2017 has punctuated this awareness (1). Despite a greater appreciation of these ramifications, the prescription of opioids for chronic pain continues. The irony is that opioids worsen pain during the course of long-term use. This phenomenon, opioid induced hyperalgesia (OIH), is the "state of nociceptive sensitization caused by exposure to opioids" (2). OIH's prevalence and optimal management have not been agreed upon (3), and a multitude of compensatory/allostatic changes have been proposed

as mechanisms for nociceptive sensitization and mu-opioid receptor desensitization (2, 4–9). OIH leads to a vicious cycle of increasing doses of opioids while increasing pain (6, 10). Such an alteration and dysfunction of the endogenous opioid system is brought about by exogenous opioid use.

Understanding the deleterious effects from chronic exogenous opioid exposure on the endogenous opioid system informs the understanding of fibromyalgia (FM), a syndrome of chronic pain that is diffuse yet accentuated at multiple tender points along with other somatic and cognitive symptoms (11–18). The endogenous opioid system has been hypothesized to play a role in FM, thus joining the numerous and controversial factors considered in FM's pathophysiology (17, 19, 20). Cerebrospinal fluid (CSF) studies of FM patients show elevated kappa-opioid peptide, dynorphin, and met-enkephalin-Arg-Phe, suggesting receptor modulation and desensitization (21, 22). There is significantly decreased mu-opioid binding in the bilateral nucleus accumbens, left amygdala, and right anterior dorsal cingulate on PET scan (23).

We conceptualize FM's alterations in the endogenous opioid system involving an autoimmune process (20). Mu-opioid receptor dysfunction from an autoimmune process may cause increased endogenous opioids produced in an attempt to maintain homeostasis. Ultimately, this mechanism cannot compensate for the diminished binding of mu-opioid receptors, resulting in brain-mediated pain experienced by patients as occurring diffusely over the body.

Given these considerations of the endogenous opioid system in OIH and FM, we present a case series to demonstrate the effect of low dose naltrexone (LDN) on pain tolerance in OIH and FM. Naltrexone's antagonism at mu, kappa, delta, and orphanin FQ/nociceptin opioid receptors and at opioid growth factor receptor (OGFr) induces a variety of cellular responses at different doses (19, 24–38). We submit that the use of low doses, up to 4.5 mg twice a day, of naltrexone restores endogenous opioid tone in OIH and improves it in FM. While the use of opioid antagonists to exert analgesic effects is not a new concept, there is still a dearth of clinical research that investigates such proposed effects in patients. This report of a case series may not elucidate the exact mechanisms underlying the effects of LDN, but we believe that the pilot data is of some interest given the widespread use of opioid medications for chronic pain and the lack of efficacious treatments for FM.

METHODS

Setting

A pain service is embedded in the Addiction Medicine Service at the State University of New York Upstate Medical University to evaluate pain complaints in patients with comorbid opioid use disorder. Patients are generally poor: 2/3 of our patients have Medicare or Medicaid insurance. Many are chronically ill with multiple medical and psychiatric diagnoses. Prospective patients are not required to have any diagnosis other than chronic pain prior to evaluation on the pain service. Many addicted patients also have chronic pain. Evaluators include medical, physician assistant and psychiatric nurse practitioner students, neurology, internal medicine and psychiatry residents, and pain medicine and addiction psychiatry fellows—along with senior staff physicians and nurse practitioners. Patients are asked to sign an IRB-approved form for their deidentified information to be used in case series reports. Treatment progress is monitored by joining subjective reports of pain with the cold pressor test (CPT), a validated, objective measure of chronic and experimental pain (39), with good test-retest reliability (40). In addition to transference-focused psychotherapy (41, 42) and holistic medical treatment, patients are treated with LDN.

Participants

We reviewed all patients who presented for an initial intake between January 2017 and July 2019. There were 786 initial evaluations. Three hundred seventy six had an initial CPT. Seventy six were treated with LDN and had follow-up CPTs. Roughly half of all patients who present to the Addiction Medicine Service are evaluated at the embedded pain service. Of these patients, a smaller proportion have fibromyalgia rather than opioid use disorder, as reflected in the larger number of OIH patients in the study sample. Of the 76 patients treated with LDN and had follow-up CPTs, 55 were diagnosed with OIH, and 21 were diagnosed with FM.

Because the evaluations are complex, and cognitive impairment is common, we require that every new patient bring a sober support person. The support person is present for the evaluation and discussion of diagnoses, proposed treatments, and whether to engage in treatment on the service. Support persons from a prior case series had average CPT of 113 seconds (43). In that study, we chose the support persons as our control group because they were close in nature to our patient population by virtue of having been asked by our patients to participate. Before testing the support persons, we asked if they had recent exposure to nicotine, opioids or cannabis. Only support persons without these potentially pain tolerance-altering exposures were used.

Evaluation

The services have a holistic nature. We start with the chief complaint and history of present illness, then the psychiatric, medical, family and social histories. A comprehensive substance use history is taken on alcohol, cannabis, nicotine, cocaine, amphetamine, benzodiazepine and opioid use. A Hamilton Rating Scale for Depression, a Modified Mini-Mental State Examination and a FACES Pain Scale (FPS) are recorded.

We use screens for common comorbid disorders. The Adult ADHD Self Report Scale for attention deficit hyperactivity disorder (ADHD) is given, followed by a DSM5 interview if ADHD is suspected. The Structured Clinical Interview for DSM5 (SCID2) checklist is used to screen for borderline personality disorder. While ADHD, borderline personality and depressive disorders are unusual in pain patients, they are present in about half of our opioid use disorder patients (44). A physical examination is part of every evaluation. If chronic pain is present, the examination focuses on the peripheral pain driver. If FM is suspected, the 18 potential tender points are palpated, and the number of tender points is reported.

Morphine Years

The dose, frequency, and duration of opioid exposure, obtained in the substance history, are rendered as morphine years (MY). A "morphine year" had been described in a previous publication as daily use for a year at 60 morphine milligram equivalents (MME). We had found a positive correlation between MY and the prevalence of depression, ADHD, and borderline personality. MY were higher in younger patients because of the use of illicit opioids, as doses sold by street dealers are about 100 times greater than prescribers. We had found a negative correlation between CPT and MY, with more cumulative opioid use leading to lower CPT, suggesting that opioid exposure causes a steady decrease in pain tolerance (43).

CPT and OIH

Exposure to opioids almost always caused short CPT. CPT was repeated on follow-up appointments to gauge changes in pain sensitivity. The test was stopped at 180 s for patients that had a high pain tolerance. Changes in pain sensitivity were used to reassess LDN treatment. Patients also reported their pain on initial evaluation via the FACES Pain Scale. On follow-up visits, patients reported if their pain was better, worse, or no change. Patients were diagnosed with OIH if they were experiencing significant pain while on opioids and had a CPT less than two-thirds of the healthy controls' average of 113 s (43).

Opioid Detoxification

The patient arrives in early withdrawal with symptoms such as gut cramps, anxiety, and increased pain. 8 mg sublingual buprenorphine tablets are taken in front of staff until withdrawal symptoms remit; usually 24 or 32 mg are sufficient. The duration of the "detox" is about 15 min. Patients were sent home with clonidine, hyoscyamine, trazodone, olanzapine, and gabapentin for attenuated withdrawal symptoms. These symptoms and their treatments were explained on a written handout topped by the senior author's cell phone number. Directions were given to "call day or night if you need help" (there are few calls). In addition to pharmacotherapy, patients received psychotherapy daily for the first week and then twice a week until discharge. After buprenorphine administration, LDN was started at 0.1 mg twice a day and titrated with the following schedule:

- 0.2 mg twice a day on day two
- 0.3 mg twice a day on day three
- 0.4 mg twice a day on day four
- 0.5 mg twice a day on day five
- 1.0 mg twice a day for days five and six
- 2.0 mg twice a day for days 7 and 8
- 4.5 twice a day thereafter

Given the difficulty with finding pharmacies that will accommodate this varied dosing, we dissolve a 50 mg pill of naltrexone in 50 ml of water, and we show patients how to use an insulin syringe to draw up 0.1 mg increments. This titration occurred more slowly if there was a return of opioid withdrawal symptoms with increased dosing, understood as if the receptor system was slow to regenerate and therefore not tolerating the increasing doses of LDN. FM patients not currently on opioids started LDN as soon as their treatment plan was agreed upon.

TABLE 1 | Averages in demographics, change in CPT, and FACES Pain Scale for OIH and FM patients, with 95% confidence interval in brackets.

	OIH ($N = 55$)	FM ($N = 21$)
Age (years)	53.8 [49.66, 57.94]	43.48 [37.1, 49.85]
Sex	50.9% Female [n/a]	90.5% Female [n/a]
Change (seconds) from 1st and last CPT	83.07 [64.61, 101.5]	16.05 [3.415, 28.68]
Days b/w 1st and last CPT	89.78 [63.3, 116.3]	48.14 [36.45, 59.83]
FACES Pain Scale on initial evaluation	5.425 [4.642, 6.207]	6.786 [6.101, 7.471]

Statistics

Stata 16 was utilized. The Wilcoxon signed-rank test was used to determine the statistical significance of the change in CPT. Ordinal least squares regression was used to determine if the relationship of change in CPT varied significantly with age, sex, days between first and last measurement, FPS, and MY. Non-parametric statistics were used because the data did not meet the normality assumption.

RESULTS

Of the 363 patients who had an initial CPT, 76 returned for follow-up and continued treatment with LDN. This reflects the nature of our service; some patients will not return for treatment because:

- They believe that they should be treated with opioids despite short CPTs that are diagnostic of OIH
- Some expect pills to fix their pain exclusively and will not engage in active treatments that include the examination of a lack of self-care during an extended evaluation that requires appearing for further visits
- Some seek a source of opioids and drop out when it becomes apparent that opioids are not part of the treatment

The remaining 20% of patients were a highly motivated group, culled from an intake system that requires active engagement. The results from these 55 OIH and 21 FM patients are summarized in **Table 1**. The patients varied on the number of follow-up CPTs (ranging from 2 to 4) and the interval between their follow-up CPTs. Therefore, the change in their pain tolerance was tabulated from the difference in the last CPT from their initial CPT. The time between their initial and final CPT was also recorded.

The average initial CPT was low for both OIH (24 s) and FM (14 s) when considering the control group from a prior case series had an initial pain tolerance of 113 s (43). The patients' low CPTs were mirrored by their high subjective pain ratings, as the FACES Pain Scale at the initial evaluation averaged 5.4/10

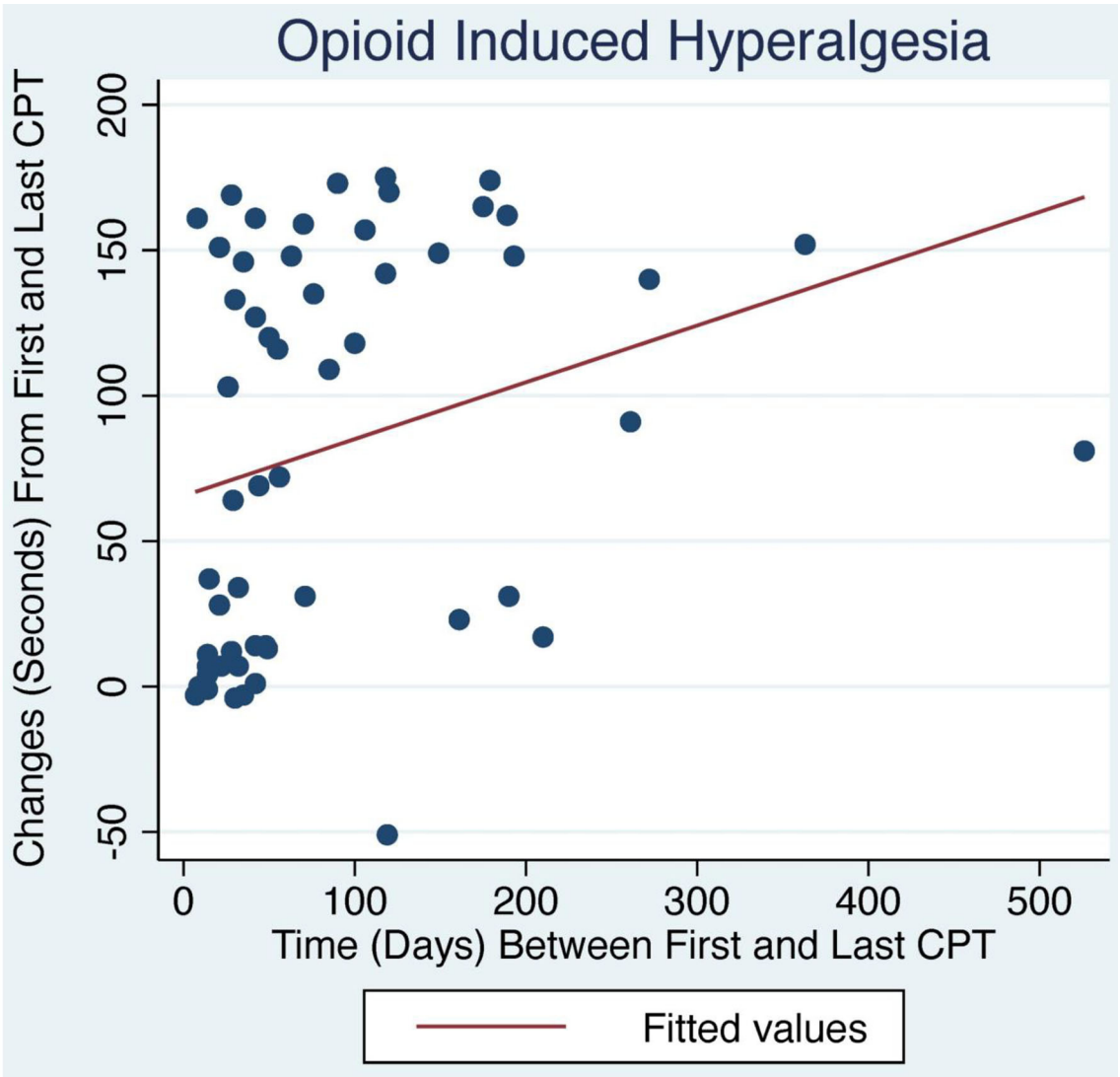

FIGURE 1 | Change in CPT over time with LDN treatment. OIH patients treated with LDN showed a positive relationship between change in CPT and number of days between first and last CPT measurement ($p < 0.04$).

for OIH and 6.8/10 for FM. OIH patients demonstrated a more robust change in their CPT over time as well as having more days between their initial and final CPT compared to FM patients. OIH patients averaged an improvement of 83 s in their pain tolerance ($p < 0.0001$). FM patients exhibited an increase in their pain tolerance of 16 s ($p < 0.003$). The effect sizes were substantial ($r = 0.82$ for OIH and $r = 0.63$ for FM). After their initial CPT, OIH patients averaged 3 months before they completed their last repeat CPT. FM patients averaged 7 weeks between their initial and final CPT. Only in OIH was there a statistically significant relationship between the change in CPT and the number of days between the first and last CPT measurement ($p < 0.04$, see **Figures 1**, **2**). The change in CPT was not significantly correlated, in either diagnosis, with age, sex, FPS, or MY.

DISCUSSION

Patients maintained on opioids for chronic pain presented with an average initial CPT of 24 s and FPS of 5.4/10, underscoring their diminished pain tolerance when compared to a prior control group's 113 s average (43). However, 3 months of treatment with LDN more than quadrupled OIH patients' pain tolerance; their average of 107 s at their last CPT suggests a restoration of their endogenous opioid tone. The small though significant correlation of the improvement in pain tolerance with number of days between the first and last CPT may indicate that the endogenous opioid system needs time to normalize, perhaps 3 months on average. FM patients started with more pain compared to OIH patients with FPS of 6.8 and initial CPT of 14 s. They were comprised of 90% women compared

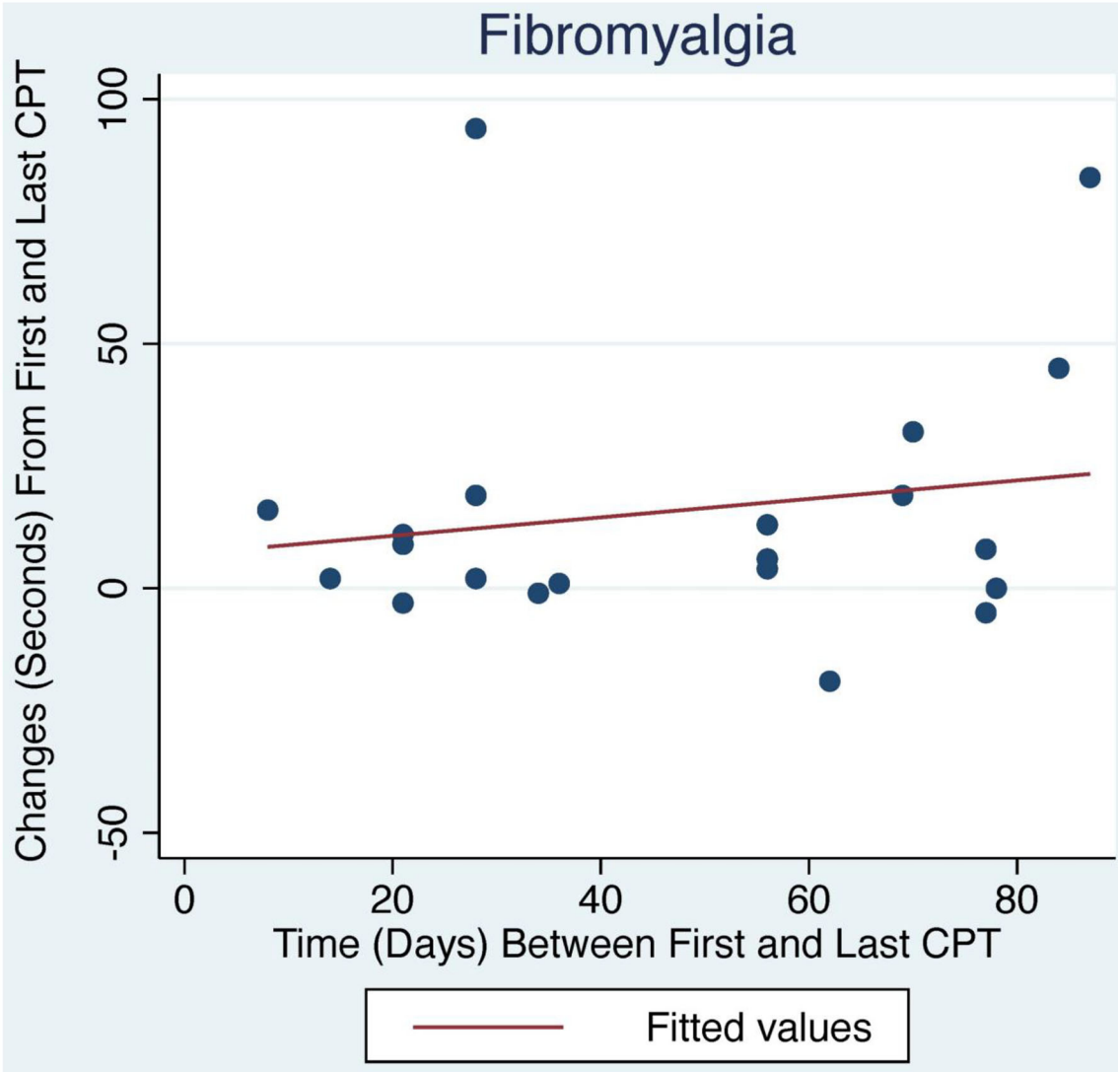

FIGURE 2 | Change in CPT over time with LDN treatment for FM patients. The relationship between change in CPT and number of days between first and last CPT measurement did not reach statistical significance.

to the equal sex distribution in OIH. Their CPT responded more sluggishly over seven weeks to 30 s, coinciding with FM patients typically reporting an improvement in pain but not complete resolution.

What accounts for the greater magnitude of response to LDN found in OIH compared to FM? While we propose that the endogenous opioid system is integral to the pathophysiology of both conditions, the mechanisms by which LDN may restore endogenous opioid tone remains largely a mystery, as varying doses and binding durations may produce different effects at each of the opioid receptor types (28, 34, 36). The restoration of endogenous opioid tone may have primacy in correcting OIH (19, 20), but FM may have a neuroimmunological component distinct from OIH. LDN may influence neuroimmunomodulation by intermittent blockade of opioid growth factor receptor (OGFr). The transient blockade of OGFr by naltrexone increases levels of OGF (37). In animal studies, the increase of OGF is associated with the decrease of neuronal damage, inflammation, and proliferation of T and B cells (29, 45–47); however, LDN may correct a disruption to the OGF-OGFr axis rather than simply increasing enkephalin levels alone. Prior findings of a possible increase in endogenous opioid levels in FM (21, 22) could be a compensatory response to receptor degradation (20), but LDN may ameliorate such receptor degradation through the upregulation of OGFr. This may be especially true for those in which signs of an active inflammatory process are present, such as increased glial activation along with increased cytokines in the CSF (and in some cases, plasma) in FM patients (48–50). Since erythrocyte sedimentation

rate levels can predict the therapeutic response to LDN (51), the variation of an inflammatory component, with its modulation via the OGF-OGFr axis, may indicate why FM patients have a significant but smaller response to LDN compared to OIH patients. Until markers for FM can be identified and targeted for treatment, LDN can alleviate most patients' pain, cognitive, affective, and systemic symptoms, all products of low opioid tone likely caused by opioid receptor degradation (20).

Alterations in the affective processing of pain in FM and OIH (52, 53) may also account for the varying baseline pain tolerance and response to LDN. Patients with FM have increased sympathetic nervous system activity compared to healthy controls (48), and decreased mu-opioid binding potential occurs in areas associated with the affective processing of pain (23). Functional imaging and gray-matter volume studies of FM patients show differences in areas implicated in the emotional modulation of pain, but results vary when controlling for comorbid mood disorders (53–55). However, similar findings in functional connectivity alterations have been found in those with long-term opioid use (56), and the emerging research on opioid receptors and mood may reveal a means for which LDN treats the opponent process' effects on mood that increase relapse and worsen pain (56–59). Therefore, the neuroimmunological component may be the best explanation at this time to account for the differences in improvement between OIH and FM.

Given these encouraging results, what are the implications for future research as well as the current status of the use of opioids in treating chronic pain? The brain rebels against chronic opioid treatment by the opponent process (10, 60, 61), increasing pain drivers such as glutamate, dynorphin, corticotrophin releasing factor, and substance P. Clinicians and patients escalate the doses of opioids to temporarily meet the body's homeostatic response. This seems to continue to diminish the brain's endogenous opioid system, amplifying the central response to peripheral pain drivers. In addition to this worsening of pain, chronic use of opioids poses risks such as falls, hypogonadism, and constipation. The chronic use of opioids may also instigate opioid use disorder, as three-quarters of heroin users begin with prescription opioids (62, 63). Finally, a seldomly-noted side-effect of chronic opioid treatment is flattened relatedness to others. Our understanding of this phenomenon has to do with the endogenous opioid system's regulation of closeness with others (20). However, should opioids be discontinued in a patient with chronic pain via a slow taper, the opponent process is left unchecked, instigating prolonged withdrawal. This is because the brain has made allostatic change to accommodate chronic opioid treatment, increasing pain drivers. The detoxification process described above provides an alternative to tapering, and the restoration of endogenous opioid tone by LDN leads to restoration of relatedness. Support persons make comments such as, "I have the woman/man I married back!" Such encouraging results from this pilot data are of interest given the continued use of opioids for chronic pain and the lack of efficacious treatments for FM, and they indicate the need for double blind, randomized-controlled trials.

LIMITATIONS

This is a chart review study of the cold pressor test in a variety of patients presenting for addiction and/or pain treatment. The topic and the concept of the study are certainly of interest, but the methodology is challenging, as the CPT data were derived from charts and was not delivered in a standardized fashion (in terms of timing, etc). Ideally, one would need demographically matched groups of controls, patients with chronic pain not on opioids, patients with chronic pain on opioids without addiction, and patients with chronic pain who are on opioids who are addicted. Patients who had no history of opioid exposure were so unusual that we were not able to find enough subjects to construct such a control group.

Since subjects were not randomized to experimental and control groups, the potential of a placebo effect could not be evaluated. However, it may be that placebo responses do not significantly affect cold pressor pain. Placebo effects are shown to be greater in clinical pain (such as low-back pain) rather than experimental pain (CPT) (64). Since our results were drawn from multiple CPTs, this may raise the possibility of a conditioned placebo response as well, yet it has been theorized that conditioned placebo responses may not be found for several reasons (65). Factors including type of pain, expectation of relief from naltrexone, expectation of pain from CPT, and the sex of patients and of the evaluators administering the test create a multitude of variables for potential placebo and nocebo responses. The evaluation of all of these factors are beyond the scope of this paper as different pathways without a unifying model are likely responsible for placebo effects when they are present (66). Moreover, if dopaminergic pathways are responsible for the placebo response (67–69), then the usurping of these pathways by addiction may alter the placebo response itself.

It is possible that patients who were experiencing positive results from the treatment remained in treatment long enough to have a second CPT, while non-responders dropped out, skewing the reported results toward responders. Our titration schedule takes into account the sensitivity of the already diminished endogenous opioid system of our patients. Recent findings suggest a dose-response relationship to LDN among FM patients (70); it is possible that our titration schedule mitigates adverse effects but can lead to dropout if an effective dose is not reached quickly enough for certain patients. Finally, given that those with opioid addiction and FM have alterations in the affective processing of pain (23, 54, 55, 58, 61, 71, 72), multiple treatment modalities that may alter affective processing could confound the effects of LDN. Psychotherapy and medications, in addition to LDN, may have a "synergistic effect on recovery of endogenous opioid tone" (73). Medications used to alleviate withdrawal symptoms may affect pain. Controlling for these variables in an RCT is warranted.

CONCLUSION

By constantly using patient feedback, we have been able to discover how to detoxify patients from opioids as an easy

outpatient procedure, assess pain tolerance with the cold pressor test, and ameliorate opioid induced hyperalgesia with low dose naltrexone. These are all innovative procedures. The weakness of our report is the lack of randomized control groups.

Routine use of CPT is helpful in diagnosing OIH. It helps patients see that using opioids for chronic pain treatment increases pain. Opioids have a high prevalence of risks, including death from accidental overdose, iatrogenic addiction, unrelatedness, falls, and constipation.

FM mimics OIH; its symptoms are congruent possibly because it is an autoimmune disease that also reduces CNS pain-damping opioid tone (20). Detoxification, attention to underlying emotional issues, and LDN can make a substantial difference for patients as shown in our case series report. Further investigation via double blind, randomized-controlled trials of LDN is indicated.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

DJ wrote the first draft. All other authors contributed intellectually to the manuscript.

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BRIEF RESEARCH REPORT
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A Smartphone-Smartcard Platform for Implementing Contingency Management in Buprenorphine Maintenance Patients With Concurrent Stimulant Use Disorder

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Background and Objectives: Opioid agonist pharmacotherapies are effective in the treatment of opioid use disorder (OUD) but concurrent stimulant use is common and can lead to relapse and treatment drop out. Contingency management in combination with opioid agonist pharmacotherapy has broad beneficial effects in polysubstance users, including promoting drug abstinence and treatment retention, but clinic-based implementation can be burdensome. The present study was conducted to evaluate a contingency management intervention delivered *via* a smartphone-smartcard platform in OUD patients who had concurrent stimulant use disorder.

Methods: Retrospective comparison of (n = 124) patients; half received the contingency management intervention and half were matched controls. Drug use and clinic attendance outcomes over four consecutive 30-day periods were analyzed with regression.

Results: The intervention group showed consistently higher rates of drug abstinence and clinic attendance which were significant at the latter two timepoints.

Discussion: Smartphone-smartcard platforms can facilitate dissemination of contingency management by surmounting or obviating key barriers to adoption. They appear to be convenient for all stakeholders, are easy to use, and facilitate high-fidelity implementation. Delivering contingency management *via* a smartphone-smartcard platform produces effects consistent with those observed when the intervention is delivered with substantially costlier and more burdensome in-person procedures.

Keywords: digital health (eHealth), opioid use disorder, cocaine, methamphetamine, incentive-based intervention, medication-assisted treatment (MAT), stimulant use disorder

INTRODUCTION

Opioid agonist pharmacotherapies such as buprenorphine and methadone are effective in the treatment of opioid use disorder. However, for people enrolled in buprenorphine maintenance pharmacotherapy, concurrent stimulant use is associated with higher rates treatment dropout (1, 2). There is currently no effective medication for the treatment of stimulus use disorder. In a recent systematic review of reviews, contingency management was the only supported treatment for stimulant use disorder (3). Contingency management typically entails the provision of material incentives (e.g., vouchers exchangeable for goods or services) contingent upon submission of drug toxicology tests that indicate recent drug abstinence. Adding contingency management to pharmacotherapy for opioid use disorder has significantly and robustly improved outcomes in polydrug users (4).

Despite its success in clinical trials, adoption of contingency management has been slow among outpatient treatment providers. Barriers have been studied extensively, and include a lack of training and expertise, a lack of time for implementing the procedures, a lack of infrastructure required to conduct the program, and the lack of a stable means of funding the program costs (5). Save for costs, these barriers are wholly obviated by delivering the intervention *via* a smartphone-smartcard platform that automates all aspects of intervention management. This delivery system for contingency management intervention has been shown to be effective in promoting smoking cessation (6), alcohol abstinence (7), and in promoting drug abstinence and clinic attendance in people receiving outpatient treatment for opioid use disorder at an inner-city clinic (8).

Given the high risk of treatment dropout for buprenorphine patients with concurrent stimulant use disorder, the historic success of contingency management for patients with similar profiles, and the need for a scalable, rapidly disseminable platform to enhance the clinical impact of contingency management, we sought to evaluate the efficacy of a smartphone-smartcard contingency management platform for increasing treatment attendance and drug abstinence in buprenorphine patients with concurrent stimulant use disorder.

MATERIALS AND METHODS

Sample

Intervention participants were recruited from a BrightView Health Center located in Cincinnati, Ohio. Enrollees were required to own their own Android or iOS smartphone. Overall, 108 patients enrolled in the smartphone-smartcard contingency management intervention. The present analysis was restricted to enrollees with an opioid use disorder who had concurrent stimulant (i.e., cocaine and/or methamphetamine) use disorder ($n = 67$). These participants were retrospectively matched, blind as to outcomes, to control patients at another BrightView clinic in the same city that did not offer the smartphone-smartcard contingency management intervention. All participants in both groups were receiving similar treatment for their substance use disorders at BrightView clinics. Matched controls (1) completed a urinary drug toxicology test at the clinic on or before the day the intervention patient started the contingency management intervention, (2) were enrolled at the clinic on the day the intervention patient started the contingency management intervention, (3) had the same primary diagnosis (e.g., Opioid Use Disorder), and (4) had the same American Society of Addiction Medicine (ASAM) Level of Care at the time of clinic enrollment (e.g., outpatient vs. intensive outpatient).

When multiple control patients met all the criteria, the control patient who first entered treatment closest to the participant's start was chosen to improve the match on treatment timeframe and duration. Five participants were excluded due to a lack of appropriately matched control patients resulting in a final sample of 124 patients (62 matched patient-pairs), all of whom were included in the clinical characterization and main outcome analyses.

Intervention

This study involved the pilot implementation of a smartphone-smartcard platform developed by DynamiCare Health, Inc. (Boston, MA) described in detail elsewhere (8). The contingency management intervention provided appointment reminders with smartphone GPS monitoring, cognitive behavioral therapy

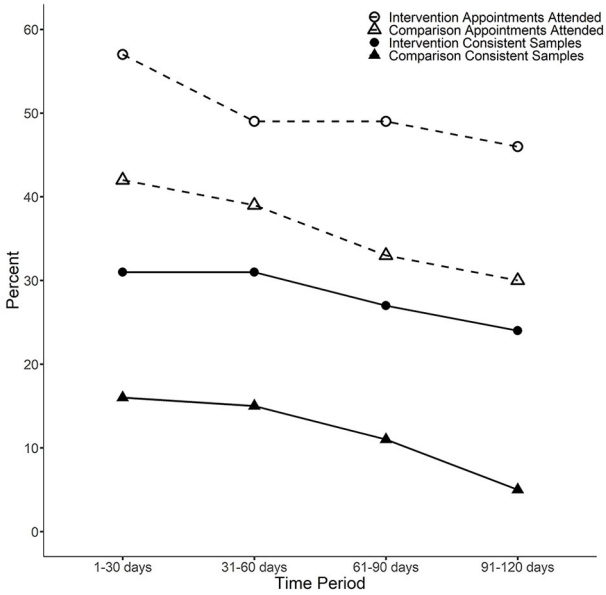

FIGURE 1 | The percentage of consistent samples and appointment attendance rate by condition and time block. Consistent urine samples: For the third and fourth time periods, a Fisher's exact p test indicates the average difference between intervention and comparison patients is statistically significant ($p < 0.05$). For the first time period (1–30 days), the p-value is $p = 0.089$ and for the second time period (31–60 days) the p-value is $p = 0.052$. Attendance: For the first, third and fourth time periods, a two-sample t-test indicates the average difference between intervention and comparison patients is statistically significant ($p < 0.05$). For the second time period (31–60 days), the p-value is $p = 0.062$.

readings with exercises and comprehension questions, and up to $100 per month in monetary incentives for these and for abstinent substance tests. Rewards were paid promptly and automatically *via* a smart debit card that offered numerous protections spending that was inconsistent with the goals of treatment.

Analysis

Main outcome analyses were conducted for attendance and urine samples consistent with illicit drug abstinence and medication adherence requirements, which were individualized based on the needs of each patient. Group outcomes were compared in four consecutive 30-day blocks. Attendance was calculated as the percentage of all scheduled appointments attended for each 30-day block and was analyzed with ordinary least squares regression. Logistic regression was used to analyze the percentage of urine samples consistent with illicit drug abstinence and medication adherence. Any missing outcome data were imputed as the undesirable outcome for the analysis. To control for possible confounders and an important predictor, the regression models included covariates for new patient status, cocaine use disorder diagnosis, and baseline urine sample result.

For continuous demographic and clinical characteristics, *p*-values were estimated using a two-sample *t*-test. For dichotomous characteristics, *p*-values were estimated using Fisher's exact *p*. Intervention group participants were classified as new patients if they enrolled in in the contingency management intervention within 5 days of starting treatment. Comparison patients enrolled in treatment at the clinic within 5 days of their matched intervention participant starting the smartphone-smartcard contingency management intervention.

RESULTS

In terms of demographics, there were no significant differences between groups. Combining the groups shows that the sample was 52% female and 89% white, with an average age of 38 ($SD = 9.2$). Further, 79% of the participants had completed high school, 48% were unemployed, and 11% were married (for these characteristics, some clinic records were incomplete, with the number of missing values ranging from 3 to 19 depending on the measure).

Clinical characterization of the sample revealed two significant baseline differences: the intervention group contained 37% new patients compared to 15% in the control group ($p < 0.05$), and the intervention group contained 74% patients with a cocaine use disorder diagnosis compared to 48% of the control patients ($p < 0.01$). In both groups, 95% of participants had opioid use disorder as their primary diagnosis. Similarly, in both groups 60% of participants were enrolled in a level 1 outpatient program, 37% were enrolled in an intensive outpatient program, and 3% were enrolled in continuing care. In the intervention group, 24% of participants' baseline urine sample was consistent with clinic requirements, compared to 21% of participants in the comparison group.

The results for the consistent urine sample and attendance record analyses are shown in **Figure 1** and **Table 1**. Participants in the intervention group were significantly more likely to attend appointments at all time points, and more likely to submit consistent urine samples at the third and fourth time points. Both groups showed declines in consistent urine samples and attendance over time, but the declines were more substantial in the control. A sensitivity analysis only including matched-pairs with complete data (i.e., treating missing urine or attendance

TABLE 1 | Consistent urine tests and appointment attendance.

	1–30 days	31–60 days	61–90 days	91–120 days
Consistent urine test outcomes				
Intercept	−2.35** (0.51)	−2.40** (0.50)	−2.55** (0.54)	−3.32** (0.70)
Intervention	0.96* (0.55) [2.60]	0.98* (0.53) [2.68]	1.46** (0.60) [4.31]	2.24** (0.76) [9.43]
New treatment patient	0.34 (0.54)	0.08 (0.54)	−1.01 (0.66)	−1.10 (0.72)
Cocaine diagnosis	−0.27 (0.52)	0.06 (0.52)	−0.23 (0.56)	−0.32 (0.63)
Consistent baseline test	2.21** (0.51)	1.82** (0.50)	1.94** (0.53)	1.58** (0.59)
Appointment attendance rate outcomes				
Intercept	48.69** (4.24)	44.32** (5.01)	35.85** (5.06)	35.18** (5.54)
Intervention	18.93** (4.81)	14.065* (5.68)	20.83** (5.73)	20.07** (6.27)
New treatment patient	−8.71 (5.32)	−10.82* (6.28)	−17.54** (6.34)	−14.86** (6.95)
Cocaine diagnosis	−8.81* (4.76)	−6.28 (5.62)	−2.10 (5.70)	−3.41 (6.21)
Consistent baseline test	−3.38 (5.40)	−2.33 (6.38)	2.60 (6.44)	−5.14 (7.05)
Adjusted R^2	0.09	0.03	0.10	0.06

*$p < 0.10$, **$p < 0.05$. *Consistent urine tests mean that the patient was negative for all tested substances and positive for expected prescribed medications. The logistic regression coefficient is the first number listed in each cell, with standard errors in parentheses. The odds ratio is in brackets and is the odds of a consistent test for intervention group patients over the odds of a consistent test for comparison patients (i.e., numbers >1 indicate a positive intervention impact). For example, between 61 and 90 days, the odds of an intervention patient having a consistent urine test are 4.31 the odds of a comparison patient having a consistent urine test ($p < 0.05$). The coefficients indicate the increase in percentage attendance (e.g., between 61 and 90 days, intervention patients had a 20.83% point higher rate of appointment attendance).*

samples as missing instead of imputing as inconsistent or zero) typically estimated similar effects, although the smaller sample sizes resulted in less statistical power.

DISCUSSION

The present study shows that contingency management delivered *via* a smartphone-smartcard platform can improve drug use and clinic attendance outcomes among patients with concurrent opioid and stimulant use disorders when used as an adjunct to care in an outpatient buprenorphine maintenance program. The present finding is broadly consistent with prior contingency management studies in general (3–5), and with prior studies of the same smartphone-smartcard platform for delivery contingency management intervention (6–8). This is a timely finding, as the Office of National Drug Control Policy (ONDCP) top priority for 2021 is, "Expanding access to evidence-based treatment", and specific actions described by the ONDCP toward this end include, "Identify and address policy barriers related to contingency management interventions (motivational incentives) for stimulant use disorder", and "Explore reimbursement for motivational incentives and digital treatment for addiction, especially stimulant use disorder" (9).

The most important limitation of the present study is the possible selection bias, as patients chose whether to enroll in the treatment. Another key limitation is that the retrospective design used in this study is not as strong as a randomized controlled trial. Nevertheless, widespread dissemination of contingency management for the treatment of polysubstance use is urgent and digital platforms offer dissemination potential that cannot be matched by training programs designed to enable outpatient providers to offer clinic-based contingency management services directly. One of the key advantages of digital platforms is that they allow for the delivery of high-fidelity contingency management. Another advantage is that commercial and Medicaid payers are beginning to support this form contingency management, which provides a pathway to addressing the issue of cost as a barrier to adoption of contingency management.

Future studies should explore combinations of drug abstinence and medication adherence contingencies, and seek to explicitly evaluate long-term treatment retention and outcomes. A recent review highlighted the success of contingency management in producing good outcomes 1-year post-treatment (10), but whether similar outcomes can be achieved with a remote digital delivery platform remains unknown. Another potential advantage of delivering contingency management *via* a remote digital platform is that a wide variety of patient behaviors can be measured and used to predict lapses and treatment dropout, and provide immediate therapeutic response (e.g., *via* peer-recovery coaching) just-in-time, in an attempt to support patients at times of elevated risk.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Sterling Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SR was principally responsible for overseeing data collection. JF was principally responsible for conducting the statistical analysis. AD was principally responsible for all aspects of manuscript preparation. All authors designed the study together and read and approved the final version of the manuscript.

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ORIGINAL RESEARCH
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Adults With Opioid and Methamphetamine Co-use Have Lower Odds of Completing Short-Term Residential Treatment Than Other Opioid Co-use Groups: A Retrospective Health Services Study

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Objective: There is an increase in persons entering substance use treatment who co-use opioids and methamphetamines in recent years. Co-using these substances may negatively impact treatment retention in the residential setting. We explored predictors of adults completing short-term residential treatment among persons with primary opioid use disorder (OUD) who co-use either alcohol, benzodiazepines, cocaine, or methamphetamines.

Methods: This study used the 2019 de-identified, publicly available Treatment Episode Dataset-Discharges. The sample included adults discharged from short-term residential treatment with primary OUD who co-used either alcohol, benzodiazepines, cocaine, or methamphetamines. The final sample size included 24,120 treatment episodes. Univariate statistics were used to describe the sample. Two logistic regression models were used to predict completing treatment. The first logistic regression model included the co-use groups as predictors and the second model added other demographic and treatment-relevant covariates.

Results: A slight majority (51.4%) of the sample prematurely discharged from treatment. Compared to the other three co-use groups, the opioid and methamphetamine co-use group had the highest proportion of individuals who were women (45.0%), unemployed (62.5%), current injection drug use (76.0%), living in the Midwest (35.9%), living in the south (33.5%), and living in the west (15.5%). The opioid and methamphetamine co-use group also had the highest proportion of individuals not receiving medications for OUD (84.9%), not having a prior treatment episode (28.7%), and not completing treatment (57.4%). In the final logistic regression model, which included covariates, the opioid and alcohol (OR = 1.18, 95% CI = 1.080–1.287, $p < 0.001$), opioid and benzodiazepine (OR = 1.33, 95% CI = 1.213–1.455, $p < 0.001$), and opioid and cocaine (OR = 1.16, 95% CI = 1.075–1.240, $p < 0.001$) co-use groups had higher odds of completing treatment than the opioid and methamphetamine co-use group.

Conclusions: Opioid and methamphetamine co-use may complicate short-term residential treatment retention. Future work should identify effective strategies to retain persons who co-use opioids and methamphetamines in treatment.

Keywords: co-use, short term treatment, methamphetamine, opioids, polysubstance use, treatment, residential, substance use disorder

INTRODUCTION

Different combinations of polysubstance use have been identified among individuals who use opioids, which must be considered in the context of opioid use disorder (OUD) treatment. One study among 356 people found over 55% of individuals with OUD co-use other substances such as alcohol, benzodiazepines, and cocaine (1). Sometimes substances are co-used to enhance or adjust for other drug effects (e.g., sedation, "comedown," and withdrawal) (2–5). A recent trend in polysubstance use is the increase of opioid and methamphetamine co-use, which has been referred to as the fourth wave of the opioid crisis. Another epidemiological study in the United States identified a 66% increase in methamphetamine use from 2015 to 2018 among persons who used heroin in the past year, and a 49.2% increase among those with past twelve month prescription opioid misuse (6). Another epidemiological study found that past year use of both heroin and methamphetamine increased from 22.5% in 2015 to 46.7% in 2019 (7). Potential reasons for the increase of methamphetamine use include substituting the substance for opioids, a synergistic high, or balancing the effects of opioids (5).

Co-use of opioids and methamphetamine is associated with low socioeconomic status and health consequences such as overdose and increased need for medical care (8–10), and it is estimated that 10% of adults with OUD have a co-occurring methamphetamine use disorder (11). Compared to adults who use opioids alone, those with opioid and methamphetamine co-use were over 200% more likely to have housing instability, and had nearly 100% more hospital overnight stays and ∼46% more visits to the emergency department (9). Regarding overdoses, data from 25 states show that methamphetamine was involved in over 10% of all opioid-related deaths (8). Along with the trends of opioid and methamphetamine co-use observed in the general population, this pattern was also identified among individuals entering treatment. One study found that adults admitted to treatment with opioid and methamphetamine co-use increased by ∼10% from 1992 to 2017 (12). Further, individuals entering treatment with heroin as a primary substance had a 490% increase in methamphetamine co-use from 2008 to 2017 (13). Since polysubstance use is so prevalent in persons with OUD, understanding the complexities of co-using substances has the potential to enhance treatment (2, 14). Compared to those who discharge from treatment prematurely, longer retention or completing treatment is a predictor of better post-treatment outcomes. Some of these outcomes include increased harm reduction, longer periods of substance abstinence, and greater social functioning (15, 16).

Residential treatment is recommended for individuals who are unstable and have moderate to severe substance use disorders (15, 17). While longer stays in treatment (e.g., >90 days) are associated with positive outcomes for opioids, methamphetamines, and other drug use generally (16, 18–21), the benefit of short-term residential treatment (e.g., 30 days or less) on the co-use of opioids and methamphetamines is unclear. Co-use of opioids and methamphetamines has the potential to impact aspects of treatment such as behavioral counseling and withdrawal management. Although medications for OUD (MOUD) are effective in improving relapse and retention outcomes, individuals who co-use substances with opioids are less likely to receive these medications (12, 22). Persons with OUD are less likely to receive MOUD in short-term residential compared with outpatient treatment (23), and there is also a large gap between availability of MOUD and use of MOUD in residential treatment facilities across the U.S (24). Treatment for co-occurring opioid and methamphetamine use disorders is further complicated by the lack of effective pharmacotherapy options for methamphetamine use (25–27).

This study examined differences in demographic, drug use, and treatment characteristics among adults discharged from short-term residential treatment in four distinct opioid co-use groups: (1) alcohol, (2) benzodiazepines, (3) cocaine, and (4) methamphetamine. These four groups were chosen because another study that examined these groups found a decrease in the prevalence of opioid and alcohol co-use and opioid and cocaine co-use, and an increase in the prevalence of opioid and benzodiazepine co-use and opioid and methamphetamine co-use (12). Further, this study examined treatment completion rates from short-term residential treatment for persons with OUD as a function of co-use drug classes.

MATERIALS AND METHODS

Sample

The publicly available de-identified Treatment Episode Dataset–Discharges (TEDS-D) 2019, which is provided annually by the Substance Abuse and Mental Health Services Administration was used for this study (28). TEDS-D contains demographic information, substance use characteristics, treatment type, and discharge information for treatment episode discharges in the year of 2019 from U.S. substance use treatment providers that receive public funds (28). States that were excluded from the dataset due to insufficient data include Oregon, Washington, and West Virginia (28). The sample was selected by using the following criteria: (1) 18 years or older, (2) admitted to short-term residential treatment, (3) discharged from short-term residential treatment, (4) has a value for the outcome, reason for discharge, (5) death was not the reason for discharge, (6) heroin,

non-prescription methadone, or other opiates and synthetics was the primary substance, and (7) alcohol, benzodiazepines, cocaine, or methamphetamine/speed was the secondary substance.

Measures

Co-use groups were created if opioids were the primary substance and alcohol, benzodiazepines, cocaine, and methamphetamine/speed were the secondary substances. The discharge reason was dichotomized as treatment completed and premature discharge. Length of stay was a continuous variable with values from 1 to 30 which describes the length of the treatment episode in days. Age was recoded to include the following age ranges 18–29 years old, 30–39 years old, 40–49 years old, and 50 years and older. Race was recoded with the following categories, Black, White, and Other. Non-Black and non-White groups were combined into the Other category due to low frequencies. Gender was a binary variable with women and men as values. Receiving medication for opioid use disorder (MOUD) in the current treatment plan was dichotomized as Yes or No. The frequency of use variables (primary substance and secondary substance) had No use, Some use, and Daily use as values. Prior substance use treatment refers to ever having a previous substance use treatment episode and was dichotomized as Yes or No.

Analyses

Univariate analyses including counts, percentages, and means were used to describe the full sample and the four co-use groups. An analysis of variance (ANOVA) was used to examine the associations between the co-use groups and length of stay in treatment. Two logistic regression models were conducted to predict completing treatment. Little's Missing Completely at Random (MCAR) test was utilized for treatment episodes missing values for variables included in the final logistic regression model. Little's MCAR test ($p = 0.134$) provided evidence that listwise deletion was adequate. Listwise deletion was used for treatment episodes that were missing values for variables included in the final logistic regression model. The first logistic regression model included only the co-use groups as predictors (reference group: Opioid and Methamphetamine co-use group). The second logistic regression model retained the co-use groups and added the following covariates: age (reference group: 18–29 years old), gender (reference group: Women), race (reference group: White), receiving MOUD (reference group: No), frequency of primary substance (reference group: Daily), frequency of secondary substance (reference group: Daily), and prior substance use treatment (reference group: No). Due to the large sample size, $p < 0.001$ was established as the threshold for significance in the bivariate and multivariate analyses. Analyses were performed using SPSS Version 27 (Armonk, NY).

RESULTS

Sample Characteristics

There were 28,483 treatment episodes that met initial eligibility criteria, however 4,363 did not have complete data and were thus excluded, leaving a final sample of $n = 24{,}120$ treatment episodes. There were 3,918 (16.2%) treatment episodes in the opioids and alcohol co-use group, 3,230 (13.4%) in the opioids and benzodiazepines co-use group, 11,575 (48.0%) in the opioids and cocaine co-use group, and 5,397 (22.4%) in the opioids and methamphetamine co-use group.

Demographic, substance use, and treatment characteristics of the full sample and the four co-use groups are shown in **Table 1**. Less than half of the full sample completed treatment (48.6%). Most of the full sample were men (63.6%), White (72.9%), and not Hispanic or Latino (86.7%). Proportionally, the opioid and methamphetamine co-use group had the largest percentage in the Midwest (35.9%), South (33.5%), and West (15.5%) regions. Similarly, the opioid and methamphetamine co-use group had the largest combined proportion of individuals ages 18–39 years old (84.5%), followed by the opioid and benzodiazepine co-use group (79.4%). Women were the largest percent in the opioid and methamphetamine co-use group (45.0%) followed by the opioid and benzodiazepine co-use group (36.4%). The opioid and methamphetamine co-use group also had a higher percentage of cases being unemployed (62.5%), engaging in injection drug use (76.0%), not currently receiving MOUD (28.7%), and not having a prior substance use treatment episode (28.7%). Regarding days in treatment, the opioid and methamphetamine co-use group had an average of 18.4 (SD = 10.8) days, opioid and alcohol co-use group had an average of 16.2 (SD = 9.8) days, opioid and cocaine co-use group had an average of 15.9 (SD = 9.8) days, and the opioid and benzodiazepine group had an average of 15.2 (SD = 9.6). Results from an analysis of variance indicated the co-use groups influenced the number of days in treatment [$F_{(3,\ 24{,}116)} = 95.97$, $p < 0.001$]. Using Tukey's honest significant difference, the opioid and methamphetamine group had a significantly higher average number of days in treatment than the other three co-use groups.

Predicting Treatment Completion

Results from the first logistic regression model are shown in **Table 2**. In model 1, which excluded covariates, the opioid and alcohol (OR = 1.37, 95% CI = 1.264–1.491, $p = <0.001$), opioid and benzodiazepine (OR = 1.454, 95% CI = 1.332–1.587, $p < 0.001$), and opioid and cocaine (OR = 1.33, 95% CI = 1.251–1.425, $p < 0.001$) co-use groups all had higher odds of completing treatment than the opioid and methamphetamine co-use group.

Results from the final logistic regression model are shown in **Table 3**. In model 2, which included covariates, the opioid and alcohol (AOR = 1.18, 95% CI = 1.080–1.287, $p < 0.001$), opioid and benzodiazepine (AOR = 1.33, 95% CI = 1.213–1.455, $p < 0.001$), and opioid and cocaine (AOR = 1.16, 95% CI = 1.075–1.240, $p < 0.001$) co-use groups also had higher odds of completing treatment than the opioid and methamphetamine co-use group. Individuals aged ≥50 years old (AOR = 1.40, 95% CI = 1.278–1.538, $p < 0.001$) had higher odds of completing treatment than those between the ages of 18–29 years old. Men (AOR = 1.26, 95% CI = 1.190–1.326, $p < 0.001$) had higher odds of completing treatment than women. Those who were Black had lower odds (AOR = 0.85, 95% CI = 0.784–0.921, $p < 0.001$) of completing treatment than those who were White.

TABLE 1 | Demographic, substance use, and treatment characteristics of the full sample and co-use groups.

	Full study sample (*n*, %)	Opioids and alcohol subsample (*n*, %)	Opioids and benzodiazepines subsample (*n*, %)	Opioids and cocaine subsample (*n*, %)	Opioids and methamphetamines subsample (*n*, %)
Sample size	24,120 (100.0%)	3,918 (100.0%)	3,230 (100.0%)	11,575 (100.0%)	5,397 (100.0%)
Days in treatment, mean (Standard deviation)	16.4 (SD = 10.1)	16.2 (SD = 9.8)	15.2 (SD = 9.6)	15.9 (SD = 9.8)	18.4 (SD = 10.8)
Region					
Northeast	11,547 (47.9%)	2,071 (52.9%)	1,789 (55.4%)	6,871 (59.4%)	816 (15.1%)
Midwest	6,570 (27.2%)	1,012 (25.8%)	677 (21.0%)	2,946 (25.5%)	2,935 (35.9%)
South	4,896 (20.3%)	732 (18.7%)	707 (21.9%)	1,649 (14.2%)	1,808 (33.5%)
West	1,107 (4.6%)	103 (2.6%)	57 (1.8%)	109 (0.9%)	838 (15.5%)
Age					
18–29 years old	7,704 (31.9%)	946 (24.1%)	1,370 (42.4%)	3,104 (26.8%)	2,284 (42.3%)
30–39 years old	9,024 (37.4%)	1,254 (32.0%)	1,194 (37.0%)	4,300 (37.1%)	2,276 (42.2%)
40–49 years old	4,023 (16.7%)	737 (18.8%)	397 (12.3%)	2,215 (19.1%)	674 (12.5%)
50 years and older	3,369 (14.0%)	981 (25.0%)	269 (8.3%)	1,956 (16.9%)	163 (3.0%)
Education level[a]					
Less than HS Diploma or GED	6,047 (25.1%)	973 (24.8%)	605 (18.7%)	3,132 (27.1%)	1,337 (24.8%)
HS Diploma or GED	11,585 (48.0%)	1,873 (47.8%)	1,581 (48.9%)	5,494 (47.5%)	2,637 (48.9%)
1–3 years of college, university, vocational	5,187 (21.5%)	844 (21.5%)	796 (24.6%)	2,334 (20.2%)	1,213 (22.5%)
4 years of college, university or higher	1,151 (4.8%)	212 (5.4%)	224 (6.9%)	548 (4.7%)	167 (3.1%)
Missing	150 (0.6%)	16 (0.4%)	24 (0.7%)	67 (0.6%)	43 (0.8%)
Gender					
Women	8,782 (36.4%)	999 (25.5%)	1,177 (36.4%)	4,175 (36.1%)	2,431 (45.0%)
Men	15,338 (63.6%)	2,919 (74.5%)	2,053 (63.6%)	7,400 (63.9%)	2,966 (55.0%)
Race					
Black	3,915 (16.2%)	880 (22.5%)	240 (7.4%)	2,636 (22.8%)	159 (2.9%)
White	17,581 (72.9%)	2,555 (65.2%)	2,736 (84.7%)	7,393 (63.9%)	4,897 (90.7%)
Other	2,624 (10.9%)	483 (12.3%)	254 (7.9%)	1,546 (13.4%)	341 (6.3%)
Ethnicity					
Hispanic or Latino	3,011 (12.5%)	531 (13.6%)	286 (8.9%)	1,752 (15.1%)	442 (8.2%)
Not Hispanic or Latino	20,913 (86.7%)	3,346 (85.4%)	2,916 (90.3%)	9,736 (84.1%)	4,915 (91.1%)
Missing	196 (0.8%)	41 (1.0%)	28 (0.9%)	87 (0.8%)	40 (0.7%)
Employment status					
Full-time	1,620 (6.7%)	341 (8.7%)	336 (10.4%)	649 (5.6%)	294 (5.4%)
Part-time	568 (2.4%)	107 (2.7%)	102 (3.2%)	271 (2.3%)	88 (1.6%)
Unemployed	9,826 (40.7%)	1,358 (34.7%)	1,096 (33.9%)	3,997 (34.5%)	3,375 (62.5%)
Not in labor force	11,944 (49.5%)	2,091 (53.4%)	1,680 (52.0%)	6,585 (56.9%)	1,588 (29.4%)
Missing	162 (0.7%)	21 (0.5%)	16 (0.5%)	73 (0.6%)	52 (1.0%)
Housing status					
Homeless	7,356 (30.5%)	1,246 (31.8%)	695 (21.5%)	3,948 (34.1%)	1,467 (27.2%)
Dependent living	4,243 (17.6%)	639 (16.3%)	515 (15.9%)	1,747 (15.1%)	1,342 (24.9%)
Independent living	12,280 (50.9%)	2,013 (51.4%)	1,990 (61.6%)	5,787 (50.0%)	2,490 (46.1%)
Missing	241 (1.0%)	20 (0.5%)	30 (0.9%)	93 (0.8%)	98 (1.8%)
Age first used primary substance					
11 years and under	363 (1.5%)	62 (1.6%)	43 (1.3%)	126 (1.1%)	132 (2.4%)
12–14 years old	1,767 (7.3%)	305 (7.8%)	209 (6.5%)	683 (5.9%)	570 (10.6%)
15–17 years old	3,799 (15.8%)	600 (15.3%)	574 (17.8%)	1,704 (14.7%)	921 (17.1%)
18–20 years old	5,030 (20.9%)	782 (20.0%)	745 (23.1%)	2,396 (20.7%)	1,107 (20.5%)
21–24 years old	4,423 (18.3%)	611 (15.6%)	677 (21.0%)	2,170 (18.7%)	965 (17.9%)
25–29 years old	3,890 (16.1%)	616 (15.7%)	477 (14.8%)	1,971 (17.0%)	826 (15.3%)
30 years and older	4,734 (19.6%)	922 (23.5%)	495 (15.3%)	2,469 (21.3%)	848 (15.7%)

(Continued)

TABLE 1 | Continued

	Full study sample (*n*, %)	Opioids and alcohol subsample (*n*, %)	Opioids and benzodiazepines subsample (*n*, %)	Opioids and cocaine subsample (*n*, %)	Opioids and methamphetamines subsample (*n*, %)
Missing	114 (0.5%)	20 (0.5%)	10 (0.3%)	56 (0.5%)	28 (0.5%)
Frequency of primary substance use					
No use in the past month	2,851 (11.8%)	396 (10.1%)	252 (7.8%)	1,025 (8.9%)	1,178 (21.8%)
Some use	4,569 (18.9%)	703 (17.9%)	457 (14.1%)	1,899 (16.4%)	1,510 (28.0%)
Daily use	16,700 (69.2%)	2,819 (71.9%)	2,521 (78.0%)	8,651 (74.7%)	2,709 (50.2%)
Age first used secondary substance					
11 years and under	751 (3.1%)	420 (10.7%)	43 (1.3%)	125 (1.1%)	143 (2.6%)
12–14 years old	2,811 (11.7%)	1,195 (30.5%)	209 (6.5%)	756 (6.5%)	563 (10.4%)
15–17 years old	4,888 (20.3%)	1,149 (29.3%)	574 (17.8%)	2,137 (18.5%)	877 (16.2%)
18–20 years old	4,456 (18.5%)	463 (11.8%)	745 (23.1%)	2,469 (21.3%)	904 (16.8%)
21–24 years old	3,133 (13.0%)	207 (5.3%)	677 (21.0%)	1,728 (14.9%)	801 (14.8%)
25–29 years old	2,905 (12.0%)	81 (2.1%)	477 (14.8%)	1,565 (13.5%)	837 (15.5%)
30 years and older	3,249 (13.5%)	124 (3.2%)	495 (15.3%)	1,603 (13.8%)	960 (17.8%)
Missing	1,927 (8.0%)	279 (7.1%)	10 (0.3%)	1,192 (10.3%)	312 (5.8%)
Frequency of secondary substance use					
No use in the past month	2,949 (12.2%)	423 (10.8%)	307 (9.5%)	1,060 (9.2%)	1,159 (21.5%)
Some use	8,618 (35.7%)	1,226 (31.3%)	1,001 (31.0%)	4,124 (35.6%)	2,267 (42.0%)
Daily use	12,553 (52.0%)	2,269 (57.9%)	1,922 (59.5%)	6,391 (55.2%)	1,971 (36.5%)
Current injection drug use					
Yes	14,526 (60.2%)	2,141 (54.6%)	1,740 (53.9%)	6,907 (59.7%)	4,102 (76.0%)
No	9,594 (39.8%)	1,777 (45.4%)	1,490 (46.1%)	4,668 (40.3%)	1,295 (24.0%)
Receiving medication for opioid use disorder					
Yes	6,504 (27.0%)	946 (24.1%)	922 (28.5%)	3,821 (33.0%)	815 (15.1%)
No	17,616 (73.0%)	2,972 (75.9%)	2,308 (71.5%)	7,754 (67.0%)	4,582 (84.9%)
Prior substance use treatment					
Yes	20,321 (84.2%)	3,377 (86.2%)	2,732 (84.6%)	10,363 (89.5%)	3,849 (71.3%)
No	3,799 (15.8%)	541 (13.8%)	498 (15.4%)	1,212 (10.5%)	1,548 (28.7%)
Discharge reason					
Treatment completed	11,719 (48.6%)	1,978 (50.5%)	1,677 (51.9%)	5,764 (49.8%)	2,300 (42.6%)
Premature discharge	12,401 (51.4%)	1,940 (49.5%)	1,553 (48.1%)	5,811 (50.2%)	3,097 (57.4%)

Some percents may not equal to 100% due to rounding error. Percents are column percents.
[a]*HS, High School; GED, General Educational Development.*

Conversely, those whose race was categorized as "Other" (AOR = 1.34, 95% CI = 1.233–1.464, $p < 0.001$) had higher odds of completing treatment than those who were White. Treatment episodes that received MOUD (AOR = 1.63, 95% CI = 1.537–1.731, $p < 0.001$) had higher odds of completing treatment than those that did not. Individuals who used their primary opioid substance sometimes (AOR = 1.15, 95% CI = 1.065–1.238, $p < 0.001$) had higher odds of completing treatment than those who used their primary substance daily. Conversely, individuals who used their secondary substance sometimes (AOR = 0.90, 95% CI = 0.843–0.955, $p < 0.001$) had lower odds of completing treatment than those who used their secondary substance daily.

TABLE 2 | Logistic regression model predicting treatment completion by co-use groups.

Variable	Odds ratio	95% CI	*p*
Co-use groups (Ref:Opioid+Methamphetamine)			
Opioid+Alcohol	1.373	1.264–1.491	<0.001
Opioid+Benzodiazepine	1.454	1.332–1.587	<0.001
Opioid+Cocaine/Crack	1.336	1.251–1.425	<0.001

DISCUSSION

The current study identified adults who co-use opioids and methamphetamine as having lower odds of completing treatment than other opioid co-use groups, namely alcohol, benzodiazepines, and cocaine. Considering the alarming increase of opioid and methamphetamine co-use in recent years (6, 7), this group's heightened risk of treatment attrition requires attention by treatment providers and researchers. This study also found the opioid and methamphetamine co-use group had significantly more days in treatment than other co-use groups. It is interesting

TABLE 3 | Logistic regression model predicting treatment completion by co-use groups and covariates.

Variable	Adjusted odds ratio	95% CI	*p*
Co-use groups (Ref:Opioid+Methamphetamine)			
Opioid+Alcohol	1.18	1.080–1.287	<0.001
Opioid+Benzodiazepine	1.33	1.213–1.455	<0.001
Opioid+Cocaine/Crack	1.16	1.075–1.240	<0.001
Age groups (Ref: 18–29 years old)			
30–39 years old	1.02	0.959–1.085	0.528
40–49 years old	1.07	0.989–1.159	0.093
50 years and older	1.402	1.278–1.538	<0.001
Gender (Ref: Women)			
Men	1.26	1.190–1.326	<0.001
Race (Ref: White)			
Black	0.85	0.784–0.921	<0.001
Other	1.34	1.233–1.464	<0.001
Receiving medication for opioid use disorder (Ref: No)			
Yes	1.63	1.537–1.731	<0.001
Frequency of use primary substance (Ref: Daily)			
Some use	1.15	1.065–1.238	<0.001
No use	1.19	1.053–1.341	0.005
Frequency of use secondary substance (Ref: Daily)			
Some use	0.90	0.843–0.955	<0.001
No use	0.89	0.784–0.999	0.048
Prior substance use treatment (Ref: No)			
Yes	1.11	1.036–1.197	0.004

Due to the large sample size $p < 0.001$ was established as the threshold for significance.

that this group had the highest proportion of not completing treatment yet had the longest number of days in treatment. Perhaps this points to treatment providers considering a longer course of treatment necessary to adequately treat individuals who co-use opioids and methamphetamines.

This study also found that the opioid and methamphetamine co-use group had a higher proportion of women than the other three co-use groups. A review of the literature found that women start using methamphetamine at an earlier age and are more dependent on methamphetamine than men (29). Among reproductive age and pregnant women, methamphetamine is one of the most abused substances (30, 31). A study based on persons who inject drugs in Seattle found a higher proportion of women co-using heroin and amphetamine instead of using these substances alone (32). Women with OUD have also been found to have higher rates of treatment attrition in multiple studies (33).

The regional distribution of opioid and methamphetamine co-use is also noteworthy. This co-use group had the highest proportion in the Southern, Midwestern, and Western regions. While data have shown that methamphetamine use and related overdose deaths are more common in the Western region (34), recent data show that methamphetamine use is expanding to other geographic areas in Southern and Midwestern regions (35, 36), which are already epicenters of the opioid crisis.

The opioid and methamphetamine co-use group had the highest proportion of injection drug use, as over three-fourths of the treatment episodes in this group indicated current injection drug use. Another study found that opioid and methamphetamine co-use was associated with a 132% higher prevalence of injection drug use when compared to those who only use opioids (37). Injection drug use is associated more severe substance use disorder, which itself increases the risk of premature discharge from treatment. Not receiving MOUD increases the risk of treatment attrition among persons with OUD (12). The opioid and methamphetamine co-use group had the lowest proportion of receiving MOUD in this study. Although effective medications to treat methamphetamine are lacking (25–27), the medications to treat OUD may increase treatment completion in this co-use group.

This study is not without limitations. One limitation is this study focused on treatment episodes from treatment providers that receive public funding. These results may not be generalizable to private substance use treatment providers. Including treatment episodes that do not use their primary or secondary substance in the past month is a limitation, although this subgroup might be fundamentally different than those who enter treatment with active use. A second limitation is only including primary and secondary substances while excluding tertiary substances. Although data were analyzed in this way to focus on the two main substances, if tertiary substances were considered there could be potential overlap between the co-use groups. For example, an individual could use heroin, methamphetamine, and cocaine prior to entering short-term residential treatment. This creates a challenge for group comparisons as there are several potential 3-group combinations of polysubstance use, and it is difficult to interpret the importance of tertiary drug use within the TEDS dataset. A third limitation is the potential duplication or overestimation of polysubstance use given that TEDS-D cases are discharges and not individuals, although we countered this limitation by controlling for prior treatment episodes in the multivariate model. Since this study utilized a secondary dataset, we were constrained by the available variables. Considering this limitation, we were unable to include other predictors such as sexual orientation, type of medication for OUD, family support, and treatment provider characteristics. Finally, we were limited by not having follow-up data beyond discharge from treatment, and although completing treatment is associated with better posttreatment outcomes, this cannot be assessed in the current study. Considering these limitations, this study provides key insight into opioid co-use groups and short-term residential treatment completion.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: https://www.datafiles.samhsa.gov/dataset/teds-d-2019-ds0001-teds-d-2019-ds0001.

AUTHOR CONTRIBUTIONS

All authors have contributed to the design, preparation, and editing of the manuscript.

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Shifting Pathways of Stimulant Use Among Individuals With Opioid Use Disorder: A Retrospective Analysis of the Last Thirty Years

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Background: Stimulant use among individuals with opioid use disorder has recently increased, driven by changes in drug distribution channels. However, our understanding of polysubstance use is often limited by a need to provide targeted treatment to a primary drug of addiction. Yet there is a crucial need to better understand pathways to addiction, and how the use of multiple substances may differ between populations, as well as time periods.

Methods: Using a national opioid surveillance system, we analyzed survey data from new entrants to 124 opioid use disorder treatment centers from 2017 to 2020. Age of first use was collected for prescription opioids, illicit opioids, prescription stimulants, crack/cocaine, and methamphetamines. Year of initial use of an opioid or stimulant was calculated and grouped by 5 year blocs, inclusive of initial use starting from 1991 and ending in 2020 ($n = 6{,}048$).

Results: Lifetime exposure to stimulants was 82.5% among individuals with opioid use disorder. Mean age of initiation increased for all drugs in 2016–2020, in particular prescription opioids (22.3 to 31.8). Stimulants were initiating drugs for a substantial proportion of individuals with opioid use throughout the analyzed time period. Those initiating opioid/stimulant use from 1991 to 1995 had a mean average of 6.8 years between first and second drug exposure, which steadily decreased to 1.5 years between exposures in 2016–2020. Sankey plots depict significantly more drug transitions in those initiating use from 1991 to 2000 (65.1% had at least two drug transitions) compared to 2010–2020 (16.0%). Opioid-stimulant use increased over time among racial/ethnic minorities, sexual minorities, and those with an educational attainment of high school or less.

Conclusion: These data highlight not only the substantial prevalence of stimulant use among individuals who develop opioid use disorder, but also the variability through which pathways of use occur. Prevention and intervention efforts need to take into account increasing ages of initial drug exposures, demographic shifts in stimulant-using

populations, and more rapid drug transitions between opioid and stimulants. But at a broader level, prevention, harm reduction ideology, and addiction medicine needs to take into account the ubiquity of polysubstance use among individuals with substance use disorders.

Keywords: opioid use disorder, opioids, stimulants, addiction, polysubstance use

INTRODUCTION

In 2020, the United States reported the greatest number of overdose fatalities on record, over 93,000 (1). Primarily driven by overdoses involving opioids, this surge occurred amidst a pandemic that resulted in interruptions to addiction medicine and social support (2–5). Over the past two decades, the opioid crisis has led to renewed understandings of addiction prevention and treatment, with a number of federal, state and local policies implemented focusing on mitigating supply-side forces such as guidelines and legislation targeting prescription practices (6, 7), prescription drug monitoring programs (8, 9), and abuse-deterrent formulations (10, 11). As the crisis has persisted, recent efforts have been made to better understand the demand-side of addiction (12–15); not only by understanding motivations tied to co-morbid conditions such as mental health and chronic pain (16–18), but also the unique role that polysubstance use (i.e., use of multiple classes of substances) plays in addiction pathways. Evidence suggests that polysubstance use is widely prevalent among individuals with addiction, particularly those with opioid use disorder (19–21).

In recent years, the use of illicit psychostimulants such as methamphetamine and cocaine have increased, particularly among those using opioids (22–27). Much of this shift is due to changes in market supply forces such as production and distribution. In the early 2000s, efforts by law enforcement agencies focused heavily on halting domestic methamphetamine production, so much so that drug seizures from domestic methamphetamine laboratories reached its lowest point in 2019 (28). However, as localized methamphetamine production decreased, there was a proliferation of synthetically produced substances such as fentanyl from foreign countries. Methamphetamine supply in the United States is now primarily driven by an influx of manufacturers from Latin and South America (28).

As a result of these new and prolific distribution channels, reports of psychostimulant use and overdose have increased markedly in recent years (22–27). These increases are partially attributable to an increased and cost-efficient supply, and identifiable or unidentifiable lacing of one drug with another (e.g., fentanyl laced cocaine, methamphetamine laced fentanyl). However, other motivations for the use of psychostimulants among individuals using opioids have been reported, including: self-management of withdrawal symptoms, particularly if opioids are not available; attaining a synergistic high; and to balance one's self out throughout the day with cyclical use of opioids and stimulants (29).

Although opioids were the largest contributor to overdose fatalities, the use of methamphetamine and cocaine has not been absent throughout the opioid crisis. However, our understanding of polysubstance use has been limited, often the result of a need to provide targeted treatment to a primary drug involved in the biological underpinnings of addiction. Yet there is a crucial need to better understand pathways to addiction, and how the use of multiple substances may differ between populations, as well as time periods.

Drug markets are no less susceptible to secular changes than other institutions; indeed, significant disruptions have occurred in recent years as a result of stricter opioid policies, reductions in domestic methamphetamine laboratories, changes in drug market supplies, and the COVID-19 pandemic (28, 30). However, the extent to which these interdictions have influenced polysubstance use is still largely unknown. Retrospective analyses have been used to demonstrate shifts in opioid pathways, primarily national trends suggesting shifts from prescription opioids to heroin. The purpose of the present study was to conduct a retrospective analysis of stimulant use over the past 30 years to investigate the prevalence of stimulant use, better understand pathways that link opioid and stimulant use, and ascertain potential shifts in opioid and stimulant use over time.

MATERIALS AND METHODS

Sample Development

All participants in this study were obtained through the Survey of Key Informants' Patients (SKIP) Program. Briefly, the SKIP Program is an opioid surveillance program that utilizes a serial cross-sectional survey, and is nested within the broader Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System. Treatment centers from across the country are selected based on their ability to treat opioid use disorder, and their willingness to participate in an ongoing study regarding opioid use disorder and its correlates. Following verbal consent to participate, each of these treatment centers (i.e., "key informants") is supplied with, anonymous paper surveys, each ascribed a unique identifier, and directed to provide one survey to persons (i.e., "patients") 18 years or older who are newly entering the facility with a primary diagnosis of an opioid use disorder, as defined by DSM-IV or V criteria (depending on the time of survey completion). Patients (hereafter, *respondents*) who agree to participate are given a $20 Wal-Mart gift card for completion of the survey, along with a self-addressed stamped envelope to mail the survey directly to Washington University in St. Louis (WUSTL). All protocols were approved by the WUSTL Institutional Review Board.

The present analysis was developed using data from 7,019 respondents who had entered any one of the 124 regionally distributed treatment centers between 2Q2017 and 4Q2020.

Opioid and Stimulant Use Over Time

Given the overlap of some of these drugs, both chemically and in illicit drug use, drug strata were delineated by having ever used opioids—consisting of two groups, namely prescription opioids and illicit opioids (i.e., heroin or illicit fentanyl)—and stimulants—consisting of prescription stimulants, crack/cocaine, or methamphetamine. Age of first use was collected for each drug of interest, which acted as a proxy for lifetime use. Prevalence estimates were subsequently calculated. However, with a respondent age range of 65 years, we sought to account for the effect that one's length of lifetime drug use (that is, the difference between age at treatment entry and age at first drug exposure) may have on these estimates, as well as the age of first drug exposure. Utilizing Random Iterative Method (RIM) weighting in IBM SPSS Statistics v28, the weighted adjusted prevalence estimates were equivalent to unadjusted rates.

In connection with the sample-wide variance in length of lifetime drug use, and to attend more closely to drug use patterns that have occurred in recent years, our sample was subsequently restricted to individuals whose first use of any drug began within the last 30 years (i.e., no earlier than 1991), thereby removing 14.4% of the original sample for an analytic sample size (N) of 6,048. Age of first use was used to calculate year of initial drug exposure, which was defined as the earliest year for which one of the five drugs of interest was used by a respondent. Additionally, to illustrate changes in drug use over time, quinquennial groupings were established and defined as the year wherein respondents first used their first drug, whatever the drug may be. In accord with this definition, prevalence estimates, mean ages, and number/types of drugs are all reported as a function of the 5 year bloc within which drug use was initiated.

Following this sketch of initial drug exposure (again, irrespective of drug), respondents were categorized into non-exclusive, drug-specific groupings based on which drug(s) they had used first. Temporal comparisons of the mean age of exposure for each are reported.

Opioid and Stimulant Pathways and Demographics Over Time

To examine polysubstance use pathways and to evaluate the general influence time has had on drug transitions, we further restricted our sample to be constituted solely of individuals who had ever used opioids and stimulants (n = 4,935, 81.6% of N). Among these, years to a drug/drug class transition were calculated based on the respondent's age upon initiating any of the respective drugs, whichever came first, and the age at which a change in drug/drug class was made. Drug-drug transitions included the difference among first using any of the five drug groups; class-class transitions included the difference among first using either of the two drug classes. Protracted comparison of these individuals' demographic characteristics and univariate statistics were developed as well.

Opioid and Stimulant Drug Transitions

In order to observe temporal differences in ordered pathways of substance use, those who initiated more than one drug in a single year were excluded from the baseline analysis sample as the order of use of more than one drug in a single year could not be discerned (n = 883). A comparison of those included vs. excluded for analyses are included in **Supplementary Table 1**. There were no significant differences between those who initiated use with a single vs. multiple substances in the year of initial drug exposure, with the exception of mean age, which differed by less than a year (multiple = 31.6 vs. single = 32.4), and mean age of initiation, which was slightly, but significantly higher for those excluded form analyses (multiple = 18.4 vs. single = 16.6). For those that remained, drugs were ordered by their age of first use and then the differences between these ages were averaged to determine number of years between drug transitions (i.e., first drug to second drug, second drug to third drug, etc.).

Sankey plots were then created, inclusive of participants who (1) reported initiation and transitions to a single substance and (2) those who initiated substance use between 1991 and 2000 or between 2011 and 2020. Participants were then exclusively stratified into one of two groups based on period of first substance initiation: group 1: 1992–2000 and group 2: 2011–2020. Counts of those transitioning from substance-to-substance were then used to construct a Sankey plot for each period. The years from 2001–2010 were excluded from these analyses in order to provide a more distinct temporal comparison of opioid and stimulant drug transitions.

RESULTS

Demographic Characteristics

Table 1 describes the demographic profiles of individuals with opioid use disorder who had lifetime exposure to stimulants by 5 year bloc. The proportion of individuals with opioid-stimulant use significantly decreased among females (65.3 to 45.5%, $p < 0.001$), urban residents (57.7 to 51.5%, $p < 0.001$), and those with an educational attainment of some college (41.2 to 32.4%, $p < 0.001$). Conversely, the proportion of opioid-stimulant users significantly increased among racial/ethnic minorities (20.3 to 36.2%, $p < 0.001$), sexual minorities (11.5 to 27.7%, $p = 0.001$), suburban residents (23.1% to 24.2%, $p = 0.002$), residents of the Western region of the United States (17.2 to 31.9%, $p < 0.001$), and those with an educational attainment of high school or less (54.5 to 58.8%, $p < 0.001$). Lifetime history of prior treatment episodes was endorsed by the majority of respondents in each 5 year bloc, but significantly decreased in the proportion, from 87.6 to 62.3% ($p < 0.001$). Mean age of respondents at the time of survey completion decreased from 40.5 to 32.3 ($p < 0.001$), while mean age of initial drug exposure increased from 15.4 to 25.6 ($p < 0.001$).

Stimulant Use Among Individuals With Opioid Use Disorder

As shown in **Figure 1**, lifetime exposure to stimulants was very high among this sample of individuals with opioid use disorder, with 82.4% reporting the use of prescription stimulants, crack/cocaine or methamphetamine, after adjusting for time since initial drug exposure to an opioid or stimulant. Crack/cocaine had the highest adjusted rate of lifetime

TABLE 1 | Demographic characteristics of individuals with opioid use disorder with lifetime exposure to stimulant drugs, grouped by year of initial drug exposure.

	1991–1995 (n = 680)		1996–2000 (n = 1,044)		2001–2005 (n = 1,399)		2006–2010 (n = 1,193)		2011–2015 (n = 550)		2016–2020 (n = 69)		Sig. (X^2)
Demographics													
Female	*441*	65.3%	*620*	59.7%	*802*	57.8%	*662*	55.8%	*296*	54.1%	*30*	45.5%	<0.001
Racial/ethnic minority	*138*	20.3%	*205*	19.6%	*227*	16.2%	*236*	19.8%	*160*	29.1%	*25*	36.2%	<0.001
Sexual minority	*38*	11.5%	*53*	11.0%	*78*	11.3%	*77*	13.4%	*56*	18.1%	*13*	27.7%	0.001
Mean age (SD)		40.5 (5.9)		36.2 (5.4)		32.0 (5.2)		28.0 (5.1)		25.7 (6.2)		32.3 (7.2)	<0.001
Mean age of initial exposure (SD)		15.4 (5.6)		15.9 (5.2)		16.6 (4.9)		17.4 (4.9)		19.5 (6.2)		25.6 (10)	<0.001
Urbanicity													
Urban	*382*	57.7%	*530*	52.0%	*668*	48.8%	*540*	46.6%	*236*	43.7%	*34*	51.5%	<0.001
Suburban	*153*	23.1%	*250*	24.5%	*380*	27.8%	*351*	30.3%	*167*	30.9%	*16*	24.2%	0.002
Rural	*127*	19.2%	*240*	23.5%	*320*	23.4%	*267*	23.1%	*137*	25.4%	*16*	24.2%	0.186
Regionality													
West	*117*	17.2%	*168*	16.1%	*261*	18.7%	*234*	19.6%	*135*	24.5%	*22*	31.9%	<0.001
Midwest	*187*	27.5%	*270*	25.9%	*369*	26.4%	*325*	27.2%	*131*	23.8%	*17*	24.6%	0.070
Northeast	*76*	11.2%	*139*	13.3%	*214*	15.3%	*172*	14.4%	*66*	12.0%	*4*	5.8%	0.030
South	*300*	44.1%	*467*	44.7%	*555*	39.7%	*462*	38.7%	*218*	39.6%	*26*	37.7%	0.023
Healthcare coverage													
None	*237*	41.0%	*341*	38.5%	*491*	40.5%	*376*	36.4%	*167*	34.7%	*19*	33.3%	0.104
Covered under another individual	*16*	2.8%	*26*	2.9%	*28*	2.3%	*70*	6.8%	*76*	15.8%	*8*	14.0%	<0.001
Medicare/Medicaid	*282*	48.8%	*440*	49.7%	*604*	49.9%	*512*	49.6%	*206*	42.8%	*24*	42.1%	0.011
Private	*33*	5.7%	*58*	6.6%	*69*	5.7%	*67*	6.5%	*28*	5.8%	*6*	10.5%	0.691
VA/Military healthcare	*10*	1.7%	*20*	2.3%	*19*	1.6%	*8*	0.8%	*4*	0.8%	*0*	0.0%	0.075
Any healthcare coverage	*341*	59.0%	*544*	61.5%	*720*	59.5%	*657*	63.6%	*314*	65.3%	*38*	66.7%	0.104
Educational attainment													
High school or less	*364*	54.5%	*561*	54.2%	*789*	56.8%	*734*	62.0%	*374*	68.1%	*40*	58.8%	<0.001
Some college	*275*	41.2%	*420*	40.5%	*534*	38.5%	*403*	34.0%	*166*	30.2%	*22*	32.4%	<0.001
Bachelor's or higher	*29*	4.3%	*55*	5.3%	*65*	4.7%	*47*	4.0%	*9*	1.6%	*6*	8.8%	0.006
Prior OUD treatment episodes	*595*	87.6%	*888*	85.1%	*1,170*	83.8%	*939*	78.8%	*405*	73.6%	*43*	62.3%	<0.001

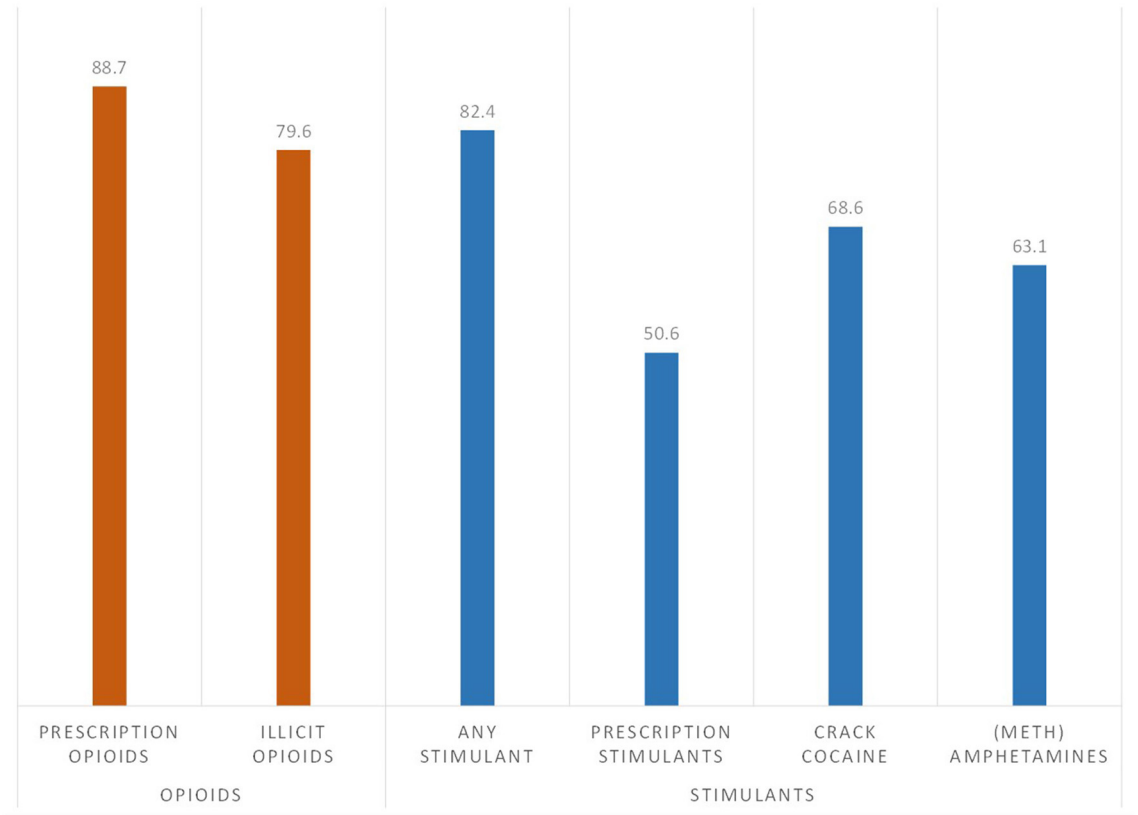

FIGURE 1 | Prevalence of lifetime exposure to opioid and stimulants among individuals with opioid use disorder (n = 7,109), adjusted for age of initial drug exposure and time since year of initial drug exposure.

use (68.6%), followed by methamphetamines (63.1%) and prescription stimulants (50.6%).

Respondents were categorized by the year of initial drug exposure to either an opioid or a stimulant and grouped into 5 year blocs across the past 30 years, from 1991 to 2020. **Figure 2** depicts lifetime use of opioid and stimulant categories by respondent's year of initial drug exposure. Of those who initiated use from 1991 to 2010, lifetime use of all three stimulant categories were reported by over half the sample; 54.0–58.5% for prescription stimulants, 68.3–68.2% for methamphetamines, and 80.3–66.0% for crack/cocaine. These rates were lower in more recent years with just 5.1% exposed to prescription stimulants, and 12–13% to crack/cocaine and methamphetamines, by 2016–2020.

Figure 3 shows that the mean age of initiation for all opioid and stimulant classes ever used stayed relatively stable from 1991 to 2015, but significantly increased in 2016–2020. Age of first exposure to prescription opioids saw the greatest increase, from a mean age of initiation of 22.3 in those first exposed in 2011–2015, to 31.8 for those initiating use in 2016–2020. Similarly, but to a lesser extent, illicit opioid initiation rose from 22.8 to 28.2 years old, crack/cocaine from 21.3 to 26.9 years old, prescription stimulants from 18.8 to 22.3 years old, and methamphetamines from 20.4 to 23.7 years old.

Initial Drug Exposure

Figure 4 shows the number of drugs respondents were exposed to in the year of initial drug exposure to an opioid (prescription opioids or illicit opioids) and/or a stimulant (prescription stimulants, crack/cocaine, or methamphetamines). Respondents primarily reported the use of a single substance in the year of initial drug exposure, although this decreased from 83.2% in 1991–1995 to 73.8% in 2011–2015, and finally increasing back up to 80.3% in 2016–2020. The specific drugs initiated in the year of initial drug exposure are shown in **Figure 5**, taking into account the use of multiple drugs in a single year (i.e., totals may equal over 100%). The use of prescription opioids as an initiating drug increased from 36.4% in 1991–1995 to 74.9% in 2016–2020. Illicit opioids as an initiating drug increased from a low of 8.7% in 2001–2005 to 32.8% in 2016–2020. Stimulants were initiating drugs for a substantial proportion of individuals with opioid use disorder in the 1990s and early 2000s, decreasing significantly to the point where <10% reported initiating use with each stimulant class: prescription stimulant as initiating drug decreased from 26.7 to 2.8%, crack/cocaine from 23.3 to 8.0%, and methamphetamine from 20.6 to 9.4%.

Figure 6 outlines the mean age of only one's initial drug of exposure by year of exposure. Similar to **Figure 3**, the mean age of those initiating their opioid/stimulant use with

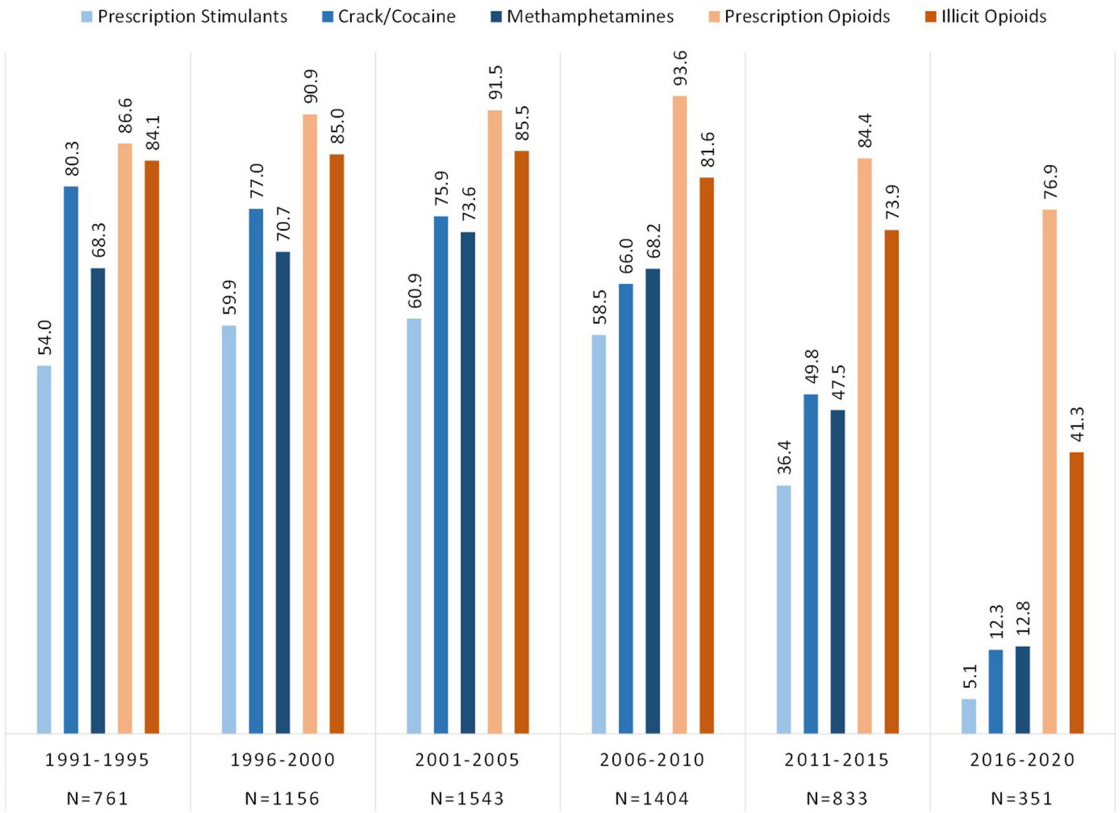

FIGURE 2 | Prevalence of lifetime exposure to opioids and stimulants grouped by year of initial drug exposure among individuals with opioid use disorder.

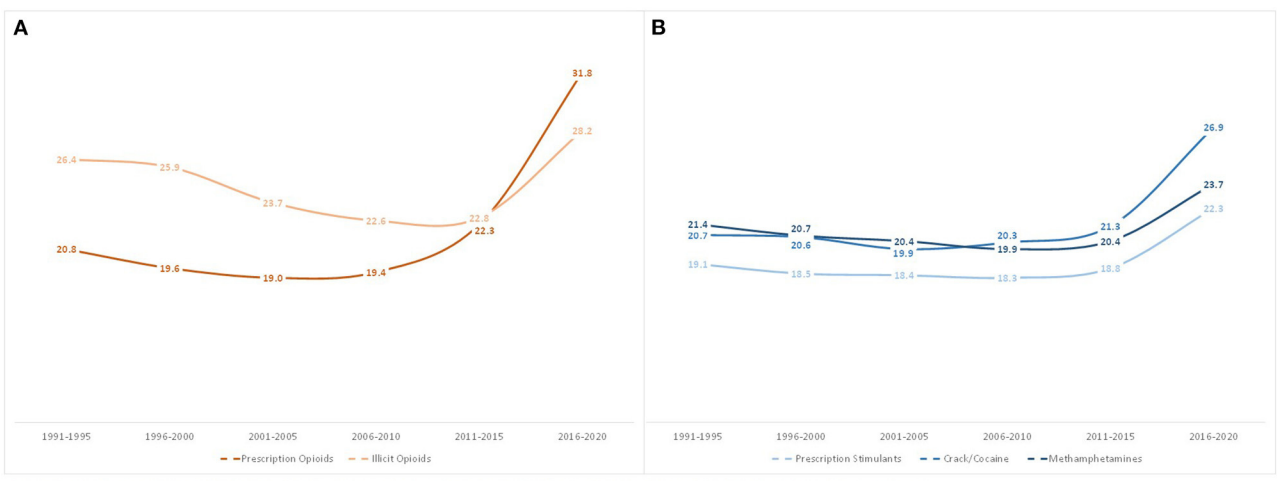

FIGURE 3 | Mean age of first use of opioids **(A)** and stimulants **(B)** among individuals with opioid use disorder by year of drug exposure.

prescription opioids increased from 17.13 in 1991–1995 to 32.1 in 2016–2020, and illicit opioid initiators had a mean age increase from 21.3 to 29.3. For those who initiated use with stimulants, the largest increase was among prescription stimulant initiators, whose mean age grew from 10.8 in 1991–1995 to 23.5 in 2016–2020. This was followed by crack/cocaine (18.4 to 27.8), and methamphetamines (15.9 to 21.8).

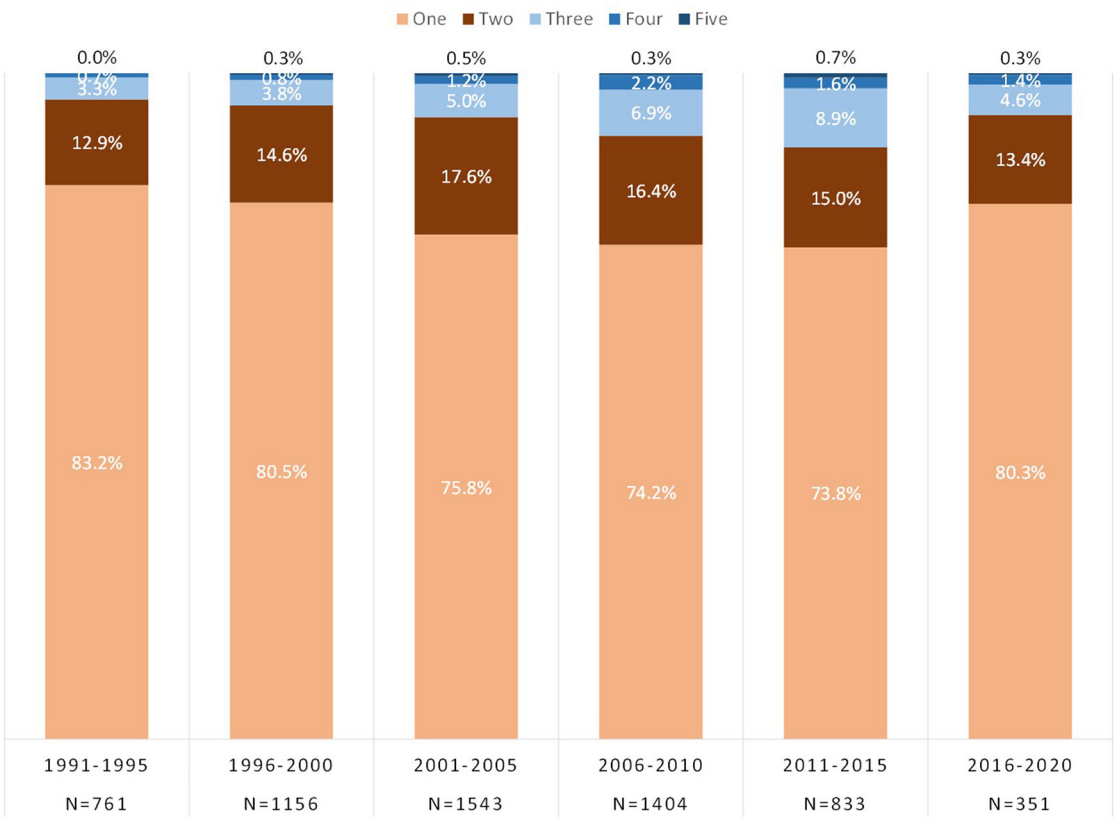

FIGURE 4 | Number of drugs (opioids and/or stimulants) used in the year of initial drug exposure.

Drug Transitions and Pathways

Using age of initial exposure, the mean number of years was calculated between a respondent's first use of an opioid and subsequent first use of a stimulant, and vice-versa, depending on the order of use (**Figure 7**). In 1991–1995, those initiating use of an opioid subsequently initiated use of a stimulant on average, 4 years later, while those initiating use of a stimulant subsequently initiated use of an opioid 7.4 years later. The mean number of years between exposures of opioids and stimulants decreased for both ordered types of respondents over time, although the decrease was more drastic for those transitioning from stimulants to opioids. Those initiating use in 2006–2020 had similar transition times regardless of the pathway, 2.2 years, and these similarly decreased to 1.3 years in 2011–2015 and 0.3–0.4 years in 2016–2020.

Excluding individuals who used multiple drugs in a single year to reduce data noise and uncertainty of order of use, 76.7% of respondents had at least one drug transition (i.e., initiated use of another drug in a subsequent year) among the five studied drug categories. **Figure 8** shows the mean number of years between initial drug exposure and the first drug transition. Those initiating use from 1991 to 1995 had a mean average of 6.8 years between first and second drug exposure. However, this steadily decreased over time to 1.5 years between exposures among 2016–2020 initiators. As shown in the figure, this trend of decreasing time between drug transitions over each 5 year bloc was consistent regardless of which drug was the initial drug of exposure. This trend also applied to subsequent drug transitions. Of those who had subsequent drug transitions across the five studied drugs, drug transition times decreased slightly after the initial drug transition, but were still relatively similar within their respective 5 year bloc (**Figure 9**). Of those who initiated use in 1991–1995, mean drug transitions took 5–6 years. This steadily decreased to where, in 2011–2015 transition times were 1–2 years. Initiators in 2016–2020 had only two drug transitions by the time of data analysis, with transition time of 1.5 years.

Figure 10 provides a comparative overview of drug transitions from 1991 to 2000 and 2010 to 2020 in order to demonstrate temporal shifts in drug transition pathways. As can be seen, there was significant variability in pathways from 1991 to 2000, with 88.8% or respondents having one drug transition, 65.1% with two drug transitions, 39.1% having three drug transitions, and 15.4% having four drug transitions; significantly different from 41.8, 16.0, 5.2, and 1.5%, respectively, in those who initiated use from 2010 to 2020. Notably, those initiating use in the last decade primarily did so through prescription opioids, compared to initiates from 1991 to 2000, who had roughly equal proportions of initiation through stimulants and prescription opioids. Illicit opioids were also more common in later stages of use from 1992 to 2000, compared to earlier stages in 2010–2020.

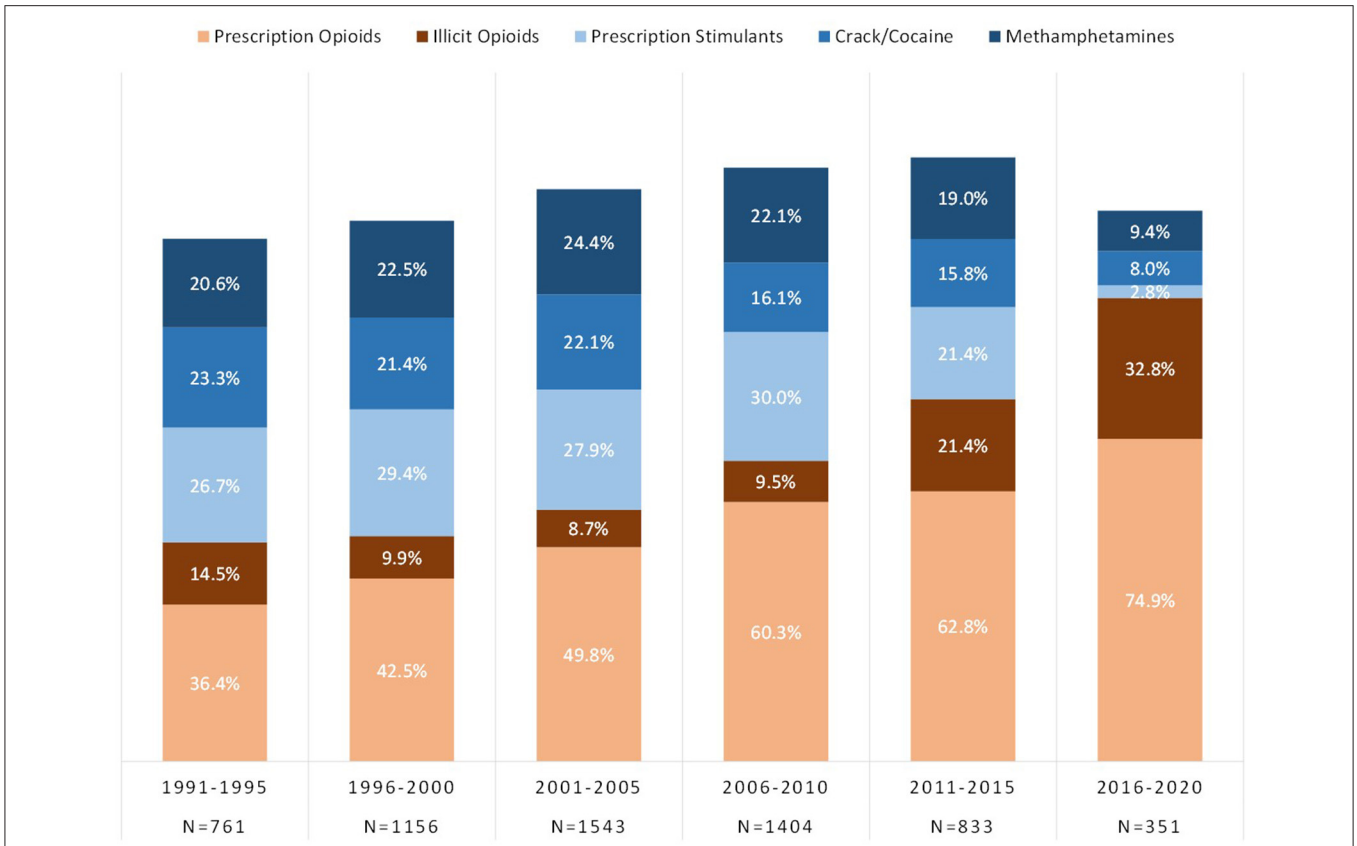

FIGURE 5 | Types of opioids and stimulants used in the year of initial drug exposure. Total percentage may exceed 100% as multiple drugs may have been used in the year of initial drug exposure.

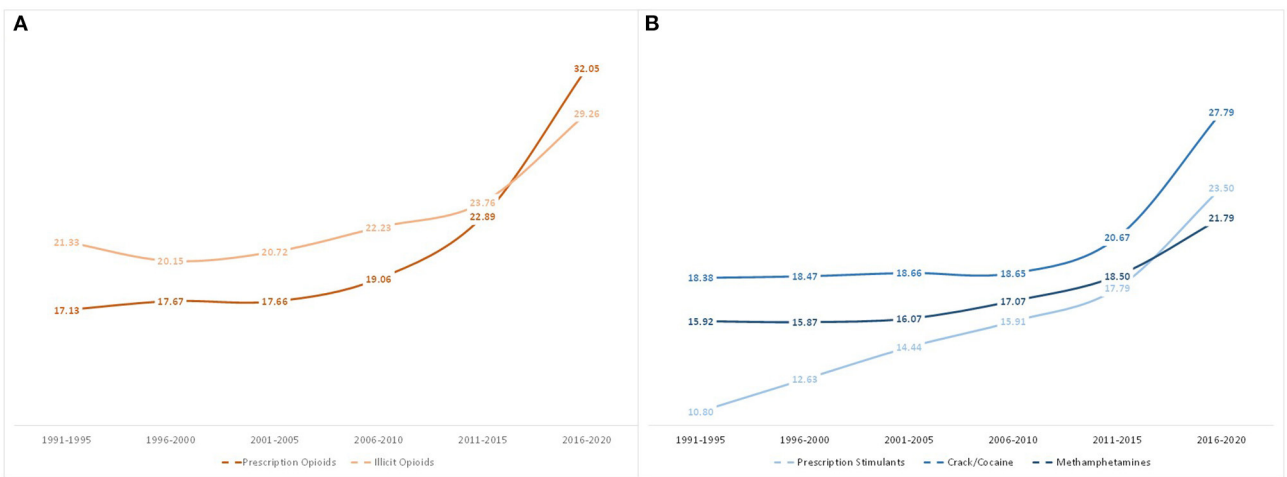

FIGURE 6 | Mean age of first use of opioids or stimulants when used as the initial drug of exposure, grouped by year of initial drug exposure.

DISCUSSION

These data suggest that exposure to stimulant drugs is extremely common among individuals who develop opioid use disorder. Unsurprisingly, this retrospective analysis indicates that stimulant exposure grows in prevalence the longer time has elapsed since initial drug exposure; greater lengths of time likely provide greater opportunities for lifetime exposure. This

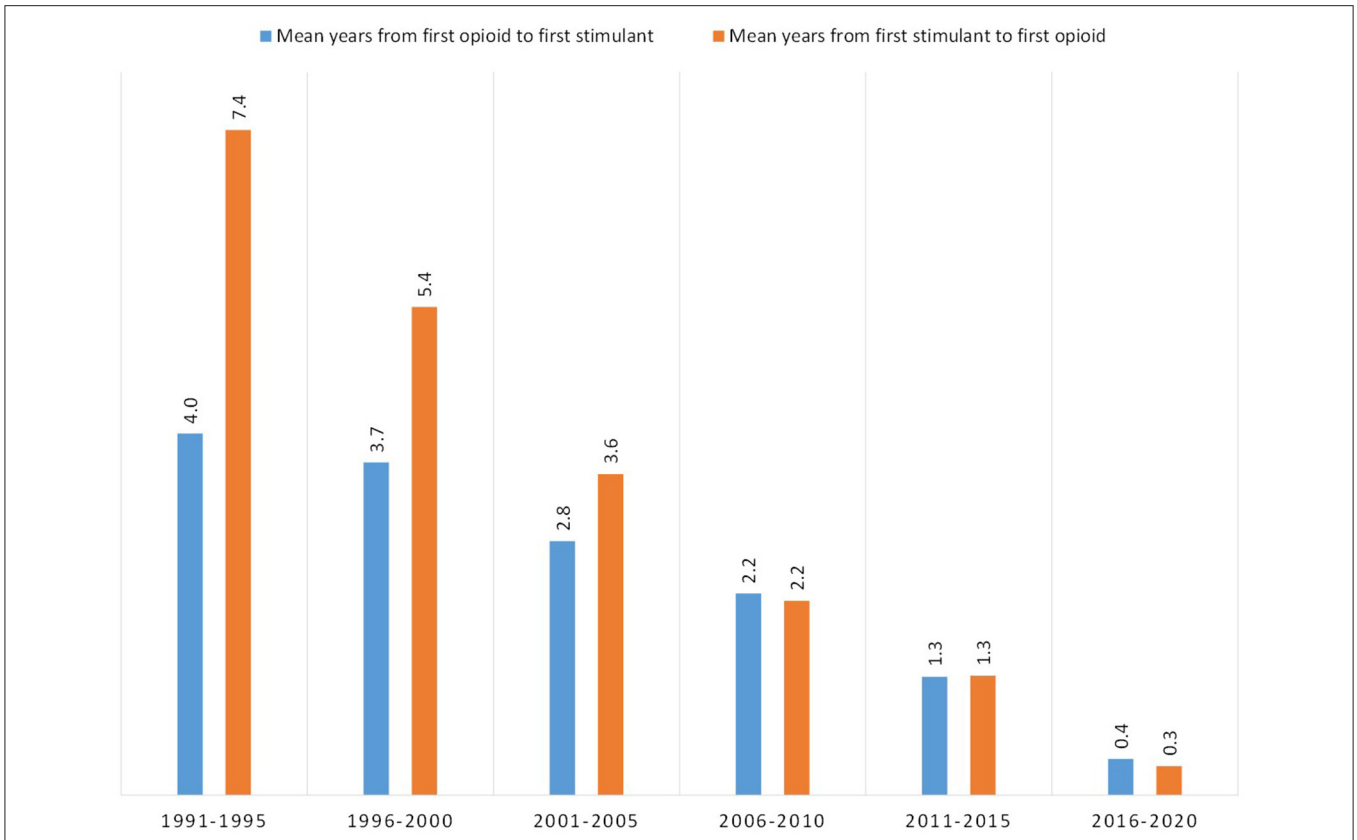

FIGURE 7 | Mean number of years between first use of an opioid and first use of a stimulant, or first use of a stimulant and first use of opioid, grouped by year of initial drug exposure.

appears to hold true not just for illicit stimulant drugs, but for prescription stimulants as well. However, there were other notable trends visible over the past 30 years.

Most notably, the time elapsed between exposures of differing drug categories significantly decreased over time. This was visible in both class-class pathways (i.e., opioid-to-stimulant and stimulant-to-opioid) and drug-drug pathways, irrespective of the initiation drug or number of drug transitions. All showed a steady decline, with an average of 5 years between drug exposures in the early 1990s, to a year or less in 2016–2020. The reasons behind this trend likely involves a multitude of factors. First, market forces significantly have changed in the past 30 years. In the early 1990s, the prescription opioid crisis was in its infancy and methamphetamine was often relegated to rural areas through domestic production, likely making access to these drugs scarcer than in ensuing years. As the prescription opioid crisis broadened, subsequent drug production shifted first to cheaper heroin and crack/cocaine, and then to even more cost-efficient synthetic drugs such as fentanyl and methamphetamine, produced through precursors obtained from one foreign country to be produced in another, eventually distributed in the United States (28). As these markets have grown, access and availability have responded accordingly. There is also likely some measure of compensatory use of other drugs when supplies of a preferred drug are limited. Shifts to heroin and methamphetamine have been observed when access to prescription opioids has become more limited as a result of supply-side policies targeting reduction in their distribution (29, 31). It is also possible that exposure has been complicated in recent years by adulterated drugs such as methamphetamine-laced fentanyl or fentanyl-laced cocaine. Current prevention and harm reduction efforts need to take into account evidence that suggests transitions from one drug to another are now occurring at a rapid rate, and will likely increase the rapidity with which oral use may graduate to non-oral use. Indeed, comprehensive care would be amiss if it did not incorporate these factors into the current regimen of naloxone promotion, pre-exposure prophylaxis, needle exchanges and educational efforts.

Prevention and intervention efforts should also take into account the shifting ages at which initiation of use has changed in recent years. Prescription opioid initiation saw the largest increase in age of exposure, increasing from late teens-early twenties to early thirties. For those whose first exposure to an opioid or stimulant was through prescription stimulants, the mean age rose from 10 years old to 23.5 years. These dramatic shifts may be the result of a greater awareness of the potential harms or consequences of these medications among healthcare providers and systems, leading to reductions of prescriptions of

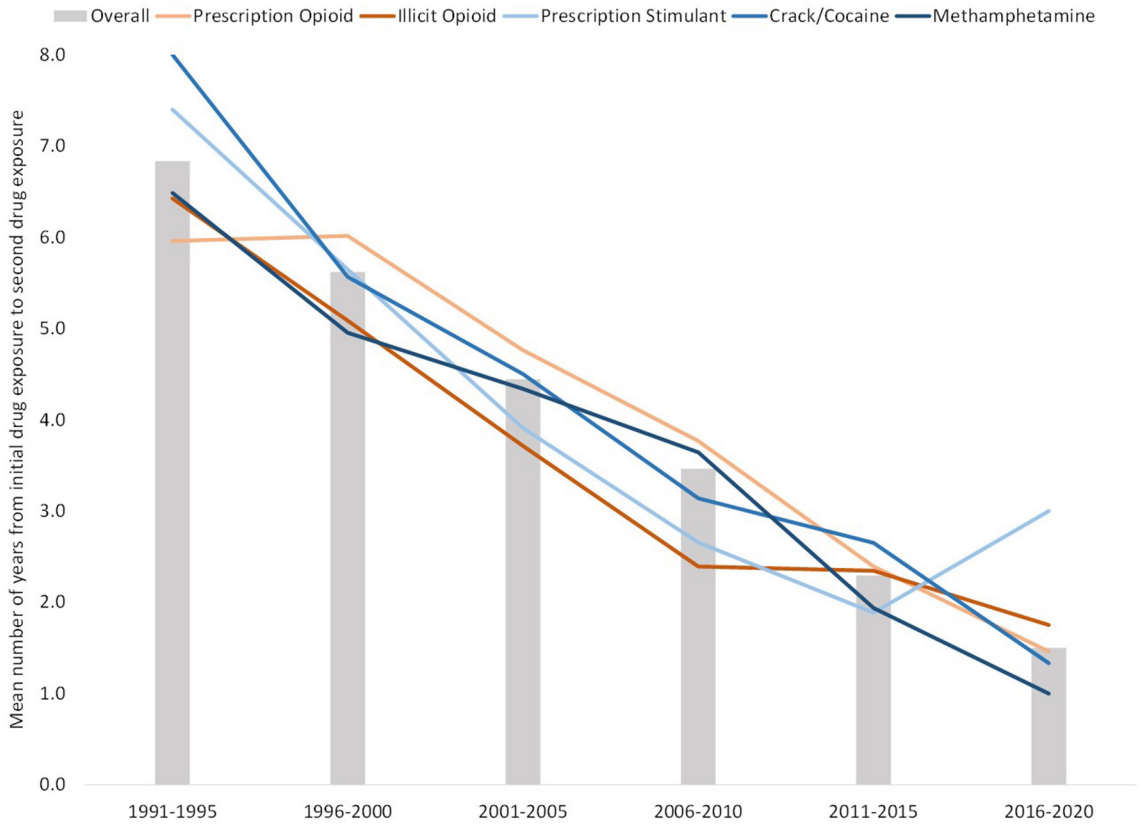

FIGURE 8 | Mean number of years between initial and second drug exposure, grouped by year of initial drug exposure. Bars reflect mean number of years between transitions for all drugs, with lines representing mean number of years between transitions between specific initial drugs and a secondary drug.

opioids and stimulants among younger individuals. This may have resulted in subsequent increases in age of exposure for other drugs that followed initial exposure through a prescription. However, there were significant increases also observed in those whose first opioid or stimulant drug was an illicit one. While further research is needed to understand these shifts, it is possible that prevention and educational efforts targeting young adults have had an effect, and further efforts are needed to target those in their late twenties or early thirties. This is particularly notable in light of the recent pandemic, as well as earlier recessions in the time period of analysis, which caused social and economic upheaval that may disproportionately have impacted individuals in these age groups who are often early in their careers and relationships. In fact, this may help explain other demographic shifts in stimulant use that occurred over time, particularly among those that are often at higher risk of being impacted economically during times of national distress, racial/ethnic minorities, sexual minorities, and those with lower educational attainment.

These data also suggest that opioid and stimulant use occurs across a variety of pathways. However, there do appear to have been shifts in these pathways over time. Interestingly, despite the focus of federal and state policies on mitigating the opioid epidemic in the 2010s, 2016–2020 had the greatest proportion of initiators through opioids, both prescription and illicit. To the latter point, a third of all initiators in 2016–2020 used illicit opioids, further reinforcing the broadening of illicit opioids as one's first experience with opioids, presenting significant dangers to opioid naïve individuals who may be inexperienced in dosing, titration and the presence of admixtures such as fentanyl-laced heroin. In terms of stimulants, since this is a sample of individuals who develop opioid use disorder, it is possible that those who initiated drug use through stimulants have not yet graduated to opioids, and thus have yet to be captured in this sample, leading to lower rates of stimulant initiation than previous years. However, the mean time lapse between transitions would counter this argument as transitions to other drugs are now occurring at a rapid rate. The important point here is that, while not all individuals with opioid use disorder used stimulants, it is notable that throughout the opioid crisis, a substantial number of individuals were exposed to stimulants prior to opioids. This further underscores the complicated nature of polysubstance use. Indeed, the transition plots demonstrate the significant variability of pathways between opioids and stimulants, particularly as time has progressed. Transition plots from 1991 to 2000 showed significant exposure to multiple drugs, but there were few clear-cut pathways that would suggest a commonality of drug pathways or "gateway" drugs, at least within the sphere of stimulants

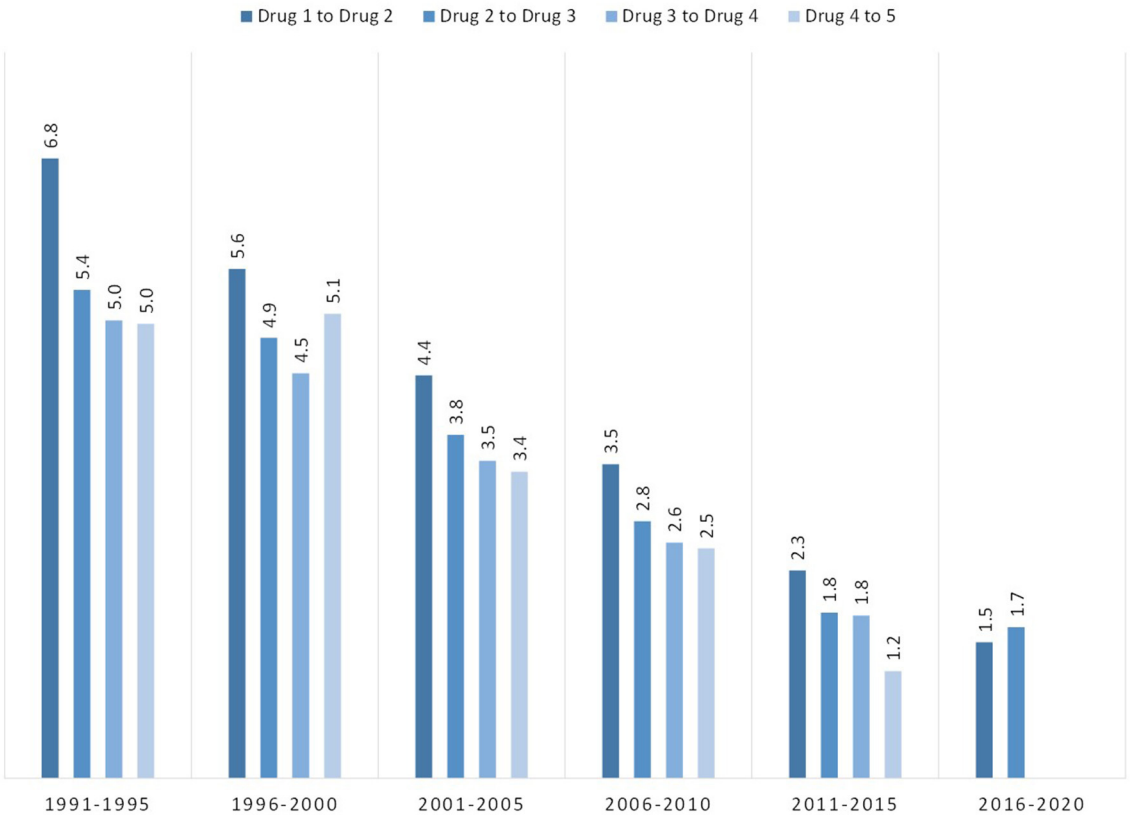

FIGURE 9 | Mean number of years between drug exposures, grouped by year of initial drug exposure.

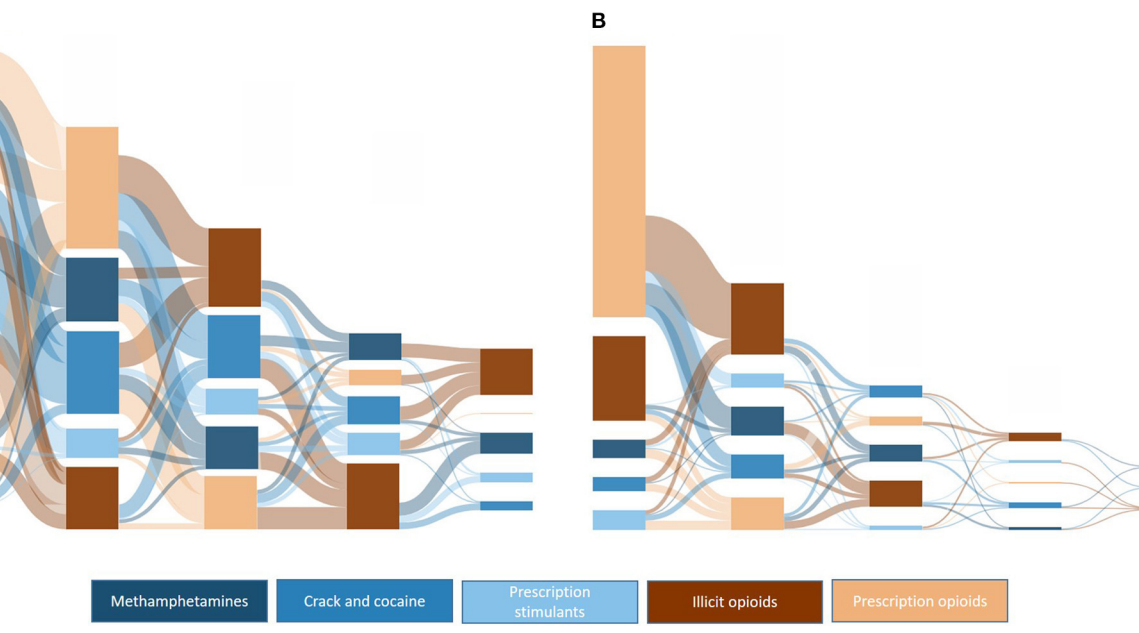

FIGURE 10 | Sankey plots of ordered drug transitions by decade of initial drug exposure: **(A)** 1991–2000, $n = 1,079$; **(B)** 2010–2020, $n = 749$.

and opioids. Pathways were somewhat easier to discern in more recent years. From 2010 to 2020, the majority of initiators started with prescription opioids and moved to illicit opioids, while those who initiated use with stimulants next went to prescription opioids. This further underscores the need for continued efforts to mitigate diversion of prescription opioids and safe prescribing practices. Despite more rapid transition times in recent years, it is possible, and may be more likely given recent increases in methamphetamine and cocaine use, these individuals will engage in polysubstance use inclusive of a wider variety of drugs as years progress. Treatment for opioid use disorder needs to take into account polysubstance use, viewing addiction as a broader condition that encompasses the use of multiple drugs, rather than a condition isolated to a single, primary drug of use. This includes a deeper understanding of motivations for the use of different classes of substances, particularly the potential for self-management of addiction to one drug with another, and perceptions that the use of other substance outside of one's primary drug of addiction are conceptually different when considering one's addiction.

There are several limitations that are important to note when interpreting these data. First, these data are reflective of individuals entering a treatment program for opioid use disorder within the past 10 years, and thus may reflect a population for which treatment retention and success is lower than average, as well as potentially including a measure of survivor bias, wherein a certain proportion likely succumbed to an overdose or drug-associated fatality. Second, our data are limited in more recent years by a "treatment-gap" bias, wherein there are likely initiators in 2016–2020 whose use has not progressed to the point where treatment is sought, thus potentially reducing generalizability to recreational or non-problematic individuals using opioids. In addition, it is possible that there are significant differences in the time and severity in the escalation of use that drives treatment-seeking behavior, which may limit direct comparisons between 5 year blocs. Third, our data assess lifetime exposure and does not assess duration or severity of use of these drugs, or the use of other substances that may have impacted pathways of stimulant and opioid use such as tobacco, alcohol, marijuana or other substances. Finally, and most notably, these data assess age of exposure, which does not take into account the motivations or reasons behind use. While less applicable to the illicit drugs, it is likely that first exposure to prescription opioids or stimulants were through therapeutic channels, for therapeutic purposes, and therefore, may not be representative of problematic use. However, therapeutic channels as initial exposures to opioids and stimulants have been shown to increase of subsequent problematic use.

These data highlight not only the substantial prevalence of stimulant use among individuals who develop opioid use disorder, but also that opioid and stimulant polysubstance use develops through a number of pathways, often a result of both supply (i.e., accessibility) and demand (i.e., motivations for use) side factors. Importantly, stimulant use played a significant introductory role to substance use prior to opioid initiation, and despite recent increases in national trends of illicit stimulant use, they have played a significant contributing role throughout from the beginning of the opioid crisis. Recent demographic shifts indicate that those initiating use of opioids and stimulants today may be different than those from years past, particularly in young adults of a greater age. Additionally, transitions to other drugs is occurring at a far faster rate than previously seen. Prevention and intervention efforts need to take these shifts into account. But at a broader level, preventative educational and screening efforts, harm reduction ideology, and treatment through addiction medicine needs to take into account the ubiquity of polysubstance use among individuals with substance use disorders.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Proprietary to the RADARS System. Requests to access these datasets should be directed to ellism@wustl.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Washington University in St. Louis Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors participated in analyzing and interpreting the data and in drafting and reviewing the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.786056/full#supplementary-material

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Conflict of Interest: ME is a member of the Scientific Advisory Group for the National Drug Early Warning System.

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frontiers in Psychiatry

ORIGINAL RESEARCH
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Negative Impact of Amphetamine-Type Stimulant Use on Opioid Agonist Treatment Retention in Ontario, Canada

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Objective: The objective of this study was to evaluate epidemiological trends of co-use patterns of amphetamine-type stimulants and opioids and the impact of co-use patterns on Opioid Agonist Treatment (OAT) retention in Ontario, Canada. The secondary objective was to assess geographical variation in amphetamine-type stimulant use in Northern Rural, Northern Urban, Southern Rural and Southern Urban Areas of Ontario.

Methods: A retrospective cohort study on 32,674 adults receiving OAT from ∼70 clinics was conducted between January 1, 2014, and December 31, 2020, in Ontario, Canada. Patients were divided into four groups base on the proportion of positive urine drug screening results for amphetamine-type stimulants during treatment: group 1 (0–25%), group 2 (25–50%), group 3 (50–75%), and groups 4 (75–100%). A Fractional logistic regression model was used to evaluate differences over time in amphetamine-type stimulant use with urine drug screening results. A Cox Proportional Hazard Ratio model was used to calculate the impact of amphetamine-type stimulant use on retention in OAT and adjusted for sociodemographic characteristics, drug use and clinical factors. Lastly, a logistic regression model was used on a subgroup of patients to assess the impact of geography on amphetamine-type stimulant use in Northern Rural, Northern Urban, Southern Rural and Southern Urban Areas of Ontario.

Results: There were significant differences in amphetamine-type stimulant positive urine drug screening results year-over-year from 2015 to 2020. Significant differences were observed between amphetamine-type stimulant groups with regards to sociodemographic, clinical and drug use factors. Compared to those with no amphetamine-type stimulant use, the number of days retained in OAT treatment for amphetamine-type stimulant users was reduced (hazard ratio 1.19; 95% confidence interval = 1.07–1.17; $p < 0.001$). Lastly, an adjusted logistic regression model showed a significant increase in the likelihood of amphetamine-type stimulant use in Northern Rural regions compared to Southern Urban areas.

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Conclusion: There was a significant increase in amphetamine-type stimulant use among individuals in OAT from 2014 to 2020, associated with decreased OAT retention. Research is required to determine if tailored strategies specific to individuals in OAT who use amphetamine-type stimulants can improve OAT outcomes.

Keywords: Opioid Agonist Treatment, amphetamine-type stimulant use, rural health, treatment discontinuation, opioid use disorder

INTRODUCTION

Stimulant use disorder is the second most common illicit substance use disorder in the world after opioids (1). Recent studies from the United States have reported increased co-use patterns of stimulants and opioids in the past year (2, 3). In Canada, the estimated prevalence of stimulant use in the population is about 1%, with higher rates of use among youth (3.5%) and some of the highest rates in rural areas (4, 5). Polydrug use among individuals with opioid use disorder (OUD) has been shown to increase poisonings and fatal overdose rates (6–10).

Several studies have documented the efficiency of Opioid Agonist Treatment (OAT) to treat OUD, and its effectiveness increases the longer a patient is retained in treatment (11–13). Unfortunately, there are currently no effective pharmacological treatments for stimulant use disorders (14). Despite other modalities having shown efficiency for treating stimulant use disorder, such as contingency management and cognitive-behavioral therapies (CM/CBT) (15–17), such treatments are not routinely available for patients with OUD in Canada apart from contingency management approaches to take-home doses of OAT medication.

Acute Pharmacological effects of stimulant use are well-known to reduce impulse control (18). There is also literature demonstrating increased psychotic episodes, aggressive behavior and cognitive problems (19, 20) from long-term methamphetamine use. Considering the increase in stimulant use in North America (5, 21–23), we hypothesize that combined with opioid use; stimulants may contribute to the rising issues with patients being retained in OAT.

Despite the evidence of increased stimulant and opioid use patterns in the United States, to our knowledge, there are no studies examining the effects of stimulant use on OAT retention in Canada. At the time of publication, the literature in Canada focused primarily on prescription stimulant use or stimulant use in youth (5); the results of these studies lack information on stimulant use among individuals with OUD. With very little research into the use of stimulants and opioids, more specifically amphetamine-type stimulants, we don't have a clear understanding of its impact on OAT outcomes in Ontario and even less is known about geographical variations in such outcomes. The lack of such insight is a critical gap in the literature, as stimulant use has been rising in the general population (5). Therefore, this study aims to evaluate epidemiological trends of co-use patterns of amphetamine-type stimulants and opioids and assess the impact on OAT retention. The secondary objective was to measure how the geographical location of residents is impacting amphetamine-type stimulant use in Ontario, Canada.

METHODS

Study Design and Setting

A retrospective cohort study was conducted based on electronic medical record (EMR) data from the largest organization providing OAT in Canada (∼70 clinics) from January 1, 2014, to December 31, 2020. Standardized evidence-based best practice policies and operating procedures are in place within the clinic network, which limits the likelihood of treatment variability between sites. A total of 31,701 adults in OAT in Ontario, Canada, were included in the study. The study data was accessed remotely using a secure server. Patient identification was anonymized. The Laurentian University Research Ethics Board provided ethical approval for this study. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to write this manuscript (24).

Study Population

OAT patients were followed from the first OAT dispensation or prescription to either the end of the study or loss to follow-up. All OAT recipients during the follow-up period were identified based on the presence of at least one OAT episode in the EMR. OAT exposure was defined as any receipt of methadone or buprenorphine/naloxone.

Amphetamine-Type Stimulants Exposure Groups

The amphetamine-type stimulant exposure groups were created based on the proportion of positive urine drug screening (UDS) results for amphetamine-type stimulants. Patients were divided into the following four groups: group 1 (0–25%), group 2 (25–50%), group 3 (50–75%), and groups 4 (75–100%).

Covariates

Patient's characteristics were measured at the time of the most recent OAT dispensation. Patient characteristics included age, sex, and geographic health care delivery region (North/South, RIO-2008 Index). Patient characteristics were chosen because they have been shown to impact OAT retention (25–27). The Ontario Medical Association (OMA) online Rurality Index of Ontario (RIO) score matching application program interface (API) was used to check RIO scores to postal codes. The health care at home API was used to corroborate Local Health Integration Network (LHIN) scores to postal codes (25). Patients

with missing postal codes (n = 4,735) could not be included in the geographical analysis. Therefore, a subgroup analysis was conducted on a subset of the cohort (n = 27,939 patients). Patients were divided into four geographical regions for the subgroup analysis: Southern Urban, Southern Rural, Northern Urban, and Northern Rural. Northern regions were defined by LHIN 13 and 14. The North/South divide has been used in several peer review studies and reports (26, 27). Rural regions were defined as any region with a RIO score of 40 or higher (28).

Clinical factors were included as covariates to isolate the impact of stimulants on treatment retention. The measured clinical characteristics included: initial OAT medication (methadone or buprenorphine/naloxone), the total number of days retained in OAT, whether a patient's starting dose was above the median starting dose for the cohort (6 mg for buprenorphine/naloxone and 30 mg for methadone), if a patient's peak dose was above the peak dose for the cohort (14 mg for buprenorphine/naloxone and 70 mg for methadone), and urine drug screening (UDS) results for cocaine, fentanyl, cannabis, and all opioids other than fentanyl and the patient's OAT medication. UDS groups were created based on the proportion of positive UDS for each drug and divided into quadrants 0–25, 25–50, 50–75, and 75–100%. Urine drug screen results were obtained using The FaStep Assay (Trimedic Supply Network Ltd., Concord, Ontario, Canada) with results for assays detecting amphetamine or methamphetamine combined for amphetamine-type stimulant results and assays detecting morphine or oxycodone combined for other opioid results. Results for fentanyl, cannabis and cocaine are based on specific assays detecting fentanyl, THC and cocaine metabolites.

Treatment Discontinuation

Treatment discontinuation was defined as an interruption in a continuous period of dispensed OAT medication lasting at least 5 days for methadone and at least 6 days for buprenorphine/naloxone (29).

Statistical Analysis

The percentage of amphetamine-type stimulant positive UDS was calculated from 2014 to 2020 in Ontario. A Fractional logistic regression model was used to assess significant change year-over-year in amphetamine-type stimulant positive UDS across Ontario from 2014 to 2020.

A descriptive analysis was conducted to compare covariates, including patient characteristics, clinical and drug use factors between stimulant groups. Chi-square test was used for categorical variables and Wilcoxon Rank Sum test for continuous variables. All p-values <0.05 were considered significant.

A Cox Proportional Hazards model was run to determine the effect of amphetamine-type stimulant use on the treatment discontinuation. First, an unadjusted model was run. The model was then adjusted for the aforementioned covariates, including geography ($n = 4{,}735$ missing data points).

A subgroup analysis of patients with geographical variables was conducted on a subset of 27,939 patients who had complete geographical information available. A multinomial logistic regression model was used to assess the association between amphetamine-type stimulant use and geography in the subset of the cohort with geographical data available between four geographical regions (Northern Rural, Northern Urban, Southern Rural, and Southern Urban). The model was then adjusted for all the covariates, including patient characteristics, clinical and substance use factors. Statistical significance was reported with 95% confidence intervals.

RESULTS

Between January 1, 2013, and December 31, 2020, 31,701 patients were included in the study. Of these patients, 27,016 (85.22%) had 0–25% of their UDS positive for amphetamine-type stimulants, 1,322 (4.17%) had 26–50% of their UDS positive for amphetamine-type stimulants, 1,153 (3.64%) had 51–75% of their UDS positive for amphetamine-type stimulants, and 2,210 (6.97%) had 76–100% of their UDS positive for amphetamine-type stimulants. Chi-Squared test for heterogeneity and the Wilcoxon-Rank-Sum/Kruskal-Wallis test showed a significant difference in each covariate except sex (p-value = 0.50). The results are presented in **Table 1**.

In the trend analysis, the amphetamine-positive UDS results increased significantly during the study period 2014–2020. Interestingly, as shown in **Figure 1**, there was a decrease in amphetamine-positive UDS between 2014 and 2015, but after 2015, positive UDS results increased significantly until the end of the study period. Detailed results including 95% CI are available in **Table 2**.

Outcome Results

The impact of amphetamine-type stimulant use on OAT discontinuation was assessed using a Cox proportional Hazard Model. **Figure 2** shows the results of the adjusted Cox Proportional Hazard Ratio model. The model was adjusted for patient characteristics, clinical and drug use factors. The adjusted model showed no significant increase in treatment discontinuation rate in group 2 (patients with 26–50% positive amphetamine-type stimulant UDS) compared to group 1. However, there was a significant increase in treatment discontinuation rate in groups 3 (patients with 51–75% positive amphetamine-type stimulant UDS) (aHR = 1.160, 95% CI 1.078–1.248) and 4 (patients with 76–100% positive amphetamine-type stimulant UDS) (aHR = 1.570, 95% CI 1.489–1.655) when compared to group 1 (patients with 0–25% positive amphetamine-type stimulant UDS). Detailed results of adjusted and unadjusted HR are available in **Table 3**.

Subgroup Analysis Results

The impact of geography on amphetamine-type stimulant use was evaluated on a subgroup of patients (n = 26,932) using the Southern Urban group as the reference group. Results are presented in **Table 3**. A total of 19,700 (73.15%) patients resided in a Southern urban region, 1,079 (4.01%) lived in a Southern rural area, 4,779 (17.74%) resided in a Northern urban area, 1,374 (5.10%) lived in a Northern rural region. After adjusting for patient characteristics, clinical and drug use factors, the results

TABLE 1 | Patient characteristics, clinical factors and substance use behaviors, stratified by amphetamine-type use groups among 31,701 people in OAT in Ontario, Canada.

	Positive urine drug screening (UDS) results for amphetamine-type stimulants				
	0–25% ***n*** **= 27,016 (85.22%)**	**25–50%** ***n*** **= 1,322 (4.17%)**	**50–75%** ***n*** **= 1,153 (3.64%)**	**75–100%** ***n*** **= 2,210 (6.97%)**	***P*-value**
Sex n (%)					0.50
Male	16,570 (61.33%)	790 (59.76%)	723 (62.7%)	1,348 (61%)	
Female	10,448 (38.67%)	532 (40.32%)	430 (37.3%)	862 (39%)	
Mean age (STD)	36 (10.9)	35 (9.4)	35 (9.3)	35 (9.0)	0.02
Location of residence (4,769 missing)					<0.01
Southern Urban	16,692 (72.89%)	802 (72.64%)	707 (73.11%)	1,499 (76.48%)	
Southern Rural	899 (3.93%)	54 (4.89%)	46 (4.76%)	80 (4.08%)	
Northern Urban	4,183 (18.27%)	176 (15.94%)	147 (15.2%)	273 (13.93%)	
Northern Rural	1,127 (4.92%)	72 (6.52%)	67 (6.93%)	108 (5.51%)	
Mean days in study (standard deviation)	718 (833.7)	821 (798.7)	637 (782.9)	441 (687.4)	<0.01
Methadone starting medication n (%)	20,984 (77.67%)	1,068 (80.79%)	929 (80.57%)	1,760 (79.64%)	<0.01
Starting dose above median starting dose n (%)	12,889 (47.71%)	639 (48.34%)	514 (44.58%)	829 (37.51%)	<0.01
Peak dose above median peak dose n (%)	6,245 (23.12%)	343 (25.95%)	287 (24.89%)	419 (18.96%)	<0.01
Average monthly UDS group *n* (%)					
1 per month or less	718 (2.66%)	0 (0%)	1 (0.09%)	23 (1.04%)	<0.01
Bi-weekly per month	1,986 (7.35%)	11 (0.83%)	19 (1.65%)	246 (11.13%)	
Weekly	3,389 (12.54%)	69 (0.26%)	61 (5.29%)	166 (7.51%)	
More than weekly	20,923 (77.45%)	1,242 (93.95%)	1,072 (92.97%)	1,775 (80.32%)	
Cocaine UDS positive group *n* (%)					<0.01
0–25% positive	19,037 (70.47%)	2,451 (9.07%)	1,914 (7.06%)	3,614 (13.38%)	
25–50% positive	698 (52.8%)	232 (17.55%)	147 (11.12%)	245 (18.53%)	
50–75% positive	626 (54.29%)	181 (15.7%)	153 (13.27%)	193 (16.74%)	
75–100% positive	1,282 (58.01%)	344 (15.57%)	232 (10.5%)	352 (15.93%)	
Fentanyl UDS positive group *n* (%)					
0–25% positive	24,555 (90.89%)	801 (2.96%)	646 (2.39%)	1,014 (3.75%)	<0.01
25–50% positive	981 (74.21%)	108 (8.17%)	104 (7.87%)	129 (9.76%)	
50–75% positive	786 (68.17%)	86 (7.46%)	113 (9.8%)	168 (14.57%)	
75–100% positive	1,275 (57.69%)	170 (7.69%)	148 (6.7%)	617 (27.92%)	
Cannabis UDS positive group *n* (%)					
0–25% positive	17,444 (64.57%)	1,213 (4.94%)	1,230 (4.55%)	7,129 (26.39%)	<0.01
25–50% positive	603 (45.61%)	107 (8.09%)	100 (7.56%)	512 (38.73%)	
50–75% positive	582 (50.48%)	73 (6.33%)	96 (8.33%)	402 (34.82%)	
75–100% positive	1,382 (60%)	110 (4.98%)	105 (4.75%)	669 (30.27%)	
Other opioid UDS positive group *n* (%)					
0–25% positive	20,293 (75.11%)	2,920 (10.81%)	1,926 (7.13%)	1,877 (6.95%)	<0.01
25–50% positive	987 (74.66%)	214 (16.19%)	97 (7.34%)	24 (1.82%)	
50–75% positive	798 (69.12%)	210 (18.21%)	121 (10.49%)	24 (2.08%)	
75–100% positive	1,374 (62.17%)	403 (18.24%)	320 (14.48%)	113 (5.11%)	

showed a significant association between living in Northern Rural areas and increased prevalence of amphetamine-type stimulant use compared to living in Southern Urban areas (aOR = 1.4, 95%CI 1.1–1.8 for patients with 26–50% positive amphetamine-type stimulant UDS; aOR = 1.6, 95%CI 1.2–2.1 for patients with 51–75% positive amphetamine-type stimulant UDS; aOR = 1.4, 95%CI 1.1–1.7 for patients with 76–100% positive amphetamine-type stimulant UDS). There was no significant difference in the prevalence of amphetamine-type stimulant use in Southern Rural or Northern Urban regions. The results are presented in **Table 4**.

DISCUSSION

This study sought to evaluate the epidemiological trends of co-use patterns of amphetamine-type stimulants and opioids and the impact on OAT retention in Ontario, Canada. Drawing

on longitudinal data from the largest organization providing OAT in Canada, a distinct upward trajectory of amphetamine-type stimulant use among individuals in OAT was observed over 5 years. Individuals in OAT who used amphetamine-type stimulants displayed lower retention rates after adjusting for individual characteristics, drug use behaviors and clinical factors. Interestingly living in Northern Rural areas of Ontario was associated with an increased likelihood of amphetamine-type stimulant use.

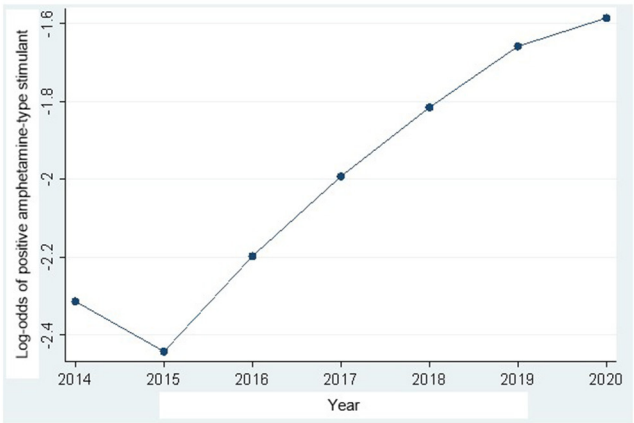

FIGURE 1 | Amphetamine-type stimulant urine drug screening (UDS) results trajectory in Ontario Canada from 2014 to 2020 (detailed results available in **Table 2**).

TABLE 2 | Odds ratios and 95%confidence intervals (95%CI) for amphetamine-type stimulant urine drug screening (UDS) in Ontario, Canada from 2014 (ref) to 2020.

Year	Odds ratio	95% CI
2014 (ref)		
2015	2.44	2.44–2.44
2016	2.2	2.19–2.20
2017	1.99	1.99–1.99
2018	1.82	1.81–1.81
2019	1.66	1.65–1.66
2020	1.59	1.58–1.59

There were significant differences between amphetamine-type stimulant groups for all patient characteristics, clinical and substance use factors except for sex. We observed that amphetamine-type stimulant use was more frequent in younger individuals. Amphetamine-type stimulant users in our study were more frequently started on methadone vs. buprenorphine/naloxone, and those who tested positive for other drugs, including cocaine, fentanyl, cannabis and other opioids. The findings in this study, including age, methadone patients and patients using other drugs, reflect the evidence that OAT has become more available to higher-risk individuals to reduce overdose deaths (30), particularly during the era of illicit fentanyl availability (31).

As shown in the trajectory plot in **Figure 1**, there was a gradually increasing frequency of amphetamine-type stimulant use between 2015 and 2020. This finding corresponds with international research showing increases in stimulant use over time (1, 22, 23). At the time of publication, the Canadian literature was limited and primarily focused on prescription stimulant use, which corresponds with our finding of increased use over time (5, 32). However, we were unable to quantify illicit vs. prescribed stimulant use in this study.

In the primary analysis, amphetamine-type stimulant use was found to be associated with higher treatment discontinuation rates. It is possible that these individuals had more exposure to behavioral and social stressors or that psychotic episodes, aggressive behavior and cognitive problems, which are more common among individuals who use amphetamine-type stimulants (19, 20), triggered early treatment discontinuation. Research has shown that treatment outcomes could be improved by incorporating integrated, comprehensive services such as behavioral therapy, psychosocial supports, mental health

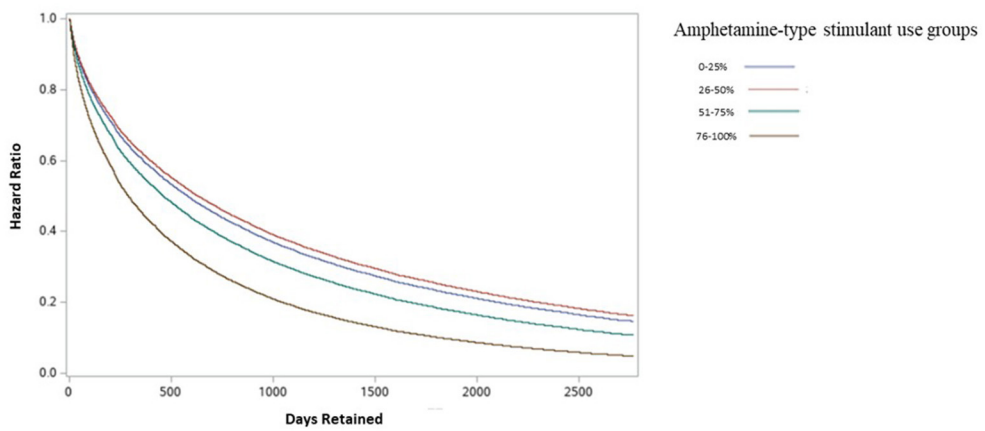

FIGURE 2 | Adjusted discontinuation probability between amphetamine-type stimulant groups among individuals in OAT in Ontario, Canada.

TABLE 3 | Unadjusted and Adjusted discontinuation probability (Hazard Ratio) between the amphetamine-type stimulant group, patient characteristics, clinical and drug use factors among individuals in OAT in Ontario, Canada.

Variable	Unadjusted hazard ratio	95% wald confidence interval	Adjusted hazard ratio	95% wald confidence interval
Stimulants use (ref = 0–25%)				
25–50%	0.85	0.80–0.90	0.94	0.88–1.01
50–75%	1.10	1.03–1.17	1.16	1.08–1.25
75–100%	1.53	1.50–1.61	1.57	1.49–1.66
Sex (ref = Female)	1.06	1.03–1.09	1.15	1.12–1.19
Age	0.86	0.85–0.87	0.80	0.79–0.82
Geography (ref = Southern Urban)				
Southern Rural	0.84	0.79–0.90	1.01	0.94–1.088
Northern Urban	0.87	0.84–0.91	0.91	0.87–0.94
Northern Rural	0.80	0.75–0.85	0.81	0.76–0.87
Starting medication (ref = buprenorphine/naloxone)	0.70	0.68–0.72	0.71	0.68.73
Starting dose above median starting dose (ref = no)	0.61	0.60–0.63	0.75	0.72–0.77
Peak dose above median peak dose (ref = no)	0.57	0.55–0.59	0.81	0.77–0.84
Average UDS per month (ref = once per month or less)				
Bi-weekly	0.41	0.38–0.45	0.48	0.43–0.52
Weekly	0.08	0.08–0.090	0.11	0.10–0.13
More than weekly	0.09	0.08–0.09	0.10	0.09–0.10
Cocaine use (ref = 0–25%)				
25–50%	1.09	1.04–1.13	1.11	1.06–1.16
50–75%	1.47	1.40–1.54	1.35	1.29–1.42
75–100%	2.16	2.09–2.24	1.75	1.68–1.82
Fentanyl use (ref = 0–25%)				
25–50%	0.77	0.72–0.82	0.68	0.63–0.73
50–75%	1.12	1.04–1.21	0.91	0.84–0.99
75–100%	2.27	2.16–2.40	1.63	1.54–1.73
Cannabis use (ref = 0–25%)				
25–50%	0.39	0.36–0.41	0.42	0.39–0.45
50–75%	0.46	0.43–0.49	0.48	0.45–0.52
75–100%	0.46	0.45–0.48	0.51	0.49–0.52
Other opioid use (ref = 0–25%)				
25–50%	1.60	1.54–1.66	1.37	1.31–1.43
50–75%	2.60	2.49–2.72	2.00	1.91–2.10
75–100%	5.21	4.97–5.46	3.25	3.08–3.44

treatment and flexible models of care (33–35). Research is needed to explore whether such strategies are effective for individuals with a history of concurrent opioid and amphetamine-type stimulant use, particularly to improve retention in OAT.

In the secondary analysis, the geographical location of residence was observed to impact amphetamine-type stimulant use. Living in Northern Rural Ontario was associated with an increased likelihood of amphetamine-type stimulant use. This result is consistent with previous findings that people in OAT residing in rural areas have higher rates of cocaine use compared to urban areas (10). Earlier studies have concluded that OAT patients in the North were more likely to be retained in treatment (10, 36). The higher retention rates in the North seem counter-intuitive, given patients often have to travel long distances to access OAT-prescribing physicians and pharmacies (36). However, Eibl et al. (36) demonstrated that patients in the North were 41% less likely to terminate treatment prematurely than were Southern patients. Given that in this study, we found that Northern patients are more likely to use amphetamine-type stimulants and that stimulant use is associated with a higher risk of treatment discontinuation, more research is needed to understand the drivers of higher OAT retention in the North.

Some limitations require consideration. First, data entry and reporting errors are possibly associated with using EMR data for research. Second, although we considered various factors associated with treatment retention, there is potential for unmeasured confounding, including confounding related comorbidities (7, 8, 37), social and interpersonal factors (38–41) and clinical characteristics (42, 43) due to our study only having access to routinely collected data within the EMR. Use of opioids,

TABLE 4 | Subgroup analysis: unadjusted and adjusted multivariable logistic regression model of geographical location associated with amphetamine-type stimulant use groups among individuals in OAT in Ontario, Canada.

Urine drug screening results for amphetamine-type stimulant groups	*OR	95% CI	*aOR	95% CI
Group 2: 25–50%				
Location of residence				
Group 2: Southern Rural	1.3	0.9–1.7	1.2	0.9–1.6
Group 3: Northern Urban	0.9	0.7–1.0	0.8	0.7–0.9
Group 3: Northern Rural	1.3	1.0–1.7	1.4	1.1–1.8
Group 3: 50–75%				
Location of residence				
Group 2: Southern Rural	1.2	0.9–1.6	1.2	0.9–1.6
Group 3: Northern Urban	0.8	0.7–0.9	0.8	0.7–1.1
Group 3: Northern Rural	1.4	1.1–1.8	1.6	1.2–2.1
Group 4: 75–100%				
Location of residence				
Group 2: Southern Rural	1.0	0.8–1.3	1.0	0.8–1.3
Group 3: Northern Urban	0.7	0.6–0.8	0.8	0.7–0.9
Group 3: Northern Rural	1.1	0.9–1.3	1.4	1.1–1.7

Geography reference group = Southern Urban.
Stimulant urine drug screening reference group = 0–25%.
**OR, Odds Ratio.*
**aOR, Adjusted Odds Ratio.*

cocaine, fentanyl, cannabis and amphetamine-type stimulants was detected solely on the results of immunoassay-based urine drug screening conducted for clinical care. It, therefore, might include false-positive or false-negative results. Confirmatory testing with more sensitive and specific laboratory techniques was not possible on the large volume of tests included within this study. Finally, some expert opinions have suggested that routine UDS testing, physician and structural characteristics reinforce a power dynamic and invite shame, stigma and judgment (44, 45). We were not able to account for such factors in our analysis.

CONCLUSION

In summary, our study identified a significant upward trajectory of amphetamine-type stimulant use, which was more common in Rural Northern areas. The results demonstrated that there are apparent differences in OAT retention rates among individuals who use amphetamine-type stimulants. The findings of this study highlight the potential value of acquiring a better understanding of the impact of increased patterns of opioids and amphetamines and the associated impacts of such patterns on OAT outcomes. The methods and findings can be generalized to other areas with similar OAT policies and programs. Our results further suggest a need to develop more comprehensive treatment strategies specific to people with different drug use patterns and geographical locations to maximize the benefits of OAT.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the datasets contain identifiable confidential patient information and cannot be shared with anyone approved by the Research and Ethics Board. Requests to access the datasets should be directed to Kristen Morin kmorin@nosm.ca.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Laurentian University Research and Ethics Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KM: conceptualization, methodology, investigation, analysis, writing—original and final draft, and submission. FV: methodology, investigation, analysis, and writing. SA: investigation, methodology, and writing. DM: investigation, writing—review and editing, and supervision. All authors contributed to the article and approved the submitted version.

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Interactions Between Opioids and Dextroamphetamine on Locomotor Activity: Influence of an Opioid's Relative Efficacy at the Mu Receptor

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Opioids and stimulants are often used in combination for both recreational and non-recreational purposes. High-efficacy mu opioid agonists generally increase the behavioral effects of stimulants, whereas opioid receptor antagonists generally attenuate the behavioral effects of stimulants; however, less is known regarding the interactions between stimulants and opioids possessing low to intermediate efficacy at the mu receptor. The purpose of this study was to examine the role of an opioid's relative efficacy at the mu receptor in altering the behavioral effects of dextro(*d*-)amphetamine. To this end, opioids possessing a range of relative efficacy at the mu receptor were examined alone and in combination with cumulative doses of *d*-amphetamine on a test of open-field, locomotor activity in male rats. Levorphanol, buprenorphine, butorphanol, nalbuphine, (-)-pentazocine, (-)-metazocine, (-)-cyclazocine, (-)-NANM, and nalorphine increased the locomotor effects of *d*-amphetamine in either an additive or greater-than-additive manner according to an effect-additive model. Only the selective, high-efficacy kappa agonist, spiradoline, and the non-selective opioid receptor antagonist, naloxone, failed to increase the effects of *d*-amphetamine under the conditions examined. These data indicate that opioids possessing a large range of relative efficacy at the mu receptor, including those possessing very low relative efficacy, significantly increase the locomotor effects of *d*-amphetamine.

Keywords: addiction, drug interaction, drug combination, pharmacotherapy, polydrug abuse

INTRODUCTION

Opioids and stimulants are often used in conjunction for both recreational and medicinal purposes. For instance, prescription and non-prescription stimulants are sometimes used in combination with licit and illicit opioids under recreational conditions to increase the euphorigenic effects and decrease the aversive effects of the other compound (1, 2). Human laboratory studies report that stimulant-opioid combinations produce subjective effects of greater intensity than either drug alone [(3–7)], and preclinical animal studies report that stimulant-opioid combinations are selected more often than either drug alone in concurrent choice procedures (8, 9). Opioids are used extensively for both acute and chronic pain conditions, whereas amphetamines are widely used in

the clinical management of medical disorders such as obesity and attention-deficit hyperactivity disorder. Importantly, these types of conditions often co-occur with one another, and it is not uncommon for an individual to use prescription opioids and amphetamines simultaneously (10–12). Given the frequency with which these drugs are co-administered in both recreational and clinical settings, it is important to understand the pharmacological mechanisms determining their interactions.

One factor determining the interactions between opioids and stimulants is an opioid's relative efficacy at mu receptors. Opioids vary in their selectivity for and efficacy at the three primary opioid receptors (mu, kappa, delta), and these pharmacological properties determine their qualitative and quantitative effects when combined with stimulants. For instance, opioids with high efficacy at the mu receptor (i.e., full mu agonists) typically increase the effects of cocaine, dextroamphetamine (*d*-amphetamine), and other stimulants (13, 14), whereas opioids with high efficacy at the kappa receptor (full kappa agonists) and opioids with null efficacy at the mu receptor (i.e., mu opioid antagonists) typically decrease or block the effects of stimulants (15–17). Opioids with low to intermediate relative efficacy at the mu receptor (i.e., partial mu agonists) may increase or decrease the effects of stimulants, depending on the assay, dependent measure, and experimental parameters [c.f. (18–27)]. For instance, we previously reported that intermediate-efficacy opioids with a large range of relative efficacy at the mu receptor (e.g., buprenorphine, butorphanol, nalbuphine) increase the effects of cocaine on locomotor activity, and only opioids with very low relative efficacy at the mu receptor (e.g., nalorphine) fail to increase cocaine's locomotor effects (28). Cocaine is a dopamine reuptake inhibitor, and it is not known whether intermediate-efficacy opioids produce similar effects when combined with stimulants possessing other mechanisms of action (e.g., promoting dopamine release).

The purpose of this study was to examine the effects of opioids possessing a range of relative efficacy at the mu receptor on locomotor activity induced by *d*-amphetamine, a monoamine releaser with a high affinity for the dopamine transporter. To this end, various doses of opioids were examined alone and in combination with cumulative doses of *d*-amphetamine in a test of open-field, locomotor activity. The opioids tested varied in their relative efficacy at the mu receptor, with an estimated rank order of levorphanol > buprenorphine > butorphanol ≥ nalbuphine > (-)-metazocine ≥ (-)-pentazocine ≥ (-)-cyclazocine (29–31). The selective high-efficacy kappa agonist, spiradoline, and the non-selective opioid receptor antagonist, naloxone, served as negative controls. We tested the hypothesis that an opioid's ability to enhance the effects of *d*-amphetamine would vary directly with its relative efficacy at the mu receptor.

MATERIALS AND METHODS

Subjects

Male, Long-Evans rats were obtained from Charles River Laboratories (Raleigh, NC, USA) and weighed ∼280 g upon arrival. Subjects were housed individually in transparent cages in a colony room maintained on a 12-h light/dark cycle (lights on 0500). Subjects were maintained at 300–350 g during behavioral testing *via* light food restriction. Drinking water was available *ad libitum* in the home cage, and environmental enrichment (e.g., bedding, gnaw sticks, plastic tubes) was provided throughout the study. All rats were tested and maintained in accordance with the guidelines of the Institutional Animal Care and Use Committee of Davidson College and the *Guide for the Care and Use of Laboratory Animals* (32). A total of 119 rats were divided between 12 groups: time-course ($n = 21$; $n = 5$–6/dose), levorphanol ($n = 10$), buprenorphine ($n = 9$), butorphanol ($n = 10$), nalbuphine ($n = 9$), (-)-pentazocine ($n = 10$), (-)-metazocine ($n = 10$), (-)-cyclazocine ($n = 10$), (-)-NANM, nalorphine ($n = 10$), spiradoline ($n = 10$), and naloxone ($n = 10$).

Materials

All behavioral tests were conducted in an open-field, locomotor activity chamber. The interior of the chamber was made of plywood, measured 50 x 50 x 40 cm, and painted white with high-gloss paint. The lid of the chamber was made of transparent Plexiglas, which allowed all activity to be monitored by a video camera suspended 1.5 m above the apparatus. Heavy black lines were drawn on the lower surface of the apparatus with indelible ink that could easily be observed from the camera mounted above. These lines divided the floor into a grid of 25 squares, each measuring 10 x 10 cm. A wire-mesh screen was permanently suspended 2 cm above the bottom of the apparatus and served as the floor of the apparatus during behavioral testing.

Behavioral Procedure

Prior to behavioral testing, rats in each group were habituated to the testing environment by being placed into the activity chamber for 300 s a day for five consecutive days. After these initial habituation sessions, non-injection control tests were conducted in which locomotor activity was measured across multiple observation periods. During these control tests, each rat was removed from its home cage and placed into the activity chamber for 130 s and the number of locomotor activity counts was recorded (see section Data Analysis). The first 10 s of this interval served as an acclimation period, and thus only data obtained during the final 120 s of the interval were used for statistical analysis. Immediately after the observation period, the rat was removed from the chamber and returned to its home cage. Fifteen minutes later, the rat was again placed into the chamber and locomotor activity was again measured. All control sessions continued for two additional intervals (i.e., a total of four intervals), with 15-min intervals separating each interval. Each rat received only one non-injection control session.

Drug Administration and Locomotor Activity Testing

The effects of *d*-amphetamine were examined under a cumulative dosing procedure. In this procedure, each rat was initially injected with saline and returned to its home cage. After a 15-min pretreatment interval, the rat was placed into the activity chamber for 130 s and the number of locomotor activity counts was recorded. Again, the first 10 s of the interval served as an acclimation period and only data from the final 120 s were

used for statistical analysis. After the observation period had elapsed, the rat was removed from the chamber, administered the lowest dose of *d*-amphetamine, and returned to its home cage. Fifteen minutes later the rat was again placed into the chamber and locomotor activity was again measured. Each test session continued for two additional intervals, with increasing doses of dextroamphetamine administered at the beginning of each subsequent interval. Cumulative doses of 0.18, 0.56, and 1.8 mg/kg dextroamphetamine were tested in all sessions.

Drug Combination Testing

In separate groups of rats, drug combination tests were conducted in which various opioids were administered in combination with *d*-amphetamine. Testing procedures were identical to those described above, with the exception that a selected dose of an opioid was administered during the first interval of the session in lieu of saline. Two doses of each opioid were examined in a randomized order, with a minimum of 5–7 days separating each session. In subjects tested with levorphanol, spiradoline, and naloxone, cumulative doses of *d*-amphetamine were tested alone, both before and after drug combination tests, to determine the stability of the dose-effect curve with repeated testing. Doses of test drugs were selected on the basis of a previous study in which these opioids were combined with cocaine in tests of locomotor activity [(28); levorphanol: 0.3, 3.0 mg/kg; spiradoline: 1.0, 10 mg/kg; naloxone: 0.1, 10 mg/kg; buprenorphine: 0.03, 0.1 mg/kg; butorphanol: 0.1, 0.3 mg/kg; nalbuphine: 0.3, 1.0 mg/kg; (-)-pentazocine: 1.0, 3.0 mg/kg; (-)-metazocine: 1.0, 3.0 mg/kg; (-)-cyclazocine: 1.0, 3.0 mg/kg; (-)-NANM: 3.0, 10 mg/kg; nalorphine: 1.0, 3.0 mg/kg].

Time Course Testing

A series of time-course tests was conducted to measure the time to peak effect and duration of action of *d*-amphetamine. In these tests, different doses of *d*-amphetamine (0.18, 0.56, 1.8 mg/kg) or saline (1 ml/kg) were administered at the beginning of the session, and locomotor activity was measured 5, 15, 30, 60, and 120 min later. Non-injection control sessions were not conducted for time-course testing.

Drugs

Dextroamphetamine hemisulfate salt, levorphanol tartrate, buprenorphine hydrocholoride, butorphanol tartrate, nalbuphine hydrochloride, nalorphine hydrochloride, naloxone hydrochloride, and spiradoline mesylate were obtained from Sigma Chemical Co. (St. Louis, MO, USA). (-)-Pentazocine, (-)-metazocine, and (-)-n-allylnormetazocine were a gift from Dr. Mitchell Picker. All compounds were dissolved in saline and administered *via* intraperitoneal injection in a volume of 1.0 ml/kg of body weight.

Data Analysis

Locomotor activity was scored by observers who were blind to the study's hypotheses. Activity counts were measured by counting the number of instances in which a rat entered a new 10 cm x 10 cm square during the 120-s observation period. Entrances were counted only if the rat crossed the grid line marking the perimeter of the square with both forepaws. Only horizontal line crossings were measured; stereotypies and pattern of movement were not recorded. Except for the time-course tests, locomotor activity was expressed as % non-injection control, with each rat serving as its own control. These non-injection control values were calculated individually for each rat by dividing the number of activity counts observed during an interval of a test session by that obtained in the corresponding interval of the non-injection control session, and then multiplying by 100. Drug interaction data were analyzed *via* two-way, repeated-measures ANOVA, with dose of *d*-amphetamine and opioid pretreatment serving as repeated measures. Time-course data were also analyzed via repeated-measures ANOVA, with time serving as a within-subjects factor and dose of *d*-amphetamine serving as a between-subjects factor. Locomotor activity counts during non-injection control tests were analyzed across intervals via one-way, repeated-measures ANOVA. Similarly, the effects of each opioid administered alone (as determined during the first interval of drug combination tests) were examined via one-way, repeated-measures ANOVA. *d*-Amphetamine was tested alone on two occasions in groups tested with levorphanol, spiradoline, and naloxone. These tests of *d*-amphetamine alone were conducted before (Day 1) and after (Day 21) drug combination tests to determine whether repeated testing altered the locomotor effects of *d*-amphetamine. These data were analyzed via two-way, repeated-measures ANOVA using dose and day as factors.

To characterize the effects of each dose of opioid in combination with *d*-amphetamine, an effect-addictive model was used. Tests of additivity were conducted using a two-way, repeated-measures ANOVA comparing the observed effects of the combination to that that predicted by an effect-additive model using dose of *d*-amphetamine and model (observed vs. predicted) as within-subject factors. The predicted effects were calculated for each rat and each dose of *d*-amphetamine by the following formula (all values depicted as % non-injection control):

$$\begin{aligned}\text{predicted effect} = &\ (\text{observed effect of opioid alone}\\ &- \text{observed effect of vehicle})\\ &+ \text{observed effect of } d\text{-amphetamine alone}\end{aligned}$$

The null hypothesis (i.e., the interaction conformed to an effect-additive model) was rejected if a significant main effect was obtained for the model factor.

RESULTS

Time Course

Locomotor activity as measured by raw activity counts increased as function of *d*-amphetamine dose and varied as function of time (**Figure 1**). Acute doses of *d*-amphetamine (0.18, 0.56, and 1.8 mg/kg) dose-dependently increased locomotor activity [main effect of dose: $F_{3,\ 7} = 5.162$, $p = 0.010$], with 0.56 and 1.8 mg/kg significantly increasing locomotor activity relative to saline ($p = 0.030$ and $p = 0.007$, respectively). Locomotor activity peaked 15 min after administration [main effect of time: $F_{1,\ 17} = 45.943$,

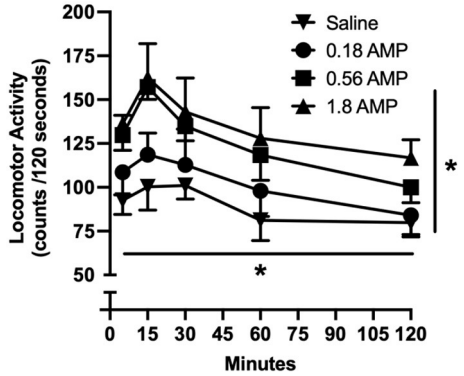

FIGURE 1 | Time-course effects of acute doses of *d*-amphetamine on locomotor activity. Vertical axis reflects locomotor activity expressed as raw activity counts over 120-s observation period. Horizontal axis reflects time after administration in minutes. All data points reflect the mean of 5–6 rats. Vertical lines represent the SEM; where not indicated, the SEM fell within the data point. Asterisk with horizontal line indicates significant effect of time. Asterisk with vertical line indicates significant effect of amphetamine dose.

$p < 0.001$]; locomotor activity counts were significantly greater at this time point than the 60- and 120-min time points ($p < 0.001$ for both time points).

Non-injection Control

Raw locomotor activity counts obtained during the non-injection control sessions varied across groups (**Table 1**). This was expected given that each group of rats was obtained from separate cohorts over an 8-year period, and some genetic drift in the stock population may have occurred (e.g., baseline locomotor activity generally increased over the 8-year period). There was some variability across intervals, but this was not significant in 8 of the 10 groups tested. In groups tested with butorphanol and nalbuphine, locomotor activity counts significantly decreased across intervals of the session [main effect of interval: $F_{3, 27} = 5.419$, $p = 0.005$; $F_{3, 24} = 5.632$, $p = 0.005$ respectively], suggesting within-session habituation in these two groups.

Levorphanol, Spiradoline, and Naloxone

The selective, high-efficacy mu agonist, levorphanol, increased locomotor activity when administered alone during the first interval of the drug combination tests [$F_{2, 18} = 4.580$, $p = 0.025$]. This effect was biphasic at the two doses tested, with the low (0.3 mg/kg) but not the high (3.0 mg/kg) dose increasing locomotor activity relative to saline (**Figure 2**). *D*-amphetamine dose-dependently increased locomotor activity [$F_{2, 18} = 4.307$, $p = 0.030$], and this effect was increased by levorphanol [$F_{2, 18} = 4.215$, $p = 0.032$]. The low dose of levorphanol increased the effects of *d*-amphetamine in a greater-than-additive manner [$F_{1, 9} = 17.124$, $p = 0.003$], whereas the effects of a high dose conformed to an effect-additive model. There was no change in the locomotor effects of *d*-amphetamine alone due to repeated testing (planned comparison of Day 1 vs. Day 21: no main effect of day or day x dose of *d*-amphetamine interaction).

The selective, high-efficacy kappa agonist, spiradoline, did not alter locomotor activity when administered alone (**Figure 2**). *d*-Amphetamine increased locomotor activity in drug combination tests [$F_{2, 18} = 6.351$, $p = 0.008$), but neither dose of spiradoline altered the effects of *d*-amphetamine relative to saline. Similar to that observed in levorphanol-treated rats, there was no change in the locomotor effects of *d*-amphetamine alone due to repeated testing.

The non-selective opioid antagonist, naloxone, did not alter locomotor activity when administered alone and functionally blocked *d*-amphetamine-induced increases in locomotor activity (**Figure 2**). Moreover, the effects of *d*-amphetamine did not differ from Day 1 to Day 21.

Intermediate-Efficacy Opioids

In drug combination tests with eight intermediate-efficacy opioids, *d*-amphetamine significantly increased locomotor activity regardless of the opioid administered (see **Table 2** for a

TABLE 1 | Raw locomotor activity counts under non-injection control conditions.

Drug	Mean	SEM	Interval	Mean	SEM
Levorphanol			**(-)-Pentazocine**		
Interval 1	110.7	7.6	Interval 1	79.2	7.9
Interval 2	100.3	10.7	Interval 2	79.4	6.4
Interval 3	114.6	11.1	Interval 3	74.3	7.2
Interval 4	101.8	9.1	Interval 4	76.0	9.4
Spiradoline			**(-)-Metazocine**		
Interval 1	87.0	5.4	Interval 1	79.8	6.2
Interval 2	96.1	7.3	Interval 2	88.0	10.4
Interval 3	92.4	9.2	Interval 3	88.8	8.3
Interval 4	98.5	7.6	Interval 4	86.7	6.6
Naloxone			**(-)-Cyclazocine**		
Interval 1	91.5	7.6	Interval 1	64.7	5.1
Interval 2	92.6	5.7	Interval 2	61.6	3.0
Interval 3	95.8	10.2	Interval 3	58.3	3.8
Interval 4	99.4	5.6	Interval 4	60.0	4.1
Buprenorphine			**(-)-NANM**		
Interval 1	62.3	4.4	Interval 1	75.9	7.9
Interval 2	58.9	4.9	Interval 2	78.0	7.2
Interval 3	56.3	4.4	Interval 3	69.7	6.7
Interval 4	55.4	2.6	Interval 4	72.8	5.6
Butorphanol			**Nalorphine**		
Interval 1	72.8	7.0	Interval 1	86.4	8.8
Interval 2	64.0	4.8	Interval 2	81.3	7.3
Interval 3	57.3	8.1	Interval 3	82.5	10.8
Interval 4	56.6	7.3	Interval 4	76.8	7.6
Nalbuphine	**Mean**	**SEM**			
Interval 1	73.4	6.3			
Interval 2	75.8	6.9			
Interval 3	58.2	4.8			
Interval 4	58.1	7.3			

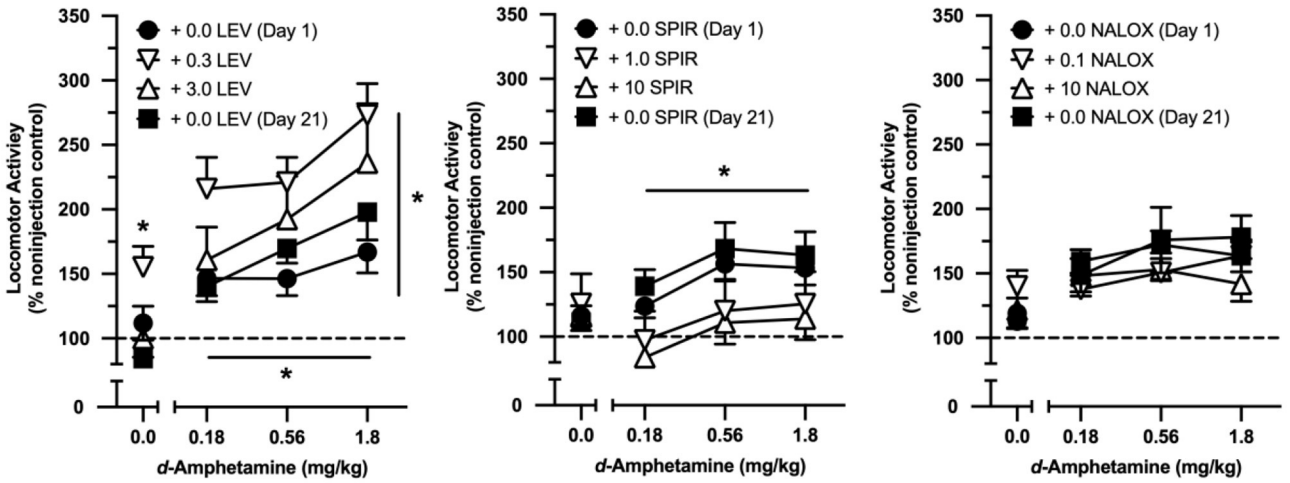

FIGURE 2 | Effects of cumulative doses of *d*-amphetamine when tested alone and when tested in combination with selected doses of levorphanol (LEV; $n = 10$), spiradoline (SPIR; $n = 10$), and naloxone (NALOX; $n = 10$). Vertical axes reflect locomotor activity expressed as a percentage of non-injection control values. Horizontal axes reflect dose of *d*-amphetamine in mg/kg. Points above "0" represent the effects of vehicle (saline) and various doses of opioids tested alone. Vertical lines represent the SEM; where not indicated, the SEM fell within the data point. Single asterisk indicates significant effect of opioid alone. Asterisk with horizontal line indicates significant effect of amphetamine dose. Asterisk with vertical line indicates significant effect of opioid pretreatment.

full ANOVA table listing all significant effects for tests conducted with the intermediate-efficacy opioids). All intermediate-efficacy opioids significantly increased the locomotor effects of *d*-amphetamine (**Table 2**, **Figure 3**). The doses of opioids tested varied in their locomotor effects when administered alone, and whether they increased the effects of *d*-amphetamine in an additive or greater-than-additive manner.

Neither dose of buprenorphine, butorphanol, nalbuphine, (-)-pentazocine, (-)-NANM, or nalorphine increased locomotor activity when administered alone; however, all six intermediate-efficacy opioids increased the effects of *d*-amphetamine (**Table 2**, **Figure 3**). All six opioids increased the effects of *d*-amphetamine in a greater-than-additive manner at the higher test dose, whereas only buprenorphine, butorphanol, and nalorphine increased the effects of *d*-amphetamine in a greater-than-additive manner at the lower test dose. In all cases, opioid-induced increases in *d*-amphetamine's locomotor effects were dose-dependent and quantitatively greater at the higher than lower test dose of the opioid.

(-)-Cyclazocine and (-)-metazocine dose-dependently increased locomotor activity when tested alone, and both drugs significantly increased the effects of *d*-amphetamine in a dose-dependent manner (**Table 2**, **Figure 3**). Both doses of (-)-metazocine increased the effects of *d*-amphetamine in a greater-than-additive manner, whereas both doses of (-)-cyclazocine conformed to an effect-additive model.

DISCUSSION

The principal finding of this study is that eight structurally and pharmacologically diverse intermediate-efficacy opioids increased the effects of *d*-amphetamine in a manner that was generally similar to the selective, high-efficacy mu agonist, levorphanol. The only opioids that failed to increase the effects of *d*-amphetamine were the selective, high-efficacy kappa agonist, spiradoline, and the non-selective opioid receptor antagonist, naloxone. The failure of spiradoline to enhance *d*-amphetamine's locomotor effects suggests that the effects of the intermediate-efficacy opioids were not mediated by the kappa receptor. Moreover, the finding that naloxone prevented *d*-amphetamine-induced locomotor activity suggests that mere occupation of opioid receptors is not sufficient to enhance *d*-amphetamine-induced locomotion. Together, these data suggest that agonist activity at the mu receptor is likely responsible for the ability of intermediate-efficacy opioids to increase the locomotor effects of d-amphetamine.

The intermediate-efficacy opioids tested vary in structure, with multiple morphinans (e.g., levorphanol, butorphanol, nalorphine) and benzomorphans [e.g., (-)-pentazocine, (-)-metazocine, (-) cyclazocine] represented. Moreover, these opioids differ in their relative selectivity for mu vs. kappa receptors, and included both mu-preferring (e.g., buprenorphine) and kappa-preferring [e.g., (-)-pentazocine] opioids (33, 34). Most importantly, the opioids differ in their relative efficacy at the mu receptor, with an estimated rank order of levorphanol > buprenorphine > butorphanol ≥ nalbuphine > (-)-metazocine ≥ (-)-pentazocine ≥ (-)-cyclazocine ≥ nalorphine > naloxone (29–31).

These findings are consistent with a previous study demonstrating that many of these same opioids increase the effects of cocaine under similar conditions (28). In that study, all intermediate-efficacy opioids except nalorphine (i.e., the opioid with the lowest estimated relative efficacy at the mu receptor of those tested) increased the effects of cocaine. Similar to the present study, the ability of an intermediate-efficacy opioid

TABLE 2 | ANOVA table for intermediate-efficacy opioids.

Drug	Pretreatment (opioid alone)	Drug combination		Effect-additive model	
		Opioid dose	d-Amp dose	Opioid: low	Opioid: high
Buprenorphine					
df_{factor}, df_{error}		2, 16	2, 16	1, 8	1, 8
F		15.889	3.700	12.56	13.38
P	*NS*	<0.001	0.048	0.008	0.006
Butorphanol					
df_{factor}, df_{error}		2, 18	2, 18	1, 9	1, 9
F		6.943	18.503	13.836	15.36
P	*NS*	0.006	<0.001	0.005	0.004
Nalbuphine					
df_{factor}, df_{error}		2, 16	2, 16		1, 8
F		10.862	31.093		44.533
P	*NS*	0.001	<0.001	*NS*	<0.001
(-)-Pentazocine					
df_{factor}, df_{error}		2, 18	2, 18		1, 9
F		12.058	7.996		19.223
P	*NS*	<0.001	0.003	*NS*	0.002
(-)-Metazocine					
df_{factor}, df_{error}	2, 18	2, 18	2, 18	1, 9	1, 9
F	24.378	3.658	62.645	31.903	9.453
P	<0.001	0.046	<0.001	<0.001	0.013
(-)-Cyclazocine					
df_{factor}, df_{error}	2, 18	2, 18	2, 18		
F	14.115	15.329	7.534		
P	<0.001	<0.001	0.004	*NS*	*NS*
(-)-NANM					
df_{factor}, df_{error}		2, 18	2, 18		1, 9
F		14.41	11.82		51.517
P	*NS*	<0.001	0.001	*NS*	<0.001
Nalorphine					
df_{factor}, df_{error}		2, 18	2, 18	1, 9	1, 9
F		18.972	7.257	13.22	8.134
P	*NS*	<0.001	0.005	0.005	0.019

NS indicates non-significant main effect. No significant interactions for the drug combination data (opioid dose × d-amphetamine dose) or the model data (model × d-amphetamine dose) were obtained. In the 2 × 2 ANOVA for model, a main effect for dose of d-amphetamine was observed under all conditions but are not shown in the table.

to increase the effects of cocaine was shared by levorphanol, but not by spiradoline or naloxone. The concordance between these studies demonstrates that the effect of opioids on stimulant-induced locomotion are consistent across stimulants with different mechanisms of actions (i.e., dopamine releasing agent vs. dopamine reuptake inhibitior).

d-Amphetamine-induced locomotor activity is mediated by the release of striatal dopamine, primarily in the nucleus accumbens. The cell bodies of dopamine-releasing nerve terminals in the nucleus accumbens are located in the ventral tegmental area (VTA). These dopamine-releasing neurons are under tonic inhibitory control by GABAergic neurons also located in the VTA. These GABAergic neurons, in turn, are under tonic inhibitory control by endogenous opioid peptides that bind to mu receptors on the cell surface. Activation of these mu opioid receptors by mu receptor agonists represents one mechanism by which high-efficacy mu agonists increase the locomotor effects of psychomotor stimulants (35). In general, opioid antagonists are more effective in blocking the effects of dopamine releasers like amphetamine than reuptake inhibitors like cocaine [e.g., (36)]. These findings have been interpreted to suggest that endogenous opioid release may contribute to some effects of *d*-amphetamine, which has several implications for the present study.

One implication of the present findings is that the endogenous tone of these mu receptors is low, given that opioids possessing very low efficacy at the mu receptor were able to increase the effects of *d*-amphetamine in either an additive or greater-than-additive manner. A second and similar implication is that the enhancement of *d*-amphetamine-induced locomotion by opioids has a very low efficacy requirement, and this assay provides a very sensitive endpoint of mu-opioid activation. Additional studies showing the effects of these intermediate-efficacy opioids

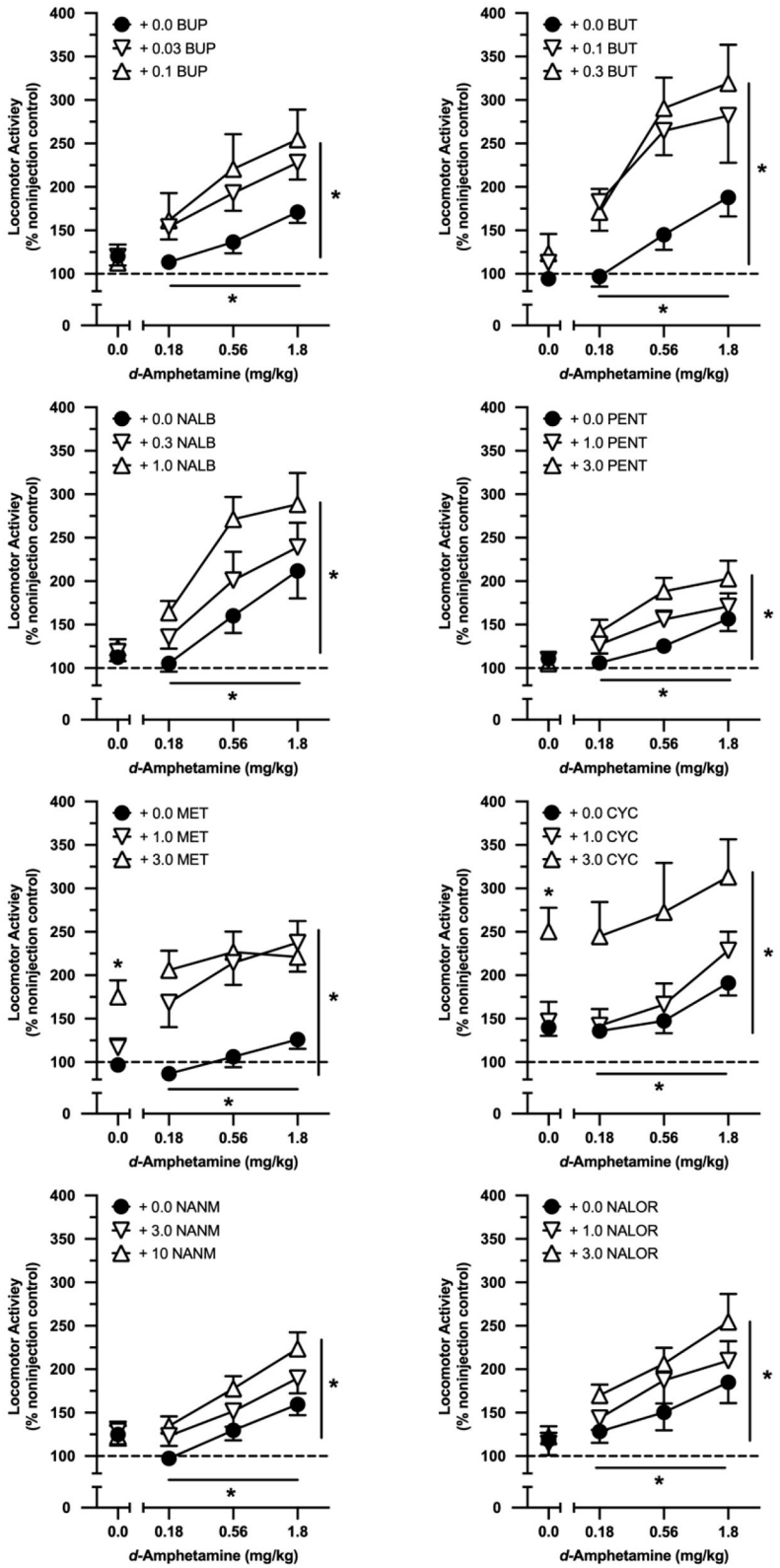

FIGURE 3 | Effects of cumulative doses of *d*-amphetamine when tested alone and when tested in combination with selected doses of buprenorphine (BUP; $n = 9$), butorphanol (BUT; $n = 10$), nalbuphine (NALB; $n = 9$), (-)-pentazocine (PENT; $n = 10$), (-)-metazocine (MET; $n = 10$), (-)-cyclazocine (CYC; $n = 10$), (-)-NANM (NANM; $n = 10$), and nalorphine (NALOR; $n = 10$). Vertical axes reflect locomotor activity expressed as a percentage of non-injection control values. Horizontal axes reflect

(Continued)

FIGURE 3 | dose of *d*-amphetamine in mg/kg. Points above "0" represent the effects of vehicle (saline) and various doses of opioids tested alone. Vertical lines represent the SEM; where not indicated, the SEM fell within the data point. Single asterisk indicates significant effect of opioid alone. Asterisk with horizontal line indicates significant effect of amphetamine dose. Asterisk with vertical line indicates significant effect of opioid pretreatment.

are reversible with mu-selective neutral antagonists would offer additional support for this possibility.

We have presented evidence that intermediate-efficacy mu opioids increase the locomotor effects of both a dopamine releaser (i.e., *d*-amphetamine; present study) and a dopamine reuptake inhibitor [i.e., cocaine (28)]. The only relevant difference between these studies is that the very low efficacy mu agonist nalorphine increased the locomotor effects of *d*-amphetamine at doses that did not alter the locomotor activity of cocaine. We are hesitant to make cross-study comparisons across studies conducted years apart, but it is notable that the locomotor effects of both drugs were very sensitive to opioid administration. Consequently, one final implication of these data is that intermediate-efficacy mu opioids can increase stimulant-induced locomotor activity under conditions that are dependent on neuronal activity and cell firing (in the case of the reuptake inhibitor, cocaine) and under conditions that are independent of neuronal activity and cell firing (in the case of the dopamine releaser, *d*-amphetamine).

Several limitations of the present study should be acknowledged. First, the study only used male rats, and we emphasize that future studies must be conducted in females to test the hypothesis that these findings can be generalized across biological sex. Second, the study only measured locomotor activity for 120 s, which is much shorter than most studies examining locomotor activity that measure behavior for 60 min or longer. Our time-course data mitigates this concern to some extent, showing that the effects observed during 2-min "snapshots" are similar to those obtained over extended and continuous testing periods [e.g., (37, 38)]. Third, only two doses of each opioid were tested. Although at least one dose of each opioid increased the effects of *d*-amphetamine, some opioids did not alter locomotor when administered alone at the doses tested. Testing a wider dose range would reveal whether higher (or lower) doses would increase locomotor activity in the absence of *d*-amphetamine. Finally, drug interactions were quantified using an effect-additive approach. This approach has several limitations relative to a dose-additive approach (39), and any conclusions regarding "synergistic" interactions between opioids and d-amphetamine should be made with an abundance of caution.

The translational relevance of this study is that intermediate-efficacy opioids with diverse chemical and pharmacological properties all increase the effects of *d*-amphetamine, including those opioids with very low efficacy at the mu receptor. These findings imply that potentially problematic dopamine-mediated effects may be observed in recreational and clinical settings when these drugs are combined. Similar to locomotor activity, the abuse-related effects of mu opioids and *d*-amphetamine are mediated by dopaminergic activity in the nucleus accumbens. Consequently, substitution of high-efficacy mu agonists for lower-efficacy agonists may not mitigate the abuse liability of these opioid-stimulant drug combinations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Davidson College Animal Care and Use Committee.

AUTHOR CONTRIBUTIONS

MS conceived of the study, analyzed the data, and wrote the manuscript. SB, CB, SB, AC, LC, MF, AG, AJ, DL, AM, CM, IR, JR, JS, MW, and SY collected the data. All living authors approved the final draft and are accountable for the work.

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Recent Increase in Methamphetamine Use in a Cohort of Rural People Who Use Drugs: Further Evidence for the Emergence of Twin Epidemics

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Appalachian Kentucky was at the epicenter of the prescription opioid epidemic in the early 2000's. As we enter the third decade of the epidemic, patterns have begun to emerge as people who use drugs (PWUD) transition from use of opioids to other drugs. The purpose of this analysis was to examine longitudinal changes in methamphetamine use in an ongoing cohort of rural people who use drugs (PWUD) in Appalachian Kentucky. All but five of the cohort participants ($N = 503$) reported nonmedical prescription opioid use (NMPOU) at baseline and those 498 are included in this longitudinal analysis encompassing eight waves of data (2008–2020). Past 6-month use of methamphetamine was the dependent variable. Given the correlated nature of the data, mixed effects logistic regression was utilized to examine changes in methamphetamine use over time. Significant increases in methamphetamine use were observed over the past decade in this cohort of PWUD, especially in recent years (2017–2020). Prevalence of recent use at baseline and each of the follow-up visits was as follows: 9.4, 5.6, 5.0, 5.4, 8.1, 6.8, 6.9, and 33.1%, respectively ($p < 0.001$). On the contrary, significant reductions in NMPO and heroin use were observed in the same time period. The odds of methamphetamine use at the most recent visit were 25.8 times greater than at baseline (95% CI: 14.9, 44.6) and 52.6% of those reporting methamphetamine use reported injecting the drug. These results provide further evidence of "twin epidemics" of methamphetamine use among NMPOU. While problematic on several fronts, of particular concern is the lack of effective treatment options for methamphetamine use disorder. As policies around the opioid epidemic continue to evolve, particular attention should be paid to the surge in stimulant use in opioid-endemic areas.

Keywords: methamphetamine, rural, Appalachian Kentucky, epidemic, opioid

INTRODUCTION

The opioid epidemic has been well documented in the United States (1, 2). However, there is still uncertainty around how the epidemic will progress. The first major shift after recognition of a prescription opioid epidemic was the transition from nonmedical prescription opioids (NMPO) to heroin use (3). While somewhat expected given the pharmacologic similarities between prescription opioids and heroin (4), this transition remains concerning due to risk of overdose (5, 6), contamination of heroin supplies with fentanyl and fentanyl-analogs and its related harms (7, 8), and a dearth of harm reduction services in many areas of the U.S. to combat heroin- and opioid-related issues (9). Recent data suggest that we may be entering yet another new era of the opioid epidemic, where those using NMPO and/or heroin begin concomitant use of methamphetamine (10–14). Coined "twin epidemics" (13), this phenomenon has now been studied in substance use disorder (SUD) treatment samples (10, 11, 13), a cross-sectional study of mid-western NMPOU's (14) and nationally-representative samples (12, 15), but has not been studied longitudinally among those using opioids. Increased methamphetamine use raises considerable concern as it is associated with a litany of harms; including, among others, dental issues (16, 17), cardiac abnormalities (18, 19), and transmission of infectious diseases, such as HIV and hepatitis C *via* sharing of infected pipes and injection implements, as well as engagement in risky sex (20–23). Methamphetamine use is not novel, especially in rural areas of the U.S. (24, 25) and among those using drugs to enhance sex ("chemsex") (26, 27); however, there is growing body of evidence that use is increasing in new populations of established people who use drugs (PWUD), and people using opioids in particular (12, 14).

The emergence of methamphetamine use among people using opioids is particularly problematic given the lack of effective treatment options for methamphetamine use disorder (MUD), especially compared to opioid use disorder (OUD). While there are several medications currently under study, no FDA-approved pharmacologic treatments exist for MUD (28, 29). A 2017 systematic review of the evidence-based treatment options identified several behavioral interventions, including cognitive behavioral therapy (CBT), motivational interviewing (MI), and contingency management (CM), among others (30). Of those, CM appeared to be most efficacious in reducing methamphetamine use in the short-run, along with CBT and exercise, in certain settings (30). A more recent overview of published systematic reviews noted significant reductions in amphetamine use when psychsocial interventions are employed (31). However, rural areas in particular may be ill-equipped to deliver interventions requiring skilled mental health providers that are often in short supply (32) and CM, while very promising, is not a reimbursable treatment because giving incentives is equated to a "kick-back" and considered unlawful by many insurers, including Medicaid (33).

Although Europe has been largely spared from a NMPO epidemic, data indicate that European countries may not be entirely immune (34, 35). There have been several reports of increasing prescribing of opioids in the Netherlands (36, 37), UK (38), Sweden (39), and France (40), which may be a signal for problematic NMPOU. A 2017 study comparing the use of opioids in the U.S. and Europe suggests troubling patterns of opioid use in the United Kingdom that mirror the U.S. (35). Reports from Australia also indicate that opioid prescribing has increased in recent years (41–43), as have concerns about the potential for NMPOU (43). Another potential signal of problematic opioid use in Australia was overdose data showing the proportion of fatal overdoses where prescription opioids were present was 2.5 times that of heroin (44). Even though the U.S. opioid epidemic is ever-evolving, what has transpired thus far may inform the response in countries where the potential for NMPOU use has increased in recent years. It is therefore important to examine long-term outcomes of the opioid epidemic, especially in cohort studies largely comprised of NMPOUs. The aims of these analyses were to examine changes in methamphetamine use over time and explore characteristics of those individuals using methamphetamine within a cohort of rural people who use opioids followed from 2008–2020.

TABLE 1 | Mixed effects for model of changes in methamphetamine use, 2008–2020.

Variable	Adjusted odds ratio	95% Confidence interval
Visit		
Baseline	1.0 (referent)	
1	0.72	0.41, 1.26
2	0.72	0.40, 1.29
3	0.87	0.49, 1.54
4	1.77	1.03, 3.03*
5	1.75	0.98, 3.13
6	1.74	0.96, 3.14
7	25.8	14.9, 44.6***
Recent (Past 6-Mo) Substance Use		
NMPO	2.52	1.61, 3.97***
Benzodiazepines	1.83	1.31, 2.57***
Cocaine	3.54	2.52, 4.97***
Lifetime Methamphetamine Use	3.07	2.06, 4.57***
Age	0.96	0.93, 0.98***
Female	1.67	1.13, 2.45**

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

MATERIALS AND METHODS

Data from the Social Networks among Appalachian People (SNAP) study were utilized for the current analysis. At baseline the cohort consisted of 503 community-dwelling residents of a

rural county in Appalachian Kentucky. Those eligible for the SNAP study reported past 30-day use of either NMPO, cocaine, methamphetamine or heroin. An extensive description of the methods for the SNAP study are provided elsewhere (45). Of note, all but five participants reported recent (past 6-month) NMPOU at baseline, and all 503 participants reported lifetime NMPOU. Those indicating recent NMPO use at baseline (99%) are included in the current analysis ($N = 498$). Participants were remunerated $50 at each visit. The study was approved by the Institutional Review Board at the University of Kentucky and a Certificate of Confidentiality was obtained from the National Institutes of Health.

Data were collected bi-annually for the first wave of the study (2008–2013), and annually thereafter (2014–2020) for a total of eight study visits. Follow-up rates were 92.3, 92, 93.7, 90, 89.1, 89.7, and 83.9% for the 1st–7th follow-up visits, respectively. The survey was approximately 90 min in length and interviewer-administered. Responses were recorded directly on to a touchscreen laptop using computer-assisted personal interviewing (CAPI) software (QDS, Bethesda, MD).

Study Variables

Data from the baseline and seven follow-up visits were utilized for the longitudinal trend analysis ($n = 498$) and data from the most recently completed follow-up visit ($n = 350$) were utilized to characterize methamphetamine use in this sample of rural people who use opioids. The dependent variable of interest was recent (past 6-month) methamphetamine use at baseline and each follow-up visit. To ascertain whether participants had used methamphetamine, they were asked "Have you ever used methamphetamine" and if so, "How often have you used methamphetamine in the past 6 months"? The second question was dichotomized to include those with any/no use to create the recent use variable that was used as the dependent in all analyses. Other substance use was assessed contemporaneously with methamphetamine use and recent use variables were created for each substance analyzed (NMPO, heroin, benzodiazepines, cocaine, marijuana, and alcohol). Participants were also queried generally about any injection drug use at the baseline and each follow-up visit, and specifically regarding the substances they injected. For the current analysis, dichotomous variables for any injection drug in the past 6-months (measured at each visit) and past-6 month injection of NMPO and/or methamphetamine were used. Finally, a variable to distinguish new onset methamphetamine use was created to differentiate those with who began using methamphetamine at one of the follow-up visits from those with a prior history of methamphetamine use (lifetime use reported at baseline). Demographic data from the baseline interview, including age, race, gender, and years of education, were used in the models. To be consistent, opioid use disorder (OUD) (formerly opioid dependence) was assessed using DSM-IV criteria across all visits since the newer criteria were published during the follow-up period. However, since opioid dependence was assessed, that is the terminology used throughout the manuscript.

Statistical Analyses

Given the correlated nature of the data over time, mixed effects logistic regression was used to examine longitudinal trends in recent methamphetamine use across the eight waves of data. Recent drug use variables were allowed to vary over time in the mixed effects model and estimates were exponentiated and reported as odds ratios. A forward elimination process was utilized by which substance use and demographic variables significantly ($p < 0.05$) associated with methamphetamine use over time in the simple mixed effects model were entered one at a time and changes in standard errors were observed with the addition of each new variable. The final model contains those variables that remained significantly associated with the outcome after all additional covariates were entered. The predictive margins and adjusted probabilities were calculated for recent use of methamphetamine, NMPO and heroin over time and are presented in graph form. To assess the independent correlates of past 6-month methamphetamine use at the most recent visit, simple and multivariable logistic regression was employed using the forward elimination process described above. All analyses were conducted using Stata, version 16.0 (College Station, TX).

RESULTS

A little less than half of the 498 NMPO in the SNAP cohort were women (45.7%) and the median age at study entry (2008–2010) was 31 years (interquartile range [IQR]: 26, 38). Consistent with the demographic composition of Appalachian Kentucky, 94.2% of NMPO were White and most participants had at least 12 years of education (IQR: 10, 12). At baseline, 84.9% of NMPOU's met DSM-IV criteria for opioid dependence and 73.5% of the sample reported injecting drugs at some point during the study timeframe, 2008–2020.

There were stark changes in past 6-month (recent) use of methamphetamine over time (3,474 observations). Reports of recent use at baseline and each of the follow-up visits were as follows: 9.4, 5.6, 5.0, 5.4, 8.1, 6.8, 6.9, and 33.1%, respectively ($p < 0.001$). The increase in recent methamphetamine use was most notable at the latest follow-up visit, which was initiated in November 2017 and completed in March 2020. As seen in **Table 1**, recent NMPO, benzodiazepines and cocaine use were associated with increased odds of methamphetamine use over time, as was younger age. The predictive margins for the methamphetamine use model were calculated and graphed (**Figure 1**). The margins were also estimated for longitudinal NMPO and heroin use and the predicted probabilities are presented alongside those for methamphetamine for comparative purposes. Significant increases in the predicted probability of methamphetamine use were contrasted by statistically significant declines in both NMPO and heroin use over the past decade.

A separate longitudinal model was constructed to examine recent methamphetamine injection over time since the number of observations ($n = 1{,}279$) was smaller for the injection-only sample of those who recently used methamphetamine. Similar to the overall model, there were significant increases in recent methamphetamine injection longitudinally ($p < 0.001$). **Figure 2**

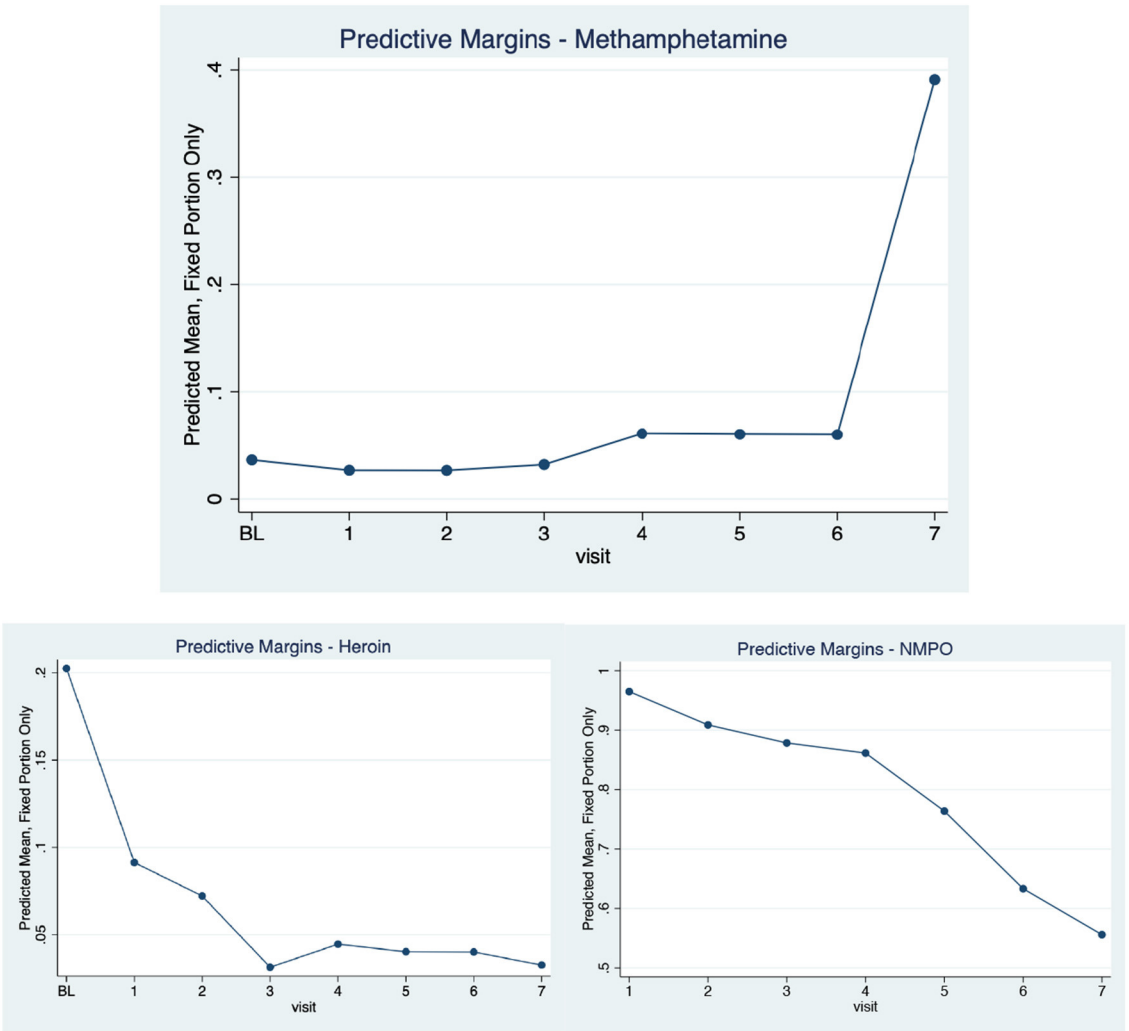

FIGURE 1 | Adjusted Predicted Probabilities of Recent Methamphetamine, NMPO and Heroin Use Over Time in a Cohort of NMPO Users, 2008–2020.

compares recent injection NMPO and methamphetamine use over time. Injection of both substances is steady and dominated by NMPO, until the most recent visit, where recent injection of methamphetamine overtakes NMPO.

Finally, given the high prevalence of methamphetamine use at the most recently completed visit, a closer examination of use at this visit ($N = 350$) was undertaken. One-third ($n = 116$) of participants reported that they had used methamphetamine in the prior 6-months, and of those, 52.6% were injecting the drug. The majority of those (84.9%) had used methamphetamine in the prior 30 days and the median number of days using in the prior 30 was 10 (interquartile range: 3, 20). Among those injecting methamphetamine, the median number of days using in the past 30 was similar (10; IQR: 2, 30), but of note, the upper quartile were injecting daily. Many (38.8%, $n = 45$) of those reporting recent use were new onset users, meaning they had not reported methamphetamine use prior to the baseline interview, or methamphetamine use at any of the prior visits. The average number of new onset users in the prior visits was just under eight. Results from the cross-sectional multinomial logistic regression were not vastly different from the longitudinal model presented above. Those reporting recent methamphetamine use were significantly more likely to be younger, and using NMPO, heroin, marijuana and cocaine (**Table 2**) in the prior 6-months, even after adjustment for gender and pre-baseline methamphetamine use.

DISCUSSION

As we navigate the third decade of the opioid epidemic in rural Kentucky it is clear that previous substance-related epidemics cannot adequately inform this particular crisis. The results from this study provide clear evidence for "twin epidemics" of emergent methamphetamine use among people using opioids, as this cohort comprised of NMPOUs was designed to be able to detect such trends. These "twin epidemics" are problematic on many fronts. First, and perhaps most importantly, unlike

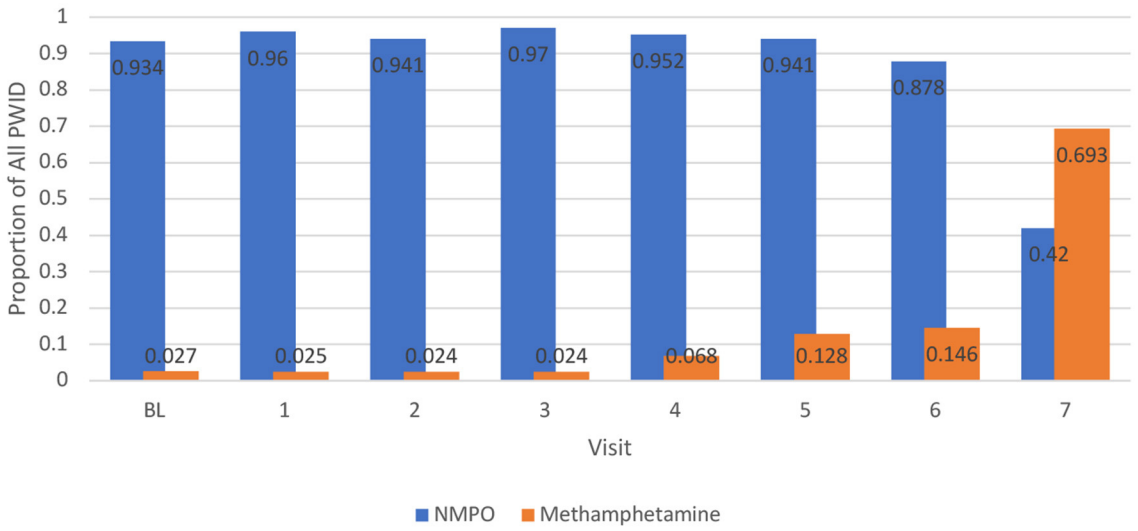

FIGURE 2 | Proportion of People who Inject Drugs (PWID) Reporting Recent Injection of Methamphetamine and NMPO Over Time, 2008–2020.

TABLE 2 | Multivariable logistic regression examining methamphetamine use at latest visit.

Variable	Adjusted odds ratio	95% Confidence interval
Recent (Past 6-Mo) Substance Use		
NMPO	1.89	1.13, 3.15*
Heroin	5.89	1.57, 22.0**
Cocaine	2.73	1.36, 5.48**
Marijuana	1.77	1.07, 2.90*
Baseline Methamphetamine Use	1.28	0.77, 2.12
Age	0.96	0.93, 0.99*
Female	1.17	0.71, 1.92

*$p < 0.05$; **$p < 0.01$.

opioids, there are very few evidence-based effective treatments for MUD that could be easily implemented in rural areas, given the paucity of trained mental health professionals (30, 32) and current limitations to the real-world use of contingency management (33). So the question becomes how to leverage the strides that have been made to increase access to treatment for OUD in rural areas to also address MUD. Given the co-occurring use of NMPO and methamphetamine, there is the potential to adapt medications for OUD (MOUD) treatment protocols to address methamphetamine use for NMPOU using methamphetamine. While the evidence is not overwhelming, two studies demonstrated that use of buprenorphine reduced methamphetamine cravings (46), and those prescribed MOUD significantly reduced stimulant use while in treatment (47). A pharmacologic approach for OUD paired with one of the evidence-based psychosocial interventions for MUD (30, 48) may be ideal for this population of PWUD, but perhaps challenging to deliver in rural areas. In addition, increased availability of online interventions due to the SARS-CoV-2 pandemic may allow for penetration of evidence-based programs in rural areas. However, access to broadband internet and internet-capable devises still lags in many rural communities (49), which may ultimately limit the utility of online treatment options.

These data also suggest that once methamphetamine became readily available in the area, use significantly increased (50). At the most recent visit, there were five times the number of new onset users compared to the average at previous follow-ups. And while other areas of the U.S. who faced similar opioid crises saw this transition with heroin (3, 51), results from this cohort demonstrate that heroin use is less prevalent in this region and on the decline over time. Efforts to address the opioid epidemic may need to take into account methamphetamine use when designing and implementing interventions. And although this study was conducted among rural NMPOU in the U.S., lessons from the opioid epidemic can be used to prevent harms in areas where there are signals of problematic prescription opioid use, such as Europe and Australia (36, 38, 43, 44).

Injection of methamphetamine also significantly increased over time and overtook NMPO as the injection drug of choice among people who inject drugs (PWID) in this cohort. Given the potential for HIV and/or HCV transmission through injection and non-injection methamphetamine use (22, 23, 52), these findings only amplify the need to continue efforts to increase access to harm reduction and syringe services programs in rural areas (9). Given the association between methamphetamine use and risky sex (53), existing programs may need to also

increase access to testing for sexually transmitted infections (STIs) and ensure condoms are distributed alongside injection equipment, in line with best practices for harm reduction programs (54).

Limitations

While the potential for bias is greatly reduced in longitudinal cohort studies compared with cross-sectional designs, one concern is differential loss to follow-up (55). The mortality rate for the cohort is 10% ($n = 50$), and an additional 103 have either been removed from the study, asked to be removed, or cannot be located. Compared to those who completed the most recent follow-up, participants who were lost-to-follow-up over the course of the study were more likely to be injecting at baseline. This is not surprising given the morbidity and mortality associated with injecting drugs (56, 57). The loss of PWID over time likely did not appreciably impact the study findings, as there was sufficient power to model the injection-related outcomes. There were no differences in baseline demographics or other drug use variables between those retained and those lost-to-follow-up. If anything, the reported findings are more conservative, because additional observations for PWID would likely have led to even greater proportion of those injecting methamphetamine. Finally, measurement of the dependent variable and the majority of independent variables was reliant on self-report, which may have led to underreporting of the main outcome. However, data have shown that self-report of substance use is highly correlated with actual use (58). Despite these limitations, this represents some of the first evidence of "twin epidemics" in a longitudinal cohort of NMPOU.

In conclusion, these results provide additional evidence of the emergence of "twin epidemics" of methamphetamine and opioid use in the United States. Continued monitoring of the evolution of the opioid epidemic is essential so the harms may be understood, new treatment paradigms can be developed to address this co-occurring substance use, and appropriate prevention or intervention efforts can be implemented in regions observing the emergence of this new pattern of substance use.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary files, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board, University of Kentucky. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JH obtained funding for the study, conducted statistical analyses and drafted the manuscript. HK provided statistical and editorial support. JCS, AY, MRL, SB, and SW provided input on study hypotheses and editorial support to the drafting of the manuscript. All authors contributed to the article and approved the submitted version.

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Intranasal Oxytocin for Stimulant Use Disorder Among Male Veterans Enrolled in an Opioid Treatment Program: A Randomized Controlled Trial

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The increasing prevalence of illicit stimulant use among those in opioid treatment programs poses a significant risk to public health, stimulant users have the lowest rate of retention and poorest outcomes among those in addiction treatment, and current treatment options are limited. Oxytocin administration has shown promise in reducing addiction-related behavior and enhancing salience to social cues. We conducted a randomized, double-blind, placebo-controlled clinical trial of intranasal oxytocin administered twice daily for 6 weeks to male Veterans with stimulant use disorder who were also receiving opioid agonist therapy and counseling ($n = 42$). There was no significant effect of oxytocin on stimulant use, stimulant craving, or therapeutic alliance over 6 weeks. However, participants receiving oxytocin (vs. placebo) attended significantly more daily opioid agonist therapy dispensing visits. This replicated previous work suggesting that oxytocin may enhance treatment engagement among individuals with stimulant and opioid use disorders, which would address a significant barrier to effective care.

Keywords: oxytocin, amphetamine-related disorders, opioid-related disorders, opiate substitution treatment, treatment adherence and compliance, stimulant, methadone, veterans

INTRODUCTION

Stimulant use among individuals seeking treatment for opioid use disorder (OUD) has drastically increased over the last decade (1). Co-use of cocaine and/or methamphetamine with opioids elevates the risk of fatal overdose and is associated with poorer medical, mental health, and substance use disorder (SUD) treatment outcomes (2). While there are effective medications to treat OUD, including methadone and buprenorphine (3, 4), there are still no Food and Drug Administration (FDA)-approved medications for stimulant use disorder. Furthermore, clinical trials investigating new treatments for stimulant use disorder typically exclude individuals with OUD (5, 6). A recent systematic review of available clinical trials targeting stimulant use among

people with co-occurring OUD reported 21 medications studied for cocaine use and only one medication for methamphetamine use (1); none of the medications studied demonstrated clear benefits.

Epidemiological research suggests that more than a third of all U.S. military Veterans meet criteria for any SUD, excluding tobacco use disorder, over their lifetime (7). Furthermore, lifetime prevalence of SUDs is higher among Veterans vs. non-veterans, and Veterans with a SUD diagnosis reported the lowest levels of functioning across multiple domains—including physical, emotional, and social functioning—compared to Veterans without SUDs or non-veterans with or without SUDs (7). Therefore, Veterans are particularly in need of innovative treatment options for SUDs.

Oxytocin is a hypothalamic peptide hormone which acts both peripherally and centrally and plays a prominent role in social attachment. A body of research suggests that a well-functioning endogenous oxytocinergic system is protective against the development of SUDs, and, conversely, that chronic substance use leads to dysregulation within the oxytocinergic system (8). Animal researchers began exploring oxytocin's anti-addiction effects over 40 years ago (9). In animal models of addiction—including stimulants and opioids—administration of exogenous oxytocin has demonstrated broad benefits, including: prevention and mitigation of drug self-administration, reduced stress- and drug-primed reinstatement of drug self-administration, and reduced signs of withdrawal and tolerance (10–12). Interestingly, laboratory animals housed socially together, vs. isolated in individual cages, respond more robustly to oxytocin administration on substance-related outcome measures (13), supporting the theory that social context can moderate the effects of oxytocin (14). Veterans are more likely to be socially avoidant compared to the general population, thus treatment interventions that promote social attachment may be particularly pertinent to Veterans (15).

More recently, human subjects research has begun to explore the effects of intranasal oxytocin on addiction-related outcomes for various substances of misuse (16, 17). As far as reduction in substance craving and use, results from these clinical trials have been largely underwhelming. Most of these trials administered only a single dose of oxytocin and/or did not pair oxytocin with a psychosocial treatment intervention. Exceptions to these limited trial designs include early phase trials of: (a) intranasal oxytocin vs. placebo administered twice daily for 2 weeks to individuals with cocaine use disorder concurrently enrolled in an opioid treatment program (OTP) for OUD (18) and (b) intranasal oxytocin vs. placebo paired with 6 weekly sessions of motivational interviewing group therapy for methamphetamine use disorder (19). While the first study showed a small effect of oxytocin vs. placebo on self-reported reduction in cocaine use, there was no significant effect of oxytocin on urine levels of cocaine metabolite (18); the second study showed no effect of oxytocin on methamphetamine use (19). Neither study detected a significant effect of oxytocin on stimulant craving or urge to use. Given promising animal data and early mixed data among human subjects, more research is needed to better understand the effects of intranasal oxytocin on SUDs.

Interestingly, a previously unpublished exploratory analysis of Stauffer et al.'s (18) pilot study of oxytocin for co-occurring cocaine use disorder and OUD found that male participants ($n = 12$) demonstrated significantly fewer clinic absences over three weeks when receiving oxytocin vs. placebo (Cohen's $d = 1.44$; $p = 0.05$). Another interesting finding from this study was that participants receiving oxytocin, but not those receiving placebo, demonstrated a significant association between self-reported cocaine use and quantitative urine levels of cocaine metabolite—suggesting that oxytocin may enhance honesty with providers. These exploratory findings infer that oxytocin improves engagement with clinical treatment, specifically treatment attendance and therapeutic alliance, despite no promising short-term effects on stimulant use and craving. Therapeutic alliance refers to the quality of the bond between a patient and therapist, measured through agreement on goals, ways to attain goals, and trust (20).

Subsequently, Stauffer et al. (19) found a significant effect of oxytocin on attendance at group therapy sessions for methamphetamine use disorder (OR 3.26, 95% CI [1.27–8.41], $p = 0.014$; $n = 48$, all male-identified). This trial also found positive effects of oxytocin on aspects of group cohesion (19) and physiological synchrony (21); although oxytocin had no significant effect on methamphetamine use or craving after 6 weeks of treatment. Of note, endogenous oxytocin has been nominated as a possible biomarker for therapeutic alliance (22); and—regardless of the therapeutic modality—the strength of the therapeutic alliance consistently predicts addiction treatment engagement and retention as well as long-term relapse (7, 23). Thus, it is important that we gain a better understanding of the relationship between oxytocin and therapeutic alliance, particularly among individuals with SUDs in controlled therapeutic environments (24, 25). Lastly, some research has suggested that adverse childhood experiences can moderate the effects of intranasal oxytocin among individuals with SUDs (26, 27).

The current study investigates the effects of intranasal oxytocin vs. placebo administered to Veterans with stimulant use disorder in the context of receiving care at an OTP for OUD. The primary clinical outcome is change in stimulant use, using both self-report and urine drug test. Secondary outcomes include: (a) stimulant craving, (b) therapeutic alliance with OTP counselor, and (c) OTP clinic attendance. We hypothesized that administration of oxytocin vs. placebo would result in reduced stimulant use and craving and improved therapeutic alliance and clinic engagement.

MATERIALS AND METHODS

Trial Design

We conducted a randomized, double-blind, placebo-controlled, clinical trial (NCT03016598) of intranasal oxytocin administered twice daily for 6 weeks. The study was approved by the University of California, San Francisco Institutional Review Board (IRB) and was conducted according to Good Clinical Practices.

Participants and Recruitment

Eligibility Criteria

Participants included in the study were (a) Veterans, (b) ≥18 years old, (c) enrolled in an OTP and on a stable dose of opioid agonist therapy (methadone or buprenorphine) for at least 2 weeks, (d) with severe stimulant use disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM*-5) criteria, and (e) with a documented urine toxicology test positive for stimulant use (cocaine and/or methamphetamine) in the past year.

We excluded participants who had (a) active suicidal or homicidal ideation, (b) conditions preventing nasal spray administration (e.g., nasal obstruction, frequent nosebleeds), or (c) known allergic reaction or sensitivity to the preservatives in the nasal spray.

Recruitment and Screening

Participants were recruited between January 2018 and February 2020 from two OTPs in the San Francisco Veterans Affairs (VA) Health Care System, the San Francisco VA Medical Center and the Oakland Behavioral Health Clinic. Potential participants were recruited through referrals from OTP counselors and flyers advertising the study posted within the OTP clinics.

To determine preliminary eligibility, staff conducted brief, structured, in-person interviews with interested participants. Preliminarily eligible Veterans were then invited to complete a full screening assessment to determine eligibility for study participation. Study staff obtained informed consent prior to conducting any study procedures. A trained clinical interviewer with at least Masters' level training in clinical psychology conducted pertinent diagnostic interviews from the Mini International Neuropsychiatric Interview (MINI) 7.0.0 (28) and a structured interview to determine lifetime and 30-day frequency of substance use (29). A study physician performed an examination of the nasal parenchyma. Participants also completed a demographics interview and the Adverse Childhood Experience (ACE) questionnaire—for which higher scores indicate a greater number of adverse childhood experiences, such as emotional, physical, and sexual abuse, and emotional and physical neglect (30).

Participants were compensated a total of $50 for completing the screening visit and up to an additional $300 for full participation in the study. Compensation was $50 per week, $30 of which they received at each of 6 weekly visits and $20 of which was added to a completion bonus disbursed at the sixth and final visit.

Randomization and Blinding

Enrolled participants were randomly allocated by the research pharmacist to receive either oxytocin or placebo (1:1) throughout the study intervention period. Participants and study staff were kept blinded to study condition until the final participant completed study termination.

Procedures

Study Drug

Oxytocin is a large hydrophilic molecule that does not cross the blood-brain-barrier in appreciable amounts when administered peripherally. However, intranasal administration is thought to reach the brain via various pathways, acutely resulting in elevated oxytocin levels in the cerebrospinal fluid and measurable behavioral effects in the laboratory for up to a few hours (31). Participants received oxytocin 40 International Units (IU) or placebo intranasally twice daily for 6 weeks. Oxytocin was purchased from Valor Compounding Pharmacy (Berkeley, CA, USA). Oxytocin concentration was 40 IU/0.5 mL. Study drug was administered in clinic every morning using a mucosal nasal atomizer (MAD300; Teleflex technologies, Mooresville, NC). In the evening—approximately 12 h after the morning dose—as well as every 12 h on days the clinic was closed (e.g., Sunday, holidays), participants self-administered study drug using a bottle with a metered-dose nasal spray pump (Aptar Classic Technology, Crystal Lake, IL). Participants were trained in proper self-administration by study staff. To monitor adherence, nasal spray bottles were weighed prior to and after weekly participant use and a timeline follow-back (TLFB) procedure was conducted for self-administered evening dosing over the prior week. Participants were incentivized to bring their bottle back for weighing, regardless of how many doses they'd self-administered, by the loss of $10 from their weekly compensation if they forgot.

Assessments

Following enrollment, participants attended a baseline and 6 additional weekly assessments. During weekly assessments, study staff asked about stimulant use and cravings over the prior week and collected a urine sample to evaluate for stimulant use. At the baseline and final assessments, each participant and their respective OTP counselor completed an assessment of therapeutic alliance. See **Table 1** for timing of measurements.

Outcome Measures

Primary Clinical Outcome—Stimulant Use

Self-Reported Stimulant Use

The Timeline Follow-back is a structured interview conducted by study staff to determine the number of days over the past week, including the day of the interview, that participants used a stimulant (32, 33).

Urine Drug Testing

We used a point-of-care, CLIA-waived, 10-panel, Toxicology iCup Dx (Alere Inc., Waltham, MA) to measure stimulant use (cocaine and/or methamphetamine).

Secondary Outcome Measures

Stimulant Craving

The self-report Stimulant Craving Questionnaire-Brief (STCQ-Br) measures current general stimulant craving (34). Each of the 10 items is scored on a 7-point Likert scale. Adaptation of the STCQ-Br for the current study involved replacing the word "stimulant" in each item with the individual's preferred term for their stimulant of choice, which was collected during screening.

TABLE 1 | Timing of measurements.

	Screening	1	2	3	4	5	6	7
Oxytocin 40 IU vs Placebo intranasally					Twice daily x 6 weeks			
Screening assessment/baseline characteristics								
Mini international neuropsychiatric interview	X							
Demographics	X							
Adverse childhood experiences (ACE)	X							
Lifetime substance use	X							
30-day substance use	X							
Outcome measures								
Self-reported stimulant use (timeline Follow-back)			X	X	X	X	X	X
Urine drug test	X	X	X	X	X	X	X	X
Cocaine craving questionnaire-brief (CCQ-Br)	X	X	X	X	X	X	X	X
Working alliance inventory-short revised (WAI-SR)		X						X
WAI-SR-T (therapist)		X						X
Clinic attendance					Daily x 6 weeks			

IU, International Units. 1, Baseline assessment, 2–7, Weekly assessments.

Therapeutic Alliance

We used the Working Alliance Inventory-Short Revised (WAI-SR) and the Working Alliance Inventory-Short Revised-Therapist Version (WAI-SR-T) to measure therapeutic alliance between participant and their OTP counselor (20). These 12-item self-report questionnaires use a 7-point Likert scale to rate therapeutic alliance based on three elements: the degree to which both parties agree on the goals of treatment, agreement on the tasks to attain those goals, and the development of trust (35).

Clinic Attendance

OTP clinic attendance was measured as the proportion of required daily opioid agonist dosing visits that the participant attended during the 6-week study intervention period. One study site required 6 days per week attendance and the other site required 5 days per week attendance for OTP patients at the initial phase of care. Two participants were higher phase and did not require daily OTP attendance; thus, they were removed from analysis for this outcome.

Analysis Plan

Sample Size Calculation

The initial sample size calculation determined that 25 participants in each group would have 81% power over 6 weeks to detect the small-medium effect size ($d = 0.31$) found in our pilot work for between-group difference in urine toxicology and >99% power to detect the large effect size ($d = 1.44$) we found in our pilot work for between-group difference in OTP attendance.

Statistical Methods

All analyses were conducted with R (version 3.6.3) and all confidence intervals (CIs) are reported at the 95% coverage level (36). Covariates were chosen based on bivariate analysis between groups as to reduce confounding by differing demographics.

Stimulant use (measured by TLFB) and self-reported craving (measured by STCQ-Br) were modeled using a linear mixed model with random intercepts for patients to account for repeated weekly measurements over the study period. The primary predictor of interest was the interaction between study drug (oxytocin vs. placebo) and week of the trial (1–6) to examine the effectiveness of oxytocin over the course of the trial. Covariates included age (continuous), race (white, black, other), and smoking status (smoker/non-smoker). Race was simplified due to small numbers of patients in non-White or non-Black categories. For the self-reported craving outcome, the model was adjusted for craving at the baseline visit. Complete cases were used in analysis, resulting in $n = 40$ for TLFB and $n = 39$ for STCQ-Br. One patient was missing a baseline STCQ-Br score and thus excluded from this analysis.

Weekly urine toxicology results (either positive or negative for stimulants) and weekly clinic attendance (proportion of OTP dosing sessions attended) was modeled using a generalized estimating equation (GEE) with a logit link for a binomial distribution. An autoregressive (level one) covariance structure was used to account for repeated measures. The primary predictor of interest was the interaction between study drug use and week of the trial. Covariates included age (continuous), race (white, black, other), and smoking status (smoker/non-smoker). Complete cases were used in analysis, resulting in $n = 40$ patients for these outcomes.

Change in the WAI-SR and WAI-SR-T was measured by taking the difference in the scores at week seven minus the scores at baseline. A positive change indicates an increase in the strength of the therapeutic alliance. This change was modeled with a linear fixed effects model, with the study drug as the primary predictor of interest. Covariates included age, race, smoking status, and the ACE sum score. In our exploratory analysis and model building process, we did not find any significant relationship between ACE and stimulant-related outcomes, nor did it appear to have a noticeable confounding effect on other covariates. As such,

ACE was only used in conjunction with therapeutic alliance in order to present more parsimonious models. Complete cases were used in analysis, resulting in $n = 38$ patients for the WAI-SR outcome, and $n = 37$ patients for the WAI-SR-T outcome. Missing observations were due to missing surveys at week seven.

RESULTS

Participants

See **Figure 1** for participant flow diagram (37). Of note, we did not meet our initial goal of 50 participants. We noted a lack of eligible participants at our primary site and gained regulatory approval to recruit from an additional site. Ultimately, we enrolled 42 participants within the grant period. See **Table 2** for demographics and baseline characteristics. While females were not excluded from participating in the study, no female participants were recruited. Generally, participants receiving placebo were older, included a higher percentage of black participants, a higher percentage of cocaine users (vs. methamphetamine users), a lower percentage of smokers, and included no participants who were without housing in the previous year (compared to $n = 5$ from the oxytocin treatment arm).

Intervention Adherence

Adherence rates for morning clinic-administered and evening self-administered study drug dosing is as follows: 92.0 and 84.1% for oxytocin, respectively, and 85.4 and 90.2% for placebo. The mean (SD) differences in bottle weight (mg) following each week of use were: Oxytocin 3.1 (1.7) and Placebo 3.2 (1.6).

Outcomes

Primary Outcome—Stimulant Use

Self-Reported Stimulant Use

For the overall sample, there was a significant reduction in stimulant use as the trial progressed by 0.10 days per week (CI: −0.19 to −0.02; $p = 0.02$), but there was no significant effect for the study drug by week interaction (estimate: 0.08; CI: −0.04 to 0.21; $p = 0.19$). None of the model covariates were significantly associated with the outcome. See **Figure 2A.**

Urine Toxicology

There was no significant difference in proportion of positive weekly urine toxicology screens over the study period between the study drug groups (OR: 0.96; CI: 0.88–1.04; $p = 0.32$). None of the model covariates were significantly associated with the outcome. See **Figure 2C**.

Secondary Outcomes

Stimulant Craving

Overall, there was a significant decrease in reported craving by week over the course of the study period of 0.07 points per week (CI: −0.13 to −0.01; $p = 0.02$), but there was no significant effect for the study drug by week interaction (estimate: −0.02; CI: −0.11 to 0.07; $p = 0.64$). See **Figure 2B**.

Therapeutic Alliance

Overall, there was not a significant relationship with study drug and change in patient WAI-SR score (estimate: 0.06; CI: −0.63 to 0.75; $p = 0.86$). See **Figure 3A**. Interestingly, those patients with higher ACE sum scores did see a significant increase in

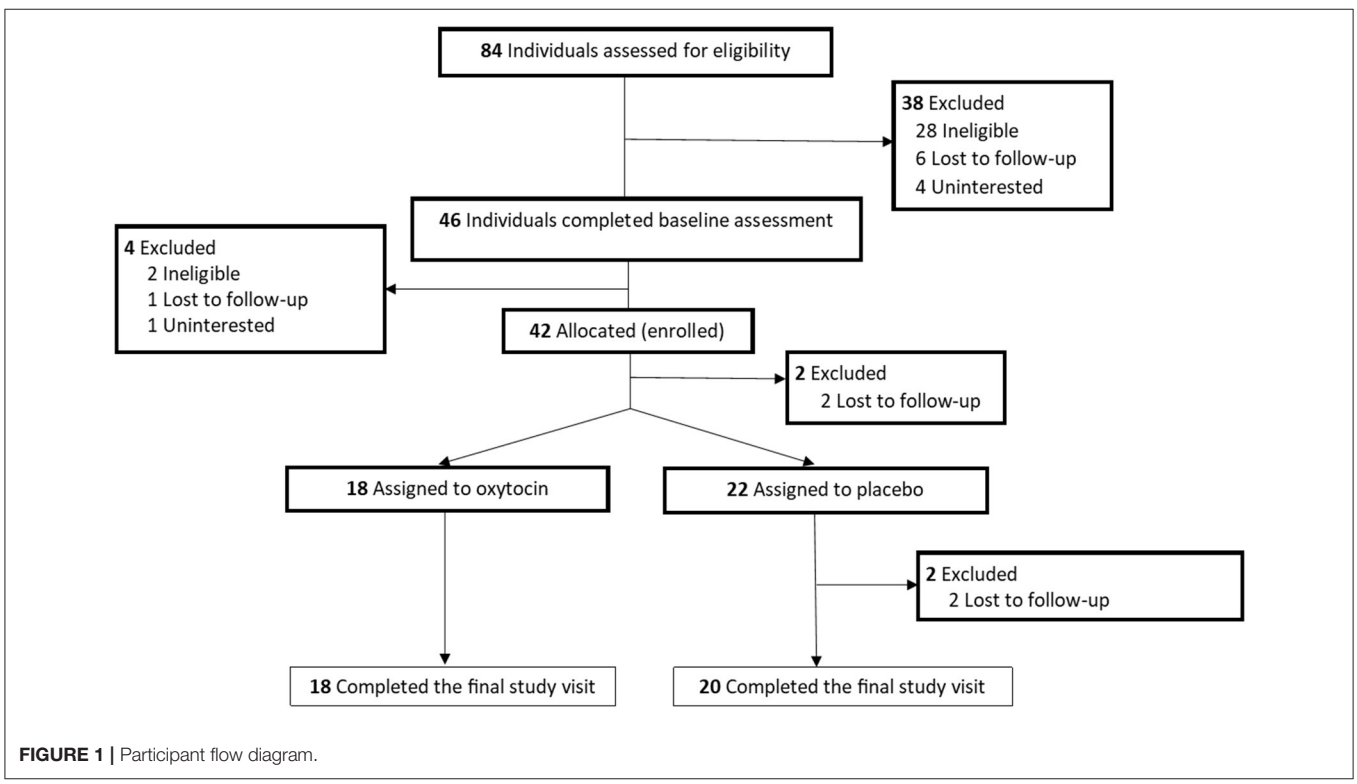

FIGURE 1 | Participant flow diagram.

TABLE 2 | Demographics and baseline characteristics.

		Oxytocin ($n = 18$)	Placebo ($n = 22$)	Overall ($n = 40$)
Age; Mean (SD)		53.9 (11.4)	63.1 (7.3)	59 (10.3)
Gender Identity				
	Male; *n* (%)	18 (100%)	22 (100%)	40 (100%)
Kinsey score[a]; Mean (SD)		0.33 (1.4)	0.18 (0.7)	0.25 (1.1)
Race; *n* (%)				
	African American/Black	7 (38.9%)	17 (77.3%)	24 (60.00%)
	Multiracial	4 (22.2%)	1 (4.5%)	5 (12.5%)
	Native American/Pacific Islander	0 (0.0%)	1 (4.5%)	1 (2.5%)
	White	7 (38.9%)	3 (13.6%)	10 (25.0%)
Ethnicity	Hispanic/Latino; *n* (%)	2 (11.1%)	2 (9.1%)	4 (10.0%)
Education; *n* (%)				
	≤High school graduate	2 (11.1%)	4 (18.2%)	6 (15.0%)
	High school grad	5 (27.8%)	8 (36.4%)	13 (32.5%)
	Some college/Trade	10 (55.6%)	9 (40.9%)	19 (47.5%)
	Bachelor's Degree	1 (5.6%)	1 (4.6%)	2 (5.0%)
Annual income; *n* (%)	≤$11,880[b]	5 (27.8%)	4 (18.2%)	9 (22.5%)
Employed; *n* (%)		2 (11.1%)	2 (18.2%)	4 (10.0%)
Disability; *n* (%)		14 (77.8%)	16 (72.7%)	30 (75.0%)
Housing	Houseless past year; *n* (%)	5 (27.8%)	0 (0.0%)	5 (12.5%)
Relationship status	Primary relationship[c]; *n* (%)	5 (27.8%)	3 (13.6%)	8 (20.0%)
Smoking status	Smoker; *n* (%)	17 (94.4%)	15 (68.2%)	32 (80.0%)
Opioid agonist therapy	Methadone (vs. buprenorphine); *n* (%)	16 (88.9%)	17 (77.3%)	33 (82.5%)
Stimulant of choice	Cocaine (vs. methamphetamine); *n* (%)	12 (66.7%)	19 (86.4%)	31 (77.5%)
Years used ≥3 times per week/Age; Mean (SD)	Cocaine	0.25 (0.2)	0.23 (0.2)	0.24 (0.2)
	Methamphetamine	0.11 (0.2)	0.05 (0.2)	0.10 (0.2)
Proportion of days used in past 30 days; Mean (SD)	Cocaine	0.14 (0.3)	0.25 (0.4)	0.20 (0.3)
	Methamphetamine	0.12 (0.2)	0.08 (0.2)	0.07 (0.2)
Stimulant craving; Mean (SD)	[range: 1–7]	2.14 (1.3)	1.92 (0.9)	1.99 (1.0)
Therapeutic alliance; Mean (SD) [range: 1–5]				
	Participant	3.60 (0.9)	3.82 (0.8)	3.72 (0.8)
	Therapist	4.09 (0.7)	3.75 (0.7)	3.91 (0.7)
Adverse childhood experiences; Mean (SD)	[range: 0–10]	3.5 (2.5)	4.55 (2.7)	4.08 (2.6)

[a] *scale from "0, exclusive heterosexuality" to "6, exclusive homosexuality".*
[b] *2016 United States Department of Health and Human Services poverty guideline.*
[c] *Someone with whom you are currently in love or feel a commitment to. SD, standard deviation.*

average WAI-SR score regardless of study drug (estimate: 0.14; CI: 0.02–0.25; $p = 0.023$). Interaction between study drug and ACE was tested but not significant and not reported for the final model. There was also no significant effect of study drug on change in therapist WAI-SR-T score (estimate: −0.02; CI: −0.38 to 0.34; $p = 0.91$). See **Figure 3B**. In contrast to the patient score change, the change in therapist rating did not have any significant relationship with baseline ACE or any other covariates.

Clinic Attendance

Overall, there was a significant decrease in proportion of clinic attendance by week (OR: 0.70; CI: 0.53–0.94; $p = 0.015$). There was a significant interaction of study drug and week, in that those patients receiving oxytocin had higher attendance rates compared to those who received placebo as the study progressed (OR: 1.39; CI: 1.04–1.86; $p = 0.03$). See **Figure 4**.

DISCUSSION

Contrary to our hypothesis, twice daily dosing of oxytocin vs. placebo over 6 weeks did not affect stimulant use as evidenced by self-report and urine drug test among Veterans with stimulant use disorder within an OTP. There was also no effect of oxytocin on our measurements of stimulant craving or therapeutic alliance. Regardless of study drug, there was a significant reduction in self-reported stimulant use and craving over the 6 weeks; however, there was no significant change in stimulant-positive urine tests. Overall, having more adverse childhood experiences was significantly associated with improved therapeutic alliance over the course of the study, but there was no interaction with oxytocin. While oxytocin had no noticeable effects on our substance-related outcome measures or therapeutic alliance, participants receiving oxytocin attended

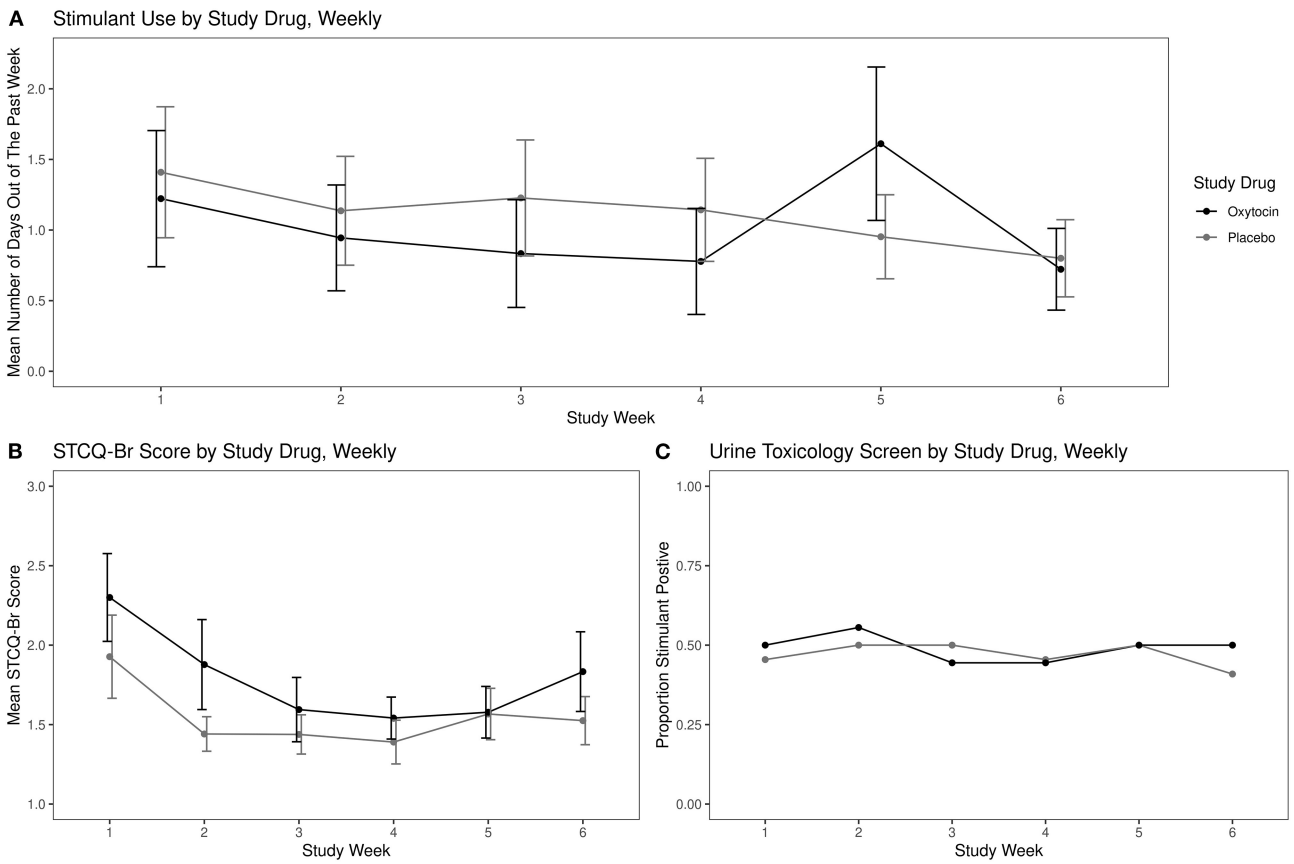

FIGURE 2 | Stimulant use and craving by study drug: **(A)** mean self-reported stimulant use using the Timeline Follow-back, **(B)** mean self-reported stimulant craving using the Stimulant Craving Questionnaire-Brief (STCQ-Br), and **(C)** proportion stimulant-positive urine toxicology. Error bars, Standard Error of the Mean.

significantly more OTP clinic visits compared to participants receiving placebo. This finding replicates earlier work showing that oxytocin administration was associated with fewer absences in addiction treatment settings (18, 19), suggesting that oxytocin may enhance treatment engagement among stimulant users.

While a large body of preclinical evidence has reliably shown that oxytocin administration reduces stimulant use and related behavior, these outcomes have not translated clearly to human clinical trials. In the present study, we expect the placebo effect contributed to the reduction in stimulant use and craving over time within both treatment arms, in addition to related phenomena such as regression to the mean, spontaneous remission, outcome expectancies, and the Hawthorne effect—or changing behavior as a response to attention received through observation and assessment (38). Of note, our sample consists of relatively chronic users (having used stimulants three or more times per week for 10–24% of their lives on average), and our 6-week assessment period was relatively brief. Nonetheless, we recognize the importance of publishing null results in moving the field forward (31).

This is the third clinical trial among individuals with stimulant use disorder to demonstrate a protective effect of oxytocin on dwindling clinic attendance over time among male participants (18, 19). Generally, dropout rates are notably higher among stimulant users compared to other SUDs (39), and 40–62% of Veterans fall out of care before completing a predetermined course of outpatient addiction treatment (40, 41). Furthermore, no significant differences in treatment retention exist between evidence-based, addiction-focused, psychosocial treatments (e.g., motivational interviewing, contingency management, cognitive-behavioral therapy) and standard care (42)—highlighting a lack of options available to address these retention issues. Perhaps obviously, a body of evidence has shown that the effectiveness of addiction treatment is weakened significantly by early dropout (43, 44). For example, community addiction treatment duration of <90 days was associated with significantly less favorable outcomes 1 year later, and single episode treatment duration beyond 90 days had a linear relationship with positive treatment outcomes at 1 year (45). Unfortunately, the current trial did not involve any follow-up assessment beyond our 6-week intervention. In a meta-analysis of medication trials for co-occurring stimulant use disorder and OUD (1), only one intervention—naltrexone implant (46)—demonstrated a positive effect on retention compared to placebo. Most other interventions had no effect on retention; while antidepressants, anticonvulsants, and disulfiram worsened retention compared to

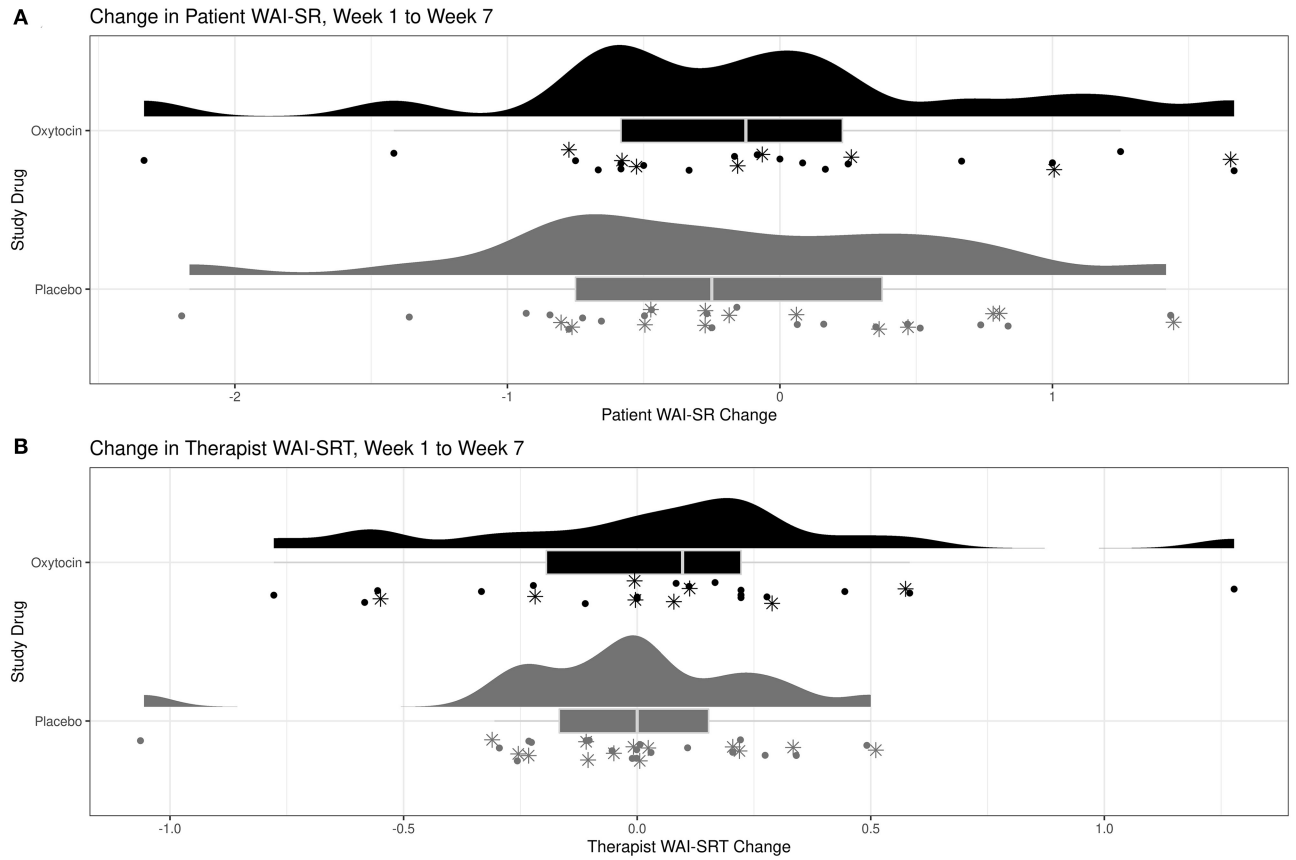

FIGURE 3 | Change in therapeutic alliance after six weeks of oxytocin vs. placebo using the Working Alliance Inventory-Short Revised (WAI-SR): **(A)** WAI-SR, patient version and **(B)** WAI-SR-T, therapist version. *Participants with ACE ≥4.

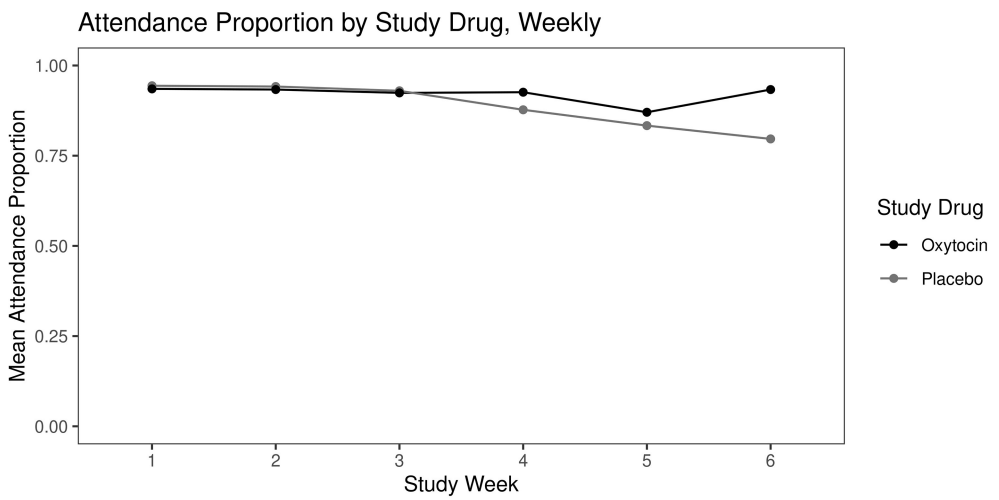

FIGURE 4 | Mean opioid treatment program clinic attendance (proportion of weekly scheduled visits attended) over 6 weeks by study drug.

placebo (1). Conversely, intranasal oxytocin and naltrexone, a μ-opioid antagonist, may act synergistically to improve retention (46–48), and the combination warrants further investigation. Because retention in addiction treatment has generally been associated with improved long-term treatment outcomes, and there is a scarcity of available interventions to effectively

address critically high dropout rates among stimulant users, further research into oxytocin's potential to improve treatment engagement is warranted.

We saw an association between adverse childhood experiences and improved therapeutic alliance over the course of our intervention. While some research has suggested that adverse childhood experiences can moderate the effects of intranasal oxytocin (26, 27), our study did not find such an effect. Nonetheless, the social salience hypothesis of oxytocin posits that, rather than having purely prosocial effects, oxytocin modulates social responsivity based on both external contextual social cues (e.g., competitive vs. cooperative environments) and individual characteristics (e.g., history of interpersonal trauma, gender, sexual orientation) (14). This highlights the potential importance of a model that pairs oxytocin dosing with supportive psychosocial treatment, rather than the typical psychopharmacology model of routine self-administration in uncontrolled social contexts. In the current study, participants' morning doses were administered by friendly staff in a clinic setting; however, the social context of their evening dosing was not controlled. On the other hand, Stauffer et al. (19) paired oxytocin administration solely with motivational interviewing group therapy for methamphetamine use disorder and saw positive effects on attendance and therapeutic alliance within 6 weeks. Flanagan et al. (49) are currently conducting a Phase II clinical trial ($N = 200$) of oxytocin vs. placebo paired with Alcohol Behavioral Couples Therapy (49). We suggest that future oxytocin studies continue to explore the effect of social context on clinical outcomes. If intranasal oxytocin enhances perceptions of social support and boosts treatment engagement in supportive social contexts, this may mitigate addiction severity over time. Future studies may also consider qualitative interviews to capture subjective experiences associated with improvements in attendance.

This study has several limitations, including limitations in its design and being underpowered to detect significant changes in the primary clinical outcome. Generalizability does not extend beyond older, male Veterans with chronic stimulant use receiving care within an OTP. While female participants were not excluded from participating, the VA OTP clinics from which we recruited had very few female patients—none of whom met eligibility criteria for study participation. Despite randomization, participant demographics between experimental groups were not well-matched by age, race, or homelessness in the past year. Past 30-day stimulant use and craving at baseline were relatively low in our sample. Both opioid replacement medication type (buprenorphine or methadone) and stimulant of choice (cocaine, methamphetamine, or both) were considered as covariates but ultimately left out as they did not improve model performance or predictive power and were not significantly related to outcomes. Additionally, with our limited sample size, using these variables as covariates presented estimation issues due to imbalances across treatment groups. Oxytocin has a short half-life (∼19 minutes) (50) but primes its own release (51, 52), perhaps contributing to prolonged elevation in oxytocin concentrations and behavioral effects after intranasal oxytocin administration (53). However, evidence also suggests that oxytocin release is inhibited by μ-opioid receptor agonists (54, 55) (as opposed to naltrexone, a μ-opioid receptor antagonist mentioned earlier as having potential synergy with oxytocin). Thus, the effects of intranasal oxytocin may be blunted in people receiving opioid agonist therapy with methadone and buprenorphine. Comparison studies of intranasal oxytocin administered to participants with stimulant use disorder both with and without co-occurring OUD are poised to help further our understanding of any clinically pertinent drug-drug interaction between oxytocin and opioids. Finally, we did not account for concomitant medication use or psychiatric diagnoses beyond our eligibility criteria, and our study design did not include any long-term follow-up assessment.

The increasing prevalence of co-morbid stimulant and opioid use poses a significant risk to public health, and current treatment options are limited. Research suggests an inverse relationship between social support and addiction severity (56–59). Twice daily administration of the social neuropeptide oxytocin for up to 6 weeks in a real-world OTP clinic setting did not seem to affect stimulant use or craving. However, we replicated previous findings in which oxytocin maintained engagement with clinical interventions over time among stimulant users (18, 19). These results suggest a potential practical application for intranasal oxytocin in bridging the gap between addiction and social connection (24, 25), which would address a significant barrier to effective care (i.e., particularly high treatment dropout rates among stimulant users). Oxytocin's effects on addiction treatment attendance warrant further investigation, including clinical trials with larger, more diverse samples and follow-up assessments to measure longer-term effects of oxytocin on treatment dropout, therapeutic alliance, and potential changes in substance craving and use beyond 6 weeks.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of California, San Francisco Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CS: conceptualization, funding acquisition, protocol design, and trained study staff. SS: recruitment manager, study implementation, data collection, and organization. AH: data analysis. WFH and SB: mentorship. All authors reviewed and edited the final manuscript.

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Modeling Stimulant and Opioid Co-use in Rats Provided Concurrent Access to Methamphetamine and Fentanyl

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Concurrent use of stimulants (e.g., methamphetamine) and opioids (e.g., fentanyl) has become increasingly common in recent years and continues to pose an enormous health burden, worldwide. Despite the prevalence, relatively little is known about interactions between the reinforcing effects of stimulants and opioids in this pattern of polysubstance use. The goals of the current study were to evaluate the relative reinforcing and relapse-related effects of methamphetamine and fentanyl using a concurrent access, drug-vs.-drug choice procedure. Male Sprague-Dawley rats were first allowed to acquire self-administration for either 0.1 mg/kg/infusion methamphetamine or 0.0032 mg/kg/infusion fentanyl, independently, after which concurrent access to both drugs was provided. When training doses of methamphetamine and fentanyl were concurrently available, a subset of rats self-administered both drugs, either within a session or alternating across sessions, whereas the remaining rats responded exclusively for one drug. When the cost of the preferred drug was increased (i.e., unit dose reduced), or the cost of the non-preferred drug was decreased (i.e., unit dose increased), choice was largely allocated toward the cheaper alternative. Following extinction of responding, methamphetamine- and fentanyl-paired cues reinstated responding on both levers. Responding reinstated by a priming injection of methamphetamine or fentanyl allocated more responding to the lever previously reinforced by the priming drug. The current studies suggest that choice of methamphetamine and fentanyl is largely allocated to the cheaper alternative, although more co-use was observed than would be expected for economic substitutes. Moreover, they lay the groundwork for more fully evaluating interactions between commonly co-abused drugs (e.g., stimulants and opioids) in order to better understand the determinants of polysubstance use and develop effective treatment strategies for individuals suffering from a polysubstance use disorder.

Keywords: concurrent access, self-administration, methamphetamine, fentanyl, polysubstance use

INTRODUCTION

In the United States alone, substance use has an estimated economic burden of $600 billion annually, and directly contributed to more than 90,000 deaths by overdose in 2020 (1–3). Adding to the complexities of understanding the pathology and developing effective treatment strategies is the increasing awareness that most individuals with a substance use disorder use more than one substance; thus, recent trends suggest the United States is in the midst of an epidemic of polysubstance use [for review, see (4–6)]. Although the co-use of stimulants and opioids has historically involved mixtures of cocaine and heroin, recently there has been a particularly alarming rise in the incidence of methamphetamine and opioid co-use and overdose (7–14). Users have reported a wide variety of reasons for using stimulants and opioids either concurrently or sequentially, including enhanced euphoria of the drug mixture relative to each constituent, use of methamphetamine to alleviate opioid withdrawal symptoms, and as tools to endure homelessness (9, 12). Importantly, the co-use of stimulants and opioids is also associated with much poorer treatment outcomes (e.g., relapse, overdose) (15, 16). Despite this sharp rise in the co-use of methamphetamine and opioids, relatively little is known about interactions between the abuse-related effects of these drugs in either clinical or preclinical settings.

Given the recent increase in problems associated with the concurrent use of stimulants and opioids, it is vitally important to gain a better understanding of the factors that drive this pattern of co-use in order to develop more effective strategies for treating individuals with a polysubstance use disorder. Indeed, although the co-injection of cocaine and heroin (i.e., "speedballs") has been common for decades (17), recent estimates suggests that the popularity of stimulant-opioid mixtures is growing, with over 50% of treatment-seeking opioid users reporting regular stimulant use (18, 19). In preclinical models, self-administration of mixtures of cocaine and heroin has been demonstrated to produce synergistic increases in extracellular dopamine levels in rats (20). Consistent with this finding are studies in both rodents (21–24) and non-human primates (25–30); but see (31) demonstrating that the reinforcing effects of cocaine and heroin mixtures are similar to, or greater than the reinforcing effects of either constituent alone. Although less is known about interactions between methamphetamine and opioids, evidence suggests that mixtures of methamphetamine and opioids can result in a more robust locomotor stimulation, and enhancements in the reinforcing effects of small, but not large, doses of methamphetamine (32, 33).

Although mixtures studies are appropriate to model the co-use of stimulant and opioid preparations (e.g., "speedballs," "goofballs"), other approaches are needed to model situations in which the pattern of polysubstance use involves the co-use of stimulants and opioids as independent entities. One powerful method to evaluate interactions between the reinforcing effects of co-abused drugs is to provide subjects concurrent access to both drugs (34). By manipulating the "cost" of the two drugs (e.g., changing the ratio requirement or the unit dose of drug available), it is possible to determine the nature of their interaction in economic terms (i.e., substitutes, complements, or independents) (35, 36). As the cost of one drug is increased, intake of the fixed cost alternative drug may increase (substitutes), decrease (complements), or stay the same (independents). Previous work from our laboratory used a concurrent access procedure in rats to characterize interactions between the reinforcing effects of two stimulant drugs, 3,4-methylenedioxypyrovalerone (MDPV) and cocaine (37). When functionally equivalent doses of MDPV and cocaine (as determined by a progressive ratio schedule of reinforcement) were made concurrently available, responding tended to be allocated toward one lever or the other, with the behavior of a subset of rats maintained almost exclusively by MDPV, whereas for the remaining rats behavior was maintained almost exclusively by cocaine. However, when the "cost" of the preferred drug was increased (or decreased) by altering the unit doses available for self-administration, all rats exclusively allocated their responding toward the cheaper alternative, suggesting that MDPV and cocaine function as economic substitutes. Although similar methods have been used in non-human primates to suggest that cocaine and the ultra-short acting mu-opioid receptor agonist, remifentanil, function as economic substitutes, the extent to which these relationships extend to methamphetamine and fentanyl is unknown (38, 39).

In addition to better understanding interactions between the reinforcing effects of stimulants and opioids, the high rates of relapse, particularly in individuals with a polysubstance use disorder, highlights the urgent need to better understand the factors contributing to drug-seeking/relapse in polysubstance using populations. For instance, although pharmacotherapies exist to treat opioid use disorder, they are largely ineffective at altering cocaine or methamphetamine use, which can in turn promote relapse to opioid use and increase the likelihood of overdose (40–42). In preclinical assays thought to model some aspects of relapse (e.g., drug-primed reinstatement), the capacity of a drug to reinstate responding is often determined by the degree to which it shares discriminative stimulus properties with the previously self-administered drug (e.g., methamphetamine reinstating responding for cocaine, caffeine reinstating responding for MDPV) (43–45). Consistent with this notion, we have recently established a concurrent reinstatement procedure to show that intravenous primes with cocaine, MDPV, or methamphetamine all reinstate comparable levels of responding on levers previously reinforced by MDPV and cocaine, whereas a priming injection of heroin failed to reinstate responding on either lever. Although this suggests that like begets like, it is unclear how histories of concurrent self-administration of drugs from different pharmacological classes would impact the patterns of cue-induced or drug-primed reinstatement. For instance, a history of concurrent use of stimulants and opioids might erode the specificity typically associated with drug-primed reinstatement, and instead expand the spectrum of drugs that will reinstate responding (e.g., opioids will now effectively reinstate responding for stimulants, and vice versa).

The current studies begin to address these gaps in knowledge by establishing a concurrent access self-administration procedure in which rats have access to both methamphetamine and fentanyl

in order to address the following hypotheses: (1) concurrent access to a stimulant and an opioid will result in both drugs maintaining responding, rather than the exclusive patterns of responding observed when two stimulants were available; (2) when the available dose of one drug is increased (cost reduced) or decreased (cost increased), responding will be largely re-allocated toward the lever reinforced by the cheaper alternative, although choice is not expected to be exclusive (i.e., methamphetamine and fentanyl will act as imperfect substitutes); and (3) although methamphetamine and fentanyl will reinstate more responding on the levers that they previously reinforced, methamphetamine will also reinstate responding for fentanyl, and fentanyl will also reinstate responding for methamphetamine, albeit at lower levels.

METHODS

Subjects

Fifteen male Sprague-Dawley rats (275–300 g upon arrival) were purchased from Envigo (Indianapolis, IN, USA) and maintained in a temperature- and humidity-controlled vivarium. Rats were individually housed and maintained on a 14/10-h light/dark cycle (lights on at 6:00 a.m.). All experiments were conducted during the light cycle and sessions were conducted at approximately the same time each afternoon. Rats were provided ad libitum access to Purina rat chow and water except during experimental sessions. All procedures were conducted in accordance with Institutional Animal Care and Use Committee at the University of Texas Health Science Center at San Antonio and the Guide for Care and Use of Laboratory Animals (46).

Surgery

Rats were anesthetized with 2–3% isoflurane and prepared with chronic indwelling catheters in the left and right femoral veins using procedures similar to those described previously (37, 47, 48). Catheters were tunneled under the skin and attached to a vascular access button placed in the mid-scapular region. Immediately following surgery, rats were administered Penicillin G (60,000 U/rat) subcutaneously to prevent infection and were allowed 5–7 days to recover. Throughout this recovery period, both catheters were flushed daily with 0.5 ml of heparinized saline (100 U/ml). Thereafter, catheters were flushed daily with 0.2 ml of saline prior to, and 0.5 ml of heparinized saline after the completion of self-administration sessions. Catheter patency was assessed using an intravenous infusion of 5 mg/kg methohexital as needed (e.g., an increase in pressure when flushing, extinction of responding). Three rats were unresponsive to methohexital prior to dose manipulation experiments and were excluded from subsequent experiments.

Drugs

Fentanyl was provided by the National Institute on Drug Abuse Drug Supply Program (Bethesda, MD). D-methamphetamine and ketamine were purchased from Sigma-Aldrich (St. Louis, MO, USA) and Henry Schein (Dublin, OH, USA), respectively. All drugs were dissolved in sterile 0.9% saline and administered intravenously in a volume of 0.1 ml/kg (for self-administration) or 1 ml/kg (for reinstatement tests) based on body weight. Additionally, methohexital was generously provided by Eli Lilly and Company (Indianapolis, Indiana, USA), dissolved in sterile 0.9% saline and administered in a volume of 1.0 ml/kg to check for catheter patency.

Apparatus

All experiments were conducted in standard operant conditioning chambers located within ventilated, sound-attenuating enclosures (Med Associates, Inc., St. Albans, VT). Each chamber was equipped with two response levers located 6.8 cm above the grid floor and 1.3 cm from the right or left wall. Visual stimuli were provided by two sets of green, yellow, and red LEDs, one set located above each of the two levers, and a white house light located at the top center of the opposite wall. Drug solutions were delivered by variable speed syringe pumps through Tygon tubing connected to a dual channel stainless-steel fluid swivel and spring tether, which was held in place by a counterbalanced arm. Experimental events were controlled, and data were collected using MED-PC IV software and a PC-compatible interface (Med Associates, Inc.).

Self-Administration

Acquisition

Behavior was initially maintained by either 0.1 mg/kg/infusion of methamphetamine or 0.0032 mg/kg/infusion of fentanyl under a fixed ratio (FR) 1: timeout (TO) 5-s schedule of reinforcement during daily 90-min sessions. Doses were chosen based on their relative positions (peak) on their respective progressive ratio dose-response curves (47, 48). Two sets of conditioned stimuli (discriminative and infusion-paired) were used in these studies. The discriminative stimuli paired with methamphetamine and fentanyl were counterbalanced across rats and different for each drug. One discriminative stimulus consisted of the illumination of a yellow LED above the active lever (left or right; counterbalanced across rats) that signaled drug availability. Completion of the response requirement on this lever resulted in a drug infusion (0.1 ml/kg over ∼1 s) that was paired with the illumination of the yellow, green, and red LEDs above that lever as well as the houselight; these lights remained illuminated for the duration of the 5-s post-infusion timeout period during which no additional infusions could be earned. The other set of discriminative stimuli consisted of the illumination of green and red LEDs above the active lever (left or right; counterbalanced across rats) that signaled drug availability. Completion of the response requirement on this lever resulted in a drug infusion (0.1 ml/kg over ∼1 s) that was paired with the flashing of the yellow, green, and red LEDs as well as the houselight, at 1 hz; this occurred throughout the 5-s post-infusion timeout period during which no additional infusions could be earned. Responses made on the inactive lever, and those made on either lever during timeouts, were recorded but had no scheduled consequences. Acquisition criteria were defined as: ≥12 infusions for two consecutive days with ≥80% responding occurring on the active relative to inactive lever. Response requirements were subsequently increased to an FR 5 where they remained for the duration of the study. After 7 days, and once behavior met stability criteria for the initial

drug (±20% of the mean of two consecutive sessions), behavior was now maintained by the alternate drug on the alternate lever (and alternate set of conditioned stimuli) under an FR 5 schedule. The initially active lever now became inactive (i.e., the discriminative stimuli were omitted and responding had no programmed consequences). This condition was kept in place for at least 10 sessions and until stability criteria were met to allow for nearly equal exposure to both drugs prior to being provided concurrent access. Throughout the entire acquisition period (i.e., acquisition of responding for both methamphetamine and fentanyl), the catheter through which drug infusions were delivered alternated daily in order to ensure that both catheters functioned equivalently.

Concurrent Access

After reaching stability under an FR 5 schedule for the second drug, access to both drugs (or saline) was provided and their associated stimuli under a concurrent FR5:FR5 schedule of reinforcement during daily 90-min sessions. For all rats, the following conditions were evaluated in quasi-random order: (1) concurrent access to 0.1 mg/kg/infusion of methamphetamine and saline; (2) concurrent access to 0.0032 mg/kg/infusion of fentanyl and saline; and (3) concurrent access to 0.1 mg/kg/infusion of methamphetamine and 0.0032 mg/kg/infusion of fentanyl. Conditions remained in place for 7 sessions. Each session began with a 1-min blackout followed by two sample trials, one on each lever, for the available drug (or saline) and stimulus conditions. A 1-min blackout followed each sample trial. The order of sample trials (i.e., drug and stimuli) was counter-balanced across rats. The session counter did not begin until 1 min after the second sample trial was completed. Throughout the remainder of the session, rats had concurrent access to both drugs (or one drug and saline) and associated stimuli.

Dose-Substitution

Subsequent to establishing preference between training doses of methamphetamine and fentanyl, the following manipulations were made in order to evaluate economic interactions between methamphetamine and fentanyl: (1) the unit dose of the more preferred drug was decreased by ½ log (i.e., cost increased); and (2) the unit dose of the less preferred drug was increased by ½ log (i.e., cost decreased). For instance, if a rat self-administered more of methamphetamine (0.1 mg/kg/infusion) than fentanyl (0.0032 mg/kg/infusion), the unit dose of methamphetamine was decreased (0.032 mg/kg/infusion methamphetamine vs. 0.0032 mg/kg/infusion fentanyl) or the unit dose of fentanyl was increased (0.1 mg/kg/infusion methamphetamine vs. 0.01 mg/kg/infusion fentanyl). The order of these dose manipulations was quasi-random, with each condition maintained for 7 sessions.

Extinction and Reinstatement

Upon completion of the dose manipulation studies, responding on both levers was extinguished and a series of reinstatement tests were conducted in order to determine the pattern of reinstatement behavior in rats with a history of concurrent access to methamphetamine and fentanyl. These tests included: (1) reintroduction of both the methamphetamine- and fentanyl-associated stimuli (cue-induced reinstatement); and (2) drug primes with methamphetamine (0.32 mg/kg; IV), fentanyl (0.032 mg/kg; IV), or ketamine (3.2 mg/kg; IV), administered 5 min before the start of a test session. Briefly, under extinction conditions, discriminative stimuli for both drugs were omitted and completion of response requirements on either lever had no programmed consequences (i.e., no infusions or infusion-paired stimuli were delivered). Extinction conditions remained in place for at least 7 sessions, and until the total number of lever responses on both levers was ≤15% of baseline responding. Once extinction criteria were met, a series of 4 reinstatement tests were performed as described previously (37, 44). Briefly, reinstatement tests were identical to self-administration conditions with the exceptions that: (1) intravenous pretreatments of saline (cue-induced reinstatement) or drug (cue + drug-primed reinstatement) were administered 5 min before the session; (2) sample trials were omitted from the session; and (3) completion of response requirements resulted in the delivery of a saline infusion in conjunction with the methamphetamine- or fentanyl-associated stimuli. Both sets of discriminative stimuli and conditioned stimuli were present in all reinstatement tests. Cue-induced reinstatement always occurred first followed by three additional cue + drug-primed reinstatement tests. Cue + drug-primed tests occurred in a quasi-random order, with each reinstatement test separated by at least two extinction sessions; additional extinction sessions were conducted until the extinction criterion was met.

Data Analysis

All data are presented as the mean ± S.E.M. For dose-substitution studies, the percent choice of 0.1 mg/kg/infusion of methamphetamine is shown as a function of fentanyl dose (or saline) whereas the percent choice of 0.0032 mg/kg/infusion of fentanyl is shown as a function of methamphetamine dose (or saline). Data represent the average of the final three sessions of each dose-substitution period and were analyzed *via* a mixed-effects repeated measure one-way analysis of variance (ANOVA) and *post-hoc* Dunnett's test comparing the percent drug choice at each dose available vs. when saline is available. Extinction data were analyzed via a two-way repeated measure ANOVA (factors being time and lever) and *post-hoc* Dunnett's test comparing the number of responses on each lever relative to the first day of extinction. Similarly, data from reinstatement tests were analyzed via a mixed-effects two-way repeated measure ANOVA (factors being pretreatment and lever) and *post-hoc* Dunnett's test when comparing responding on each lever to extinction responding, and Bonferroni's test when comparing allocation of responding on each lever produced by each pretreatment.

RESULTS

Acquisition and Single-Drug Access

All rats provided access to methamphetamine (0.1 mg/kg/infusion) met acquisition criteria by the 7th session (**Figure 1**; upper left), and methamphetamine intake was

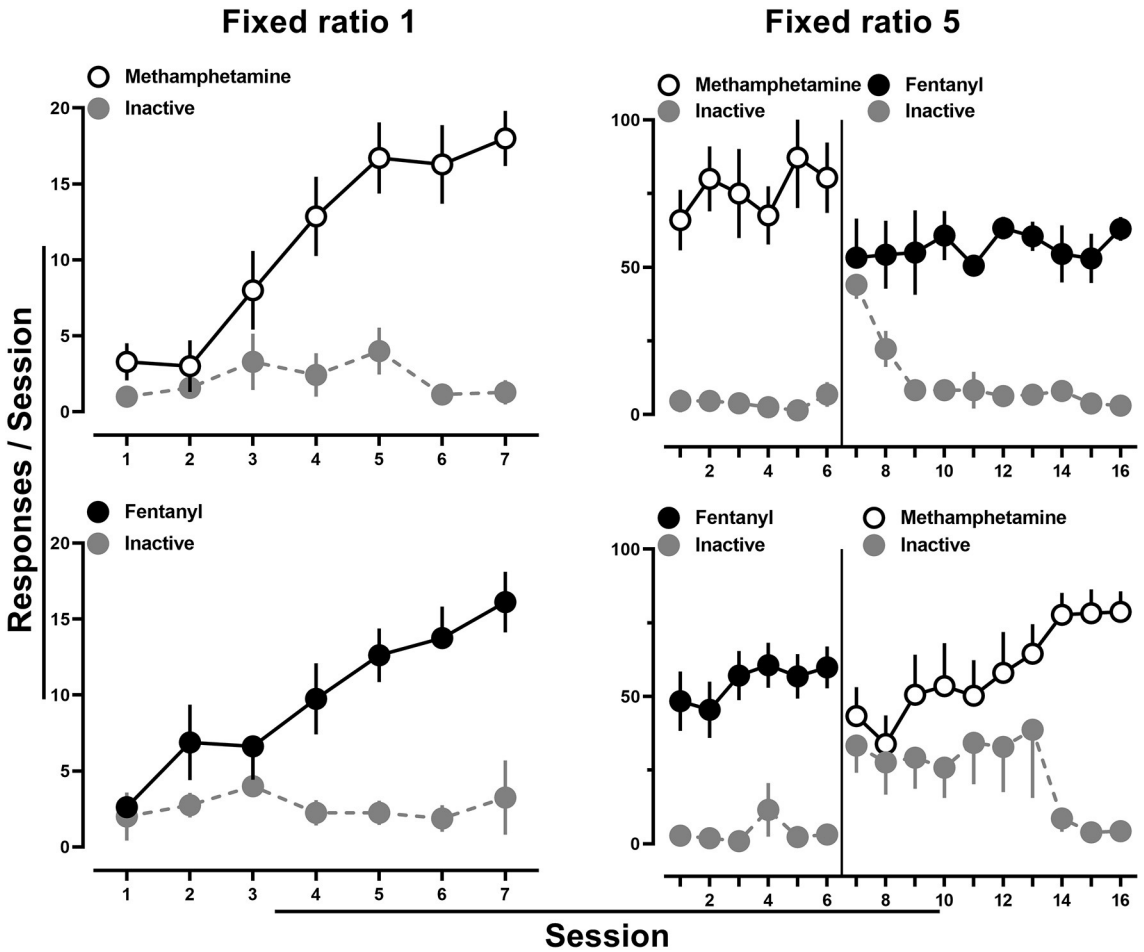

FIGURE 1 | Number of active and inactive lever responses throughout the 7-day acquisition period for methamphetamine (0.1 mg/kg/infusion) (upper left) or fentanyl (0.0032 mg/kg/infusion) (lower left). Subsequent responding under a fixed ratio five schedule of reinforcement for methamphetamine and when fentanyl was substituted on the previously inactive lever (upper right). Similarly, responding under a fixed ratio five schedule of reinforcement for fentanyl followed by methamphetamine substitution on the previously inactive lever (lower right). The solid line represents when the alternate drug and drug-paired stimuli were made available on the alternate lever. Data represent the mean ± S.E.M., and each point represents 7–8 rats.

maintained upon increasing the fixed ratio to 5 (**Figure 1**; upper right). When fentanyl (0.0032 mg/kg/infusion) was then introduced and made available for responding on the previously inactive lever, rats readily reallocated their responding to this lever, with nearly exclusive responding on the now fentanyl-reinforced lever observed by the end of 10 sessions (**Figure 1**; upper right). Similarly, acquisition criteria were met in all rats provided access to fentanyl (0.0032 mg/kg/infusion) (**Figure 1**; lower left), and intake was maintained upon increasing the fixed ratio to 5 (**Figure 1**; lower right). When methamphetamine (0.1 mg/kg/infusion) was next introduced and made available for responding on the previously inactive lever, rats readily reallocated responding to this lever, with nearly exclusive responding on the methamphetamine lever observed by the end of 10 sessions (**Figure 1**; lower right). Throughout this period, there were no apparent differences in drug intake as a function of the catheter through which drug was infused.

Concurrent Access

Subsequently, rats were provided access to methamphetamine (0.1 mg/kg/infusion) and saline, fentanyl (0.0032 mg/kg/infusion) and saline, or methamphetamine (0.1 mg/kg/infusion) and fentanyl (0.0032 mg/kg/infusion), in a pseudorandom order. When methamphetamine and saline (**Figure 2**; left) or fentanyl and saline (**Figure 2**; middle) were concurrently available, responding was nearly exclusively allocated toward the lever that was reinforced by drug by the end of the 7 sessions. In contrast, when the training doses of methamphetamine and fentanyl were available concurrently, responding, at the group level, occurred at comparable levels on both the methamphetamine- and fentanyl-reinforced levers (**Figure 2**; right). Upon examination of individual subject data, three general patterns of responding were observed. One group ($n = 6$) of rats tended to respond nearly exclusively for either methamphetamine ($n = 2$) or fentanyl ($n = 4$) over the course of the seven sessions (**Figure 3**; left; representative

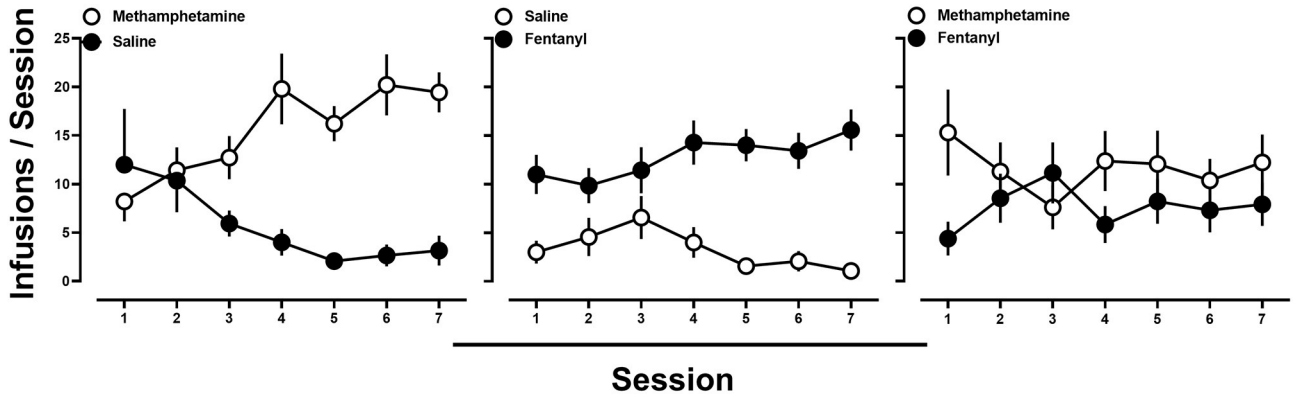

FIGURE 2 | (Left) Average number of infusions of 0.1 mg/kg/infusion methamphetamine (open circles) and saline (filled circles) when methamphetamine and saline were concurrently available. **(Middle)** Average number of infusions of 0.0032 mg/kg/infusion fentanyl (filled circles) and saline (open circles) when fentanyl and saline were concurrently available. **(Right)** Average number of infusions of 0.1 mg/kg/infusion of methamphetamine (open circles) and 0.0032 mg/kg/infusion of fentanyl (filled circles) when methamphetamine and fentanyl were concurrently available. Data represent the mean ± S.E.M., and each point represents 14–15 rats.

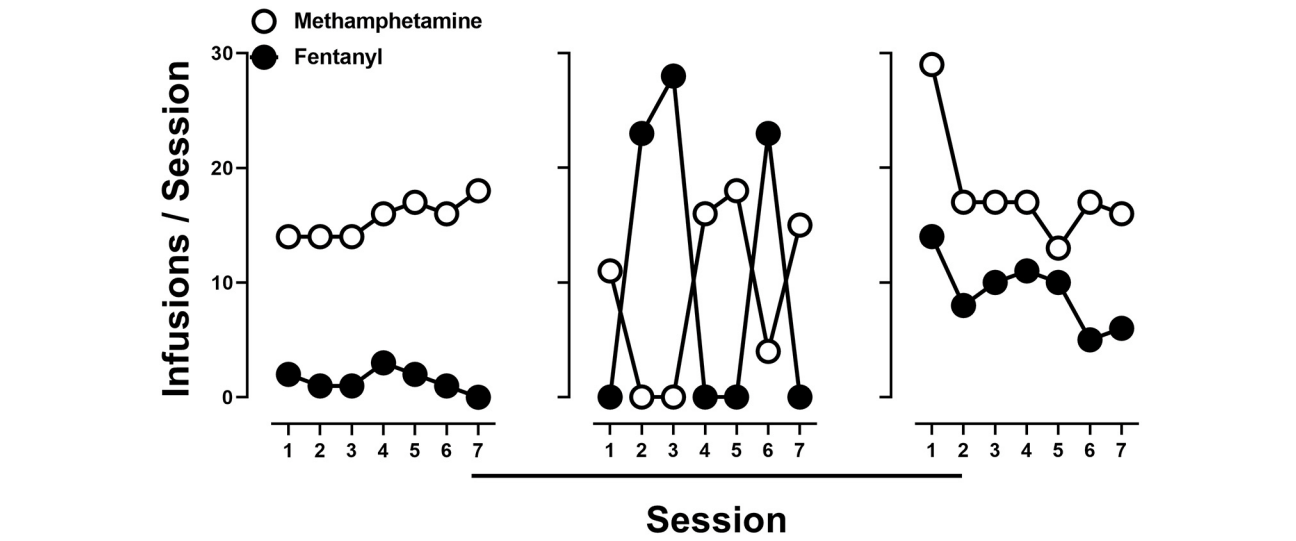

FIGURE 3 | Number of infusions of 0.1 mg/kg/infusion of methamphetamine (open circles) and 0.0032 mg/kg/infusion of fentanyl (filled circles) when methamphetamine and fentanyl were concurrently available in representative rats demonstrating different patterns of drug intake.

rat), whereas another subset of rats ($n = 3$) tended to exhibit exclusive responding for one drug, but preference for methamphetamine or fentanyl alternated across days (**Figure 3**; middle; representative rat), and the remaining rats ($n = 5$) consistently responding for both methamphetamine and fentanyl across each of the seven sessions (**Figure 3**; right; representative rat).

Dose Substitution

To evaluate economic interactions between methamphetamine and fentanyl, the cost of one drug was either increased (unit dose decreased) or decreased (unit dose increased) while the cost of the alternative drug remained fixed. When the cost of methamphetamine remained constant, choice of methamphetamine increased as the cost of fentanyl increased (i.e., rats chose 0.1 mg/kg/infusion methamphetamine over 0.001 mg/kg/infusion fentanyl) (**Figure 4**; left). A significant effect of dose [$F_{(2,17.7)} = 11.2$; $p < 0.0001$] was revealed by a one-way repeated measure ANOVA, with *post-hoc* tests indicating that choice of methamphetamine was significantly reduced when either 0.0032 mg/kg/infusion (48.4%) or 0.01 mg/kg/infusion (33.6%) of fentanyl was made concurrently available, as compared to when methamphetamine and saline were concurrently available (91.9%). Similarly, when the cost of fentanyl remained constant (FR5 for 0.0032 mg/kg/infusion), choice of fentanyl increased as the cost of methamphetamine increased (i.e., rats chose 0.0032 mg/kg/infusion fentanyl over 0.032 mg/kg/infusion methamphetamine) (**Figure 4**; right). A significant effect of dose [$F_{(2.5,21.5)} = 12.4$; $p < 0.0001$] was revealed by a one-way repeated measure ANOVA, with *post-hoc*

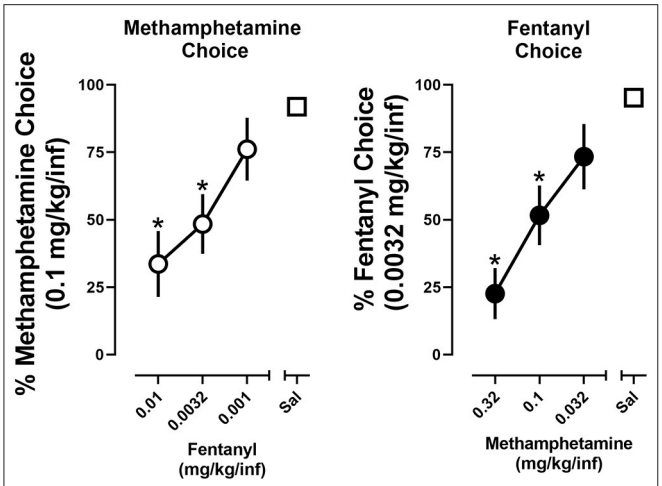

FIGURE 4 | Percent choice of 0.1 mg/kg/infusion of methamphetamine as a function of concurrently available fentanyl dose (or saline) **(left)**. Percent choice of 0.0032 mg/kg/infusion of fentanyl as a function of concurrently available methamphetamine dose (or saline) **(right)**. Data represent the mean ±S.E.M. Each point represents 8–12 rats. Asterisks represent a significant decrease from saline ($p < 0.05$).

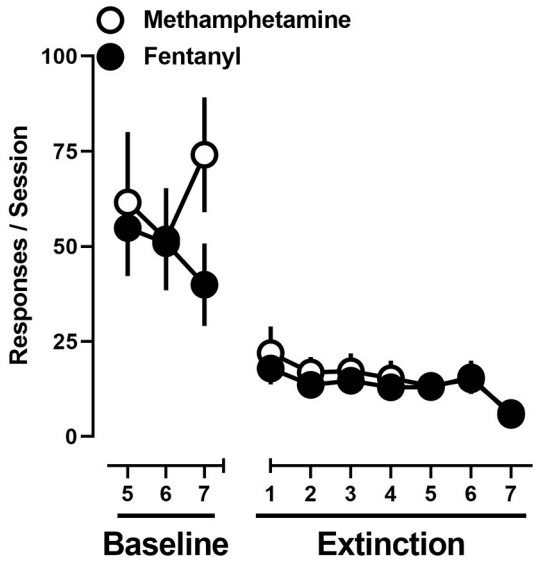

FIGURE 5 | Responses made on the methamphetamine (open circles) and fentanyl (filled circles) levers on the final 3 days of concurrent access to methamphetamine and fentanyl self-administration, and extinction conditions. Data represent the mean ± S.E.M., and each point represents 12 rats.

tests indicating that choice of fentanyl was significant reduced when either 0.1 mg/kg/infusion (51.6%) or 0.32 mg/kg/infusion (22.6%) of methamphetamine was made concurrently available, as compared to when fentanyl and saline were concurrently available (95.2%).

Extinction and Reinstatement

Under baseline conditions in which rats were provided concurrent access to 0.1 mg/kg/infusion methamphetamine and 0.0032 mg/kg/infusion of fentanyl, responding, at the group level, was allocated toward both levers. Upon instituting extinction conditions, responding on levers previously reinforced by methamphetamine or fentanyl decreased across sessions with extinction criteria met on day 6 ± 0.8. A two-way repeated-measure ANOVA revealed that there was no significant difference in extinction of responding on the methamphetamine and fentanyl levers [$F_{(1,11)} = 0.26$; $p > 0.05$], nor a main effect of time [$F_{(2.3,24.9)} = 2.8$; $p = 0.08$] (**Figure 5**).

After extinction criteria were met, a series of reinstatement tests were conducted. Reintroduction of drug-paired cues produced 95 ± 18 responses on the methamphetamine lever and 58 ± 14 responses on the fentanyl lever. When drug-paired cues were reintroduced in conjunction with a priming injection of methamphetamine, a greater number of responses occurred on the methamphetamine lever (247 ± 51) relative to the fentanyl lever (120 ± 28). The opposite was true when a priming injection of fentanyl was administered, with more responding being produced on the fentanyl lever (41 ± 9) than the methamphetamine lever (22 ± 9). Ketamine produced the fewest number of responses, with 13 ± 3 and 9 ± 3 responses being made on the methamphetamine and fentanyl levers, respectively (**Figure 6**; left).

A two-way repeated measures ANOVA revealed no significant main effect of lever [$F_{(1,11)} = 4$; $p > 0.05$], but a significant main effect of drug primes [$F_{(1.3,14.1)} = 29.3$; $p < 0.0001$] and a significant interaction between lever and drug primes [$F_{(1.2,13.2)} = 5.5$; $p < 0.05$]. *Post-hoc* analyses indicated that reintroduction of drug-paired cues significantly increased responding on both the methamphetamine and fentanyl levers ($p < 0.05$), relative to the final day of extinction. Similarly, drug-paired cues in conjunction with a prime with methamphetamine significantly increased responding on both the methamphetamine and fentanyl levers ($p < 0.05$), relative to the final day of extinction. In contrast, a priming injection of fentanyl significantly increased responding on the fentanyl, but not methamphetamine, lever, relative to the final day of extinction. No significant increases in responding were observed following primes with ketamine. When comparing total responding on each lever as a function of pretreatment, there were no significant differences in the number of responses on each lever within each reinstatement test (**Figure 6**; left).

When analyses were restricted to the first ten ratios completed, reintroduction of drug-paired cues resulted in similar allocation of responding, resulting in 60% of ratios completed on the methamphetamine lever and 40% completed on the fentanyl lever. In contrast, a priming injection of methamphetamine shifted this ratio, resulting in 75% of the first 10 completed ratios completed on the methamphetamine lever, and 25% completed on the fentanyl lever. A priming injection of fentanyl produced more completed ratios on the fentanyl lever (81%) relative to the methamphetamine lever (19%). A two-way repeated measures

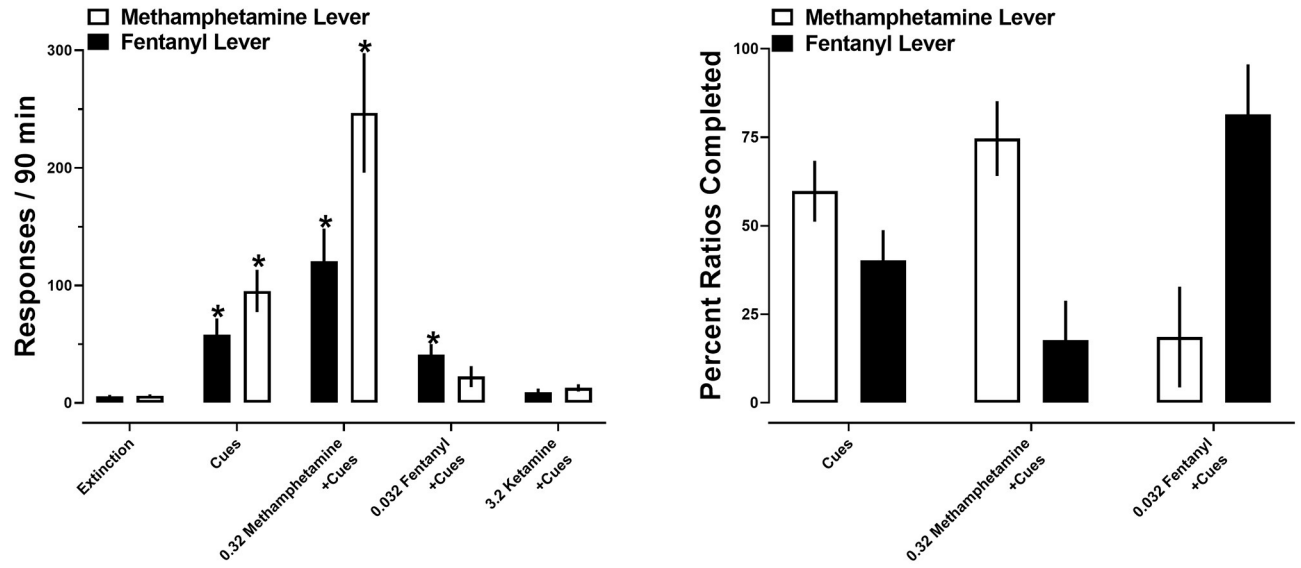

FIGURE 6 | (Left) Responses made on the methamphetamine (open bars) and fentanyl (closed bars) levers on the final day of extinction and during reinstatement tests. Asterisks represent a significant increase from extinction ($p < 0.05$). Each bar represents 12 rats. **(Right)** percent of the first 10 ratios completed on the methamphetamine (open bars) and fentanyl (closed bars) levers during reinstatement tests. Each set of bars represents 8–12 rats. All data represent the mean ± S.E.M.

ANOVA no main effects of lever [$F_{(1,54)} = 0.24$; $p > 0.05$] or drug primes [$F_{(1,27)} = 0.09$; $p > 0.05$] (**Figure 6**; right).

DISCUSSION

Polysubstance use involving methamphetamine and fentanyl is common within substance using populations, yet little is known about the pharmacological and behavioral factors that drive this growing threat to public health. The current studies established a concurrent access self-administration procedure to model the co-use of methamphetamine and fentanyl in rats and to determine economic interactions between methamphetamine and fentanyl and how a history of concurrent access to both drugs impacts relapse-related behaviors. There were 3 main findings: (1) when rats were provided concurrent access to methamphetamine and fentanyl, responding for methamphetamine and fentanyl was comparable at the group level; however, at the individual subject level different patterns of drug-taking were observed with some rats responding on both reinforced levers whereas others exhibited exclusive choice of one drug; (2) methamphetamine and fentanyl acted as imperfect substitutes, that is to say, when the cost of one drug was increased, responding was largely, but not exclusively, reallocated toward the fixed cost alternative, and when the cost of one drug was decreased responding was largely, but not exclusively, reallocated toward the now cheaper alternative; and (3) reintroduction of the drug-paired cues reinstated responding on both the methamphetamine and fentanyl levers whereas drug-paired cues in conjunction with priming injections of methamphetamine or fentanyl produced responding that was largely allocated toward the levers previously reinforced by methamphetamine or fentanyl, respectively. Taken together, these data suggest that methamphetamine and fentanyl can act as imperfect substitutes and increase the breadth of conditions that produce relapse-related behaviors.

Rats provided concurrent access to methamphetamine and fentanyl exhibited different patterns of intake. Although a subset of rats responded exclusively for methamphetamine or fentanyl across the 7-day testing block, the majority of rats responded for both methamphetamine and fentanyl, albeit in slightly different manners. Some rats alternated exclusive responding for either methamphetamine or fentanyl across days, whereas the remaining rats maintained concurrent methamphetamine and fentanyl intake within each session. The prevalence of rats responding for both methamphetamine and fentanyl in the current studies is in stark contrast to what was observed when rats are provided concurrent access to two drugs from the same class, MDPV and cocaine (37). In those studies, MDPV and cocaine acted as economic substitutes with nearly exclusive choice occurring in all subjects and determined by the relative cost of each drug. Rats oftentimes responding for both methamphetamine and fentanyl in the current studies mirrors reports of human drug users preferring to use stimulant and opioids together rather than in isolation. Indeed, concurrent use of methamphetamine and opioids has been reported to produce an enhanced euphoria or, "high" while circumventing the unwanted side effects of each drug, and aid in forestalling opioid withdrawal (9), suggesting a potentially synergistic interaction between the two drugs. Preclinical models, such as the concurrent access procedure employed herein, capable of elucidating the factors contributing to these different patterns of intake will result in a better understanding of the human condition and ultimately aid in the development

of more effective therapeutic strategies for those engaged in polysubstance use.

In addition to simply evaluating patterns of intake, concurrent access procedures allow for the economic analyses of the interactions between co-used drugs (e.g., substitutes, complements, or independents) which can provide additional insights into the reinforcing effects of each drug under situations more closely related to polysubstance use (35, 36). In the current studies, when rats were provided concurrent access to varying intravenous doses of methamphetamine and fentanyl (i.e., the cost of each drug was manipulated in the presence of the training dose of the alternative), more responding was allocated toward the cheaper alternative, however, responding tended not to be exclusive, suggesting that stimulants and opioids appear to function as imperfect substitutes. This is in contrast to the largely exclusive choice that was observed when two drugs of the same class, MDPV and cocaine, were concurrently available (37) and suggests that although cost might largely dictate choice of methamphetamine or fentanyl, there are other contributors to drug choice when a stimulant and opioid are concurrently available (e.g., a possible synergistic interaction between the two drugs). One consideration regarding the interpretation of these data is that for this initial study, varying doses of each drug were evaluated only when the training dose of the other drug was concurrently available. Regardless, methamphetamine and fentanyl acting as substitutes in the current studies support previous work demonstrating poorer treatment outcomes for individuals suffering from polysubstance use disorder (15, 16, 42). For instance, if an individual using stimulants and opioids is effectively treated for their opioid use disorder, but continues to use stimulants, it is possible that the ongoing use of stimulants could increase the likelihood of relapse to opioid-taking, thereby paving the way for a return to regular polysubstance use (15). Although a more thorough evaluation of doses will need to be completed in both male and female subjects in order to more fully define the nature of the economic interactions between methamphetamine and fentanyl, the present data suggest that methamphetamine and fentanyl act as imperfect substitutes, likely contributing to the high prevalence of co-use of these two drugs either together, or in place of one another.

Although available evidence from treatment-seeking individuals suggest that polysubstance use is associated with poorer treatment outcomes, including higher rates of relapse and overdose (15, 16), relatively few preclinical studies have investigated relapse-related behaviors in the context of polysubstance use. In the current studies, reintroduction of drug cues previously associated with concurrent access to methamphetamine and fentanyl reinstated responding on both levers to a similar degree. Although methamphetamine- and fentanyl-primed reinstatement increased responding on both drug-paired levers, more responding was allocated to the lever associated with the priming drug administered. This is consistent with what has been observed in reinstatement studies wherein rats have a history of self-administering cocaine and heroin (49). Analysis of the first ten ratios that were completed in reinstatement tests demonstrated that when drug-paired cues were reintroduced alone, the first ten ratios completed were equally distributed across both methamphetamine and fentanyl levers on the group level, the result of all rats responding on both levers to varying degrees. In contrast, a pretreatment with methamphetamine or fentanyl resulted in a larger number of ratios being completed on the lever associated with methamphetamine or fentanyl, respectively. Our laboratory has recently demonstrated that reintroduction of drug-paired cues alone, as well as in conjunction with primes of MDPV, cocaine, or methamphetamine, produced responding on both drug paired levers in rats with a history of concurrent MDPV and cocaine self-administration, with more responding generally occurring on the cocaine-paired lever, regardless of priming drug or drug preference (37). Analyses of the first ten ratios completed during reinstatement tests reveal subtle differences in reinstatement behavior when drugs previously self-administered belong to the same class, or different classes. The initial ratios completed in MDPV- or cocaine-primed reinstatement tests in subjects having a history of concurrent MDPV and cocaine self-administration were largely allocated toward the previously reinforced cocaine lever, regardless of which drug was administered or the drug preference of a given subject. However, the current studies demonstrate that methamphetamine- or fentanyl-primed reinstatement results in the initial ten ratios largely being completed on the lever associated with the priming drug, in subjects having a history of concurrent methamphetamine and fentanyl self-administration. Importantly, in the current studies, a drug with non-overlapping discriminative stimulus effects with methamphetamine or fentanyl, in this case ketamine, did not increase responding greater than that produced by cues alone. This is not altogether surprising given the concordance between drug discrimination and drug-primed reinstatement. Indeed, in rats trained to discriminate two drugs on different operanda, administration of a compound producing non-overlapping discriminative stimuli with either training drug can result in a lack of responding (50–52). It is also possible that the dose of ketamine was sufficient to suppress responding, however, rats will self-administer this unit dose of ketamine, with total levels of ketamine intake in excess of 40 mg/kg during a 90-min session (53, 54). These findings support a primary role for discriminative stimulus effects in drug-primed reinstatement, but also suggest that a history of concurrent self-administration of drugs from different classes (e.g., methamphetamine and fentanyl) may degrade the specificity of drug-primed reinstatement of responding. Although this notion is supported by the current studies, additional studies are needed to more fully characterize the consequences of co-use of methamphetamine and fentanyl on reinstatement behavior, including the evaluation of a larger range of priming doses, and evaluating reinstatement behavior following priming injections of mixtures of methamphetamine and fentanyl. Taken together, these data suggest that environmental and pharmacological stimuli associated with the use of a particular substance (e.g., a spoon and syringe for heroin, or a glass pipe for methamphetamine) might trigger a more general drug-seeking

response in individuals with a history of polysubstance use, rather than a more specific desire to use the substance associated with those stimuli.

Despite the growing awareness that polysubstance use is the norm rather than the exception, the vast majority of preclinical substance use research continues to focus on the effects of individual drugs, studied in isolation. The current studies established a concurrent access self-administration procedure to investigate interactions between the reinforcing effects of methamphetamine and fentanyl and found them to function as imperfect substitutes with at least three different patterns of drug-taking emerging when both drugs were concurrently available. This is in contrast to what is observed when rats are provided concurrent access to two stimulants (37), but consistent with reports from polysubstance users that suggest that concurrent co-use of stimulants and opioids is preferable to the use of either drug alone (9, 12). Although reintroduction of both sets of drug-paired stimuli would be expected to reinstate responding on both the methamphetamine and fentanyl levers, that priming injections of methamphetamine or fentanyl also increased responding on both levers was somewhat unexpected and suggests that environmental and pharmacological stimuli may have a more general, but complex, influence on relapse-related behaviors in polysubstance users. These studies lay the groundwork for a deeper evaluation of the interactions between the reinforcing effects of methamphetamine and fentanyl using drug-vs.-drug choice. For instance, previous studies from our laboratory and others have demonstrated that the reinforcing effects of opioids, but not stimulants, are enhanced when subjects are in a state of opioid withdrawal (47, 55, 56). However, the degree to which opioid withdrawal would impact preference for and/or economic interactions between methamphetamine and fentanyl is an important and underexplored aspect of the current epidemic of polysubstance use.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The animal study was reviewed and approved by Institutional Animal Care and Use Committee at the University of Texas Health Science Center at San Antonio.

AUTHOR CONTRIBUTIONS

RS and GC contributed to study design and wrote the manuscript. RS and CL conducted behavioral experiments. RS performed data analysis. All authors critically reviewed content and approved final version for publication.

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Patterns of and Rationale for the Co-use of Methamphetamine and Opioids: Findings From Qualitative Interviews in New Mexico and Nevada

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Introduction: Methamphetamine use and methamphetamine-involved deaths have increased dramatically since 2015, and opioid-related deaths now frequently involve methamphetamine. Nevada and New Mexico are states with elevated rates of opioid and methamphetamine use. In this paper, we report results from a qualitative analysis that examined patterns of methamphetamine and opioid co-use over participants' lifespan, factors that influence those patterns, and implications for health outcomes among users.

Methods: Project AMPED was a multisite, mixed-methods study of methamphetamine use in Northern New Mexico and Northern Nevada. Between December 2019 and May 2020, qualitative interview participants were asked to describe their patterns of and reasons for co-administration of opioids and methamphetamine.

Results: We interviewed 21 people who reported using methamphetamine in the past 3 months. Four primary patterns of methamphetamine and opioid co-use were identified: [1] using both methamphetamine and heroin, either simultaneously or sequentially ($n = 12$), [2] using methamphetamine along with methadone ($n = 4$), [3] using prescription opioids and methamphetamine ($n = 1$), and [4] using only methamphetamine ($n = 4$). Among those who used methamphetamine and heroin simultaneously or sequentially, motivations drew from a desire to enhance the effect of one drug or another, to feel the "up and down" of the "perfect ratio" of a goofball, or to mitigate unwanted effects of one or the other. Among those who used methamphetamine and methadone, motivations focused on alleviating the sedative effects of methadone.

Conclusion: To address the emergent trend of increasing methamphetamine-related deaths, researchers, health care professionals, and community health workers must acknowledge the decision-making processes behind co-use of opioids and methamphetamine, including the perceived benefits and harms of co-use. There is an

urgent need to address underlying issues associated with drug use-related harms, and to design interventions and models of treatment that holistically address participants' concerns.

Keywords: methamphetamine, opioid, rural, injecting drug use, drug smoking, Western U.S

INTRODUCTION

On the heels of the 21st-century opioid overdose death crisis in the United States, a "fourth wave" of drug overdose deaths has emerged (1). Methamphetamine use and methamphetamine-involved deaths have increased dramatically, and opioid-related deaths now frequently involve multiple drugs, including methamphetamine (2–4). Some authors have discussed this phenomenon as a "twin epidemic" of opioid and methamphetamine-involved morbidity and mortality (5).

While recent surveillance data have focused national attention on the co-administration of opioids and methamphetamine, this phenomenon is not new. One of the most well-known patterns of co-administration, the simultaneous administration of heroin and methamphetamine in a single injection, colloquially referred to as a goofball, has been documented in numerous cities in the US and Mexico, principally in the West, since at least 2000 (6–9). More recent data suggest that the prevalence of this behavior may be increasing. For example, a 2019 study of syringe exchange program (SSP) clients in Seattle, Washington mentioned that 55% of participants reported using a goofball in the last three months, and the prevalence of reporting goofball as one's main drug increased from 10% in 2017 to 20% in 2019 (10). A 2017 study using National HIV Behavioral Surveillance (NHBS) data from Denver, Colorado, found that 28% of the sample reported using goofballs, 43.9% reported using heroin and methamphetamine separately, and 24% reported doing both (11). Demographic correlates of methamphetamine and opioid co-administration include younger age (9–11), experiencing homelessness (10–12), and recent incarceration (10).

Another common pattern of combining opioids and methamphetamine is the use of methamphetamine while using methadone (13–15). Globally, methadone maintenance therapy (MMT) is a predominant form of medication for opioid use disorder and it has been shown to help reduce injecting drug use, syringe sharing, engaging in risky sexual behaviors, and overall, the chances of HIV acquisition (13, 15, 16). In Iran, opioids are among the most frequently used substances, but methamphetamine has gained popularity. In 2013, Shariatirad et al. (17) documented co-use of methamphetamine among men enrolled in a methadone maintenance program; men said they did this to counter the sedative effects of the methadone, improve sexual performance, and increase energy. Finally, an Iranian study with women enrolled in a methadone program also reported frequent co-use of methamphetamine and heroin kerack (a high-purity synthetic heroin available locally), with 82/119 women (68%) reporting co-use (18). In a Chinese study, 13% of methadone clinic patients tested positive for methamphetamine and 9% tested positive for morphine and methamphetamine; methamphetamine use was associated with being on a higher dose of methadone (19).

The co-administration of methamphetamine and opioids, whether simultaneously or sequentially, can have important implications for the health and well-being of people who use drugs (PWUDs). This includes increased risk for overdose (6, 9, 11), and syringe sharing (9–11), which in turn increases the risk for bloodborne pathogen transmission (i.e., HIV, HCV) and soft tissue infections (10). In a study conducted in Denver, Colorado, participants who reported sequential use of heroin and methamphetamine more frequently reported an overdose in the past year, compared to those who reported injecting goofballs (38.9% vs. 20.7%) (11). Injecting both heroin and methamphetamine (vs. injecting only heroin) was associated with a 2.8 fold increase in the risk of past year overdose. In Seattle, Washington, participants who injected goofballs reported several high-risk injection behaviors, including neck injection, more frequent injection, public injection, and sharing injection equipment (10).

Less is known about how methamphetamine and opioid co-administration has evolved in other areas, including more rural Western states. Nevada and New Mexico are two mostly rural Mountain West states with elevated rates of opioid-related overdose death and prevalent methamphetamine use (3). Northern New Mexico, in particular, has had a long history of elevated opioid overdose deaths, a trend that preceded the current opioid overdose crisis across the US, and which has been characterized as a multigenerational phenomenon (20). Recently, however, anecdotal reports from harm reduction providers suggested that people who historically used heroin were initiating methamphetamine use. Nevada has also consistently ranked in the top quartile of opioid overdose deaths in the US, and the per capita rate of methamphetamine use was highest in the nation in 2018 (21). The objective of this paper was to identify and characterize patterns of methamphetamine and opioid co-use over participants' lifespan and to examine motivations and rationale for co-use (4). Implications of findings on better addressing the escalating overdose crisis and reducing harm related to methamphetamine and opioid use are discussed.

MATERIALS AND METHODS

Recruitment and Data Collection

Data for the current study were collected as part of a larger sequential mixed-methods study (22). Between December 2019 and February 2020, we recruited people who use methamphetamine in Reno, Nevada and Rio Arriba County, New Mexico. Reno is a small city in northwest Nevada (population 250,000), located approximately 20 miles from the California border and 440 miles from Las Vegas in the

southern part of the state. Rio Arriba County (population 40,000) is located in the north-central part of New Mexico, bordering Colorado. The closest major city is Santa Fe (∼25 miles; population 84,000). Recruitment used a combination of street and agency-based outreach. This includes in-house recruitment at harm reduction/syringe services programs and street-based outreach in which outreach workers visited areas where PWUD congregate (e.g., homeless encampments, bus stations) to distribute flyers and inform people about the study. Three of the seven authors participated in outreach activities. We also conducted chain-referral recruitment through existing participants. Inclusion criteria were age 18 years and older and self-reported methamphetamine use in the past 3 months.

Trained qualitative interviewers used a loosely structured interview guide, which began with broad questions about the respondents' drug use, including reasons for using methamphetamine, current drug use patterns, and changes over time. Most relevant to the current analysis, we asked respondents to describe the context of their methamphetamine use, how their use began and how it has changed over time, how and when they use methamphetamine with or without other drugs, and what benefits and what drawbacks or negative experiences they are deriving from their methamphetamine use. Interviews were conducted in private or semi-private locations that were acceptable to the participants. Data were collected in English or Spanish, depending on participants' preferences. Written informed consent was obtained from all participants. A US$30 compensation was provided to all those who consented. All study activities were approved by the University of Nevada, Reno (UNR) Institutional Review Board (IRB). The University of New Mexico (UNM) IRB deferred oversight to the UNR IRB under a single IRB agreement.

Analysis

Interviews were digitally recorded and transcribed verbatim for analysis. After conducting a quality assurance review and redaction of the transcripts, data were analyzed using an inductive thematic approach. An MPH-level analyst reviewed all the transcripts and began by making a series of memos documenting the drug use history and patterns reported by each respondent, including types of drugs used and routes of administration. Those memos were discussed with a study PI, a Ph.D.-level mixed methods researcher with 20 years of qualitative research experience, and together they began identifying dominant patterns of opioid and methamphetamine co-administration, based on the type of drug, timing, and route of administration of each drug. We categorized participants into mutually-exclusive groups that were based on the participants' most common pattern of co-administration. This was determined in one of two ways: [1] The participants stated a distinct preference, or [2] They talked predominantly about one pattern of drug use. For the purpose of this analysis, we have excluded 4 individuals who only used methamphetamine and focused only on those who report co-use of opioids and methamphetamine. Then, the analyst developed a set of codes that identified the rationale for using that way and perceived benefits and harms associated with each drug and route of administration. These codes were then systematically applied to each transcript. After an initial round of coding, the coded transcripts were reviewed and discussed with the PI, and codes were further defined and refined, while memos were expanded to include a description of each pattern. Finally, the analyst and the study PI discussed the output from the coding and identified illustrative quotes. Quotes are provided using respondent ID, ethnicity, race, sex, age, and location of the interview.

RESULTS

We examined patterns of co-use of opioids and methamphetamine among a sample of 21 participants from Northern Nevada ($n = 11$) and Northern New Mexico ($n = 10$). Respondents were 48% female and 40% Latinx. The median age was 35 years (IQR: 30–43). Just under half (48%) reported being homeless and 38% were employed full or part-time.

Seventeen of the 21 respondents (81%) reported co-administration of opioids and methamphetamine (four reported only using methamphetamine and were excluded from this analysis, as described above). We categorized participants into three primary groups of methamphetamine and opioid co-use patterns and identified patterns within each group. The groups include using: [1] both methamphetamine and heroin, either simultaneously or sequentially ($n = 12$); [2] methamphetamine and methadone ($n = 4$); [3] prescription opioids and methamphetamine ($n = 1$). However, it is important to note that most people had long-term histories of substance use and moved back and forth between different patterns of co-use within a given timeframe, so many people provided data about different patterns throughout their interviews. For example, Participant 4, a Hispanic/Latino Black/African American man in his 40's from New Mexico, began his drug use career snorting heroin. Subsequently, he switched to smoking heroin and began injecting methamphetamine, then switched to smoking methamphetamine. Now he is on methadone and smokes a "steady amount" of methamphetamine. Accounts of the transitions between patterns were particularly informative when identifying the motivations or rationales for preferring one pattern over another, which are discussed in the Materials and Methods section.

Section 1: Patterns of Opioid and Methamphetamine Co-use

Group 1: Heroin and Methamphetamine

People whose preference was using methamphetamine and heroin represented the majority ($n = 12$; 71%) of our sample. Within that group, three sub-patterns were identified: simultaneous injection (i.e., "goofball") or injection and smoking both drugs in quick succession, injecting heroin and smoking methamphetamine at separate times, and injection use of both drugs at separate times.

Simultaneous Injection or Injection and Smoking Both Drugs in Quick Succession ("Goofballs")

"Goofballs" refers to the simultaneous use of methamphetamine and heroin. For most people, this meant combining

methamphetamine and heroin in the same syringe which, when optimized, creates the "best of both worlds." In the quote below, a respondent describes the "perfect ratio" that can be achieved. However, it is difficult for him to reliably achieve that perfect ratio, so he often uses them separately instead:

> "Me and my girlfriend, we had shots together. She likes it together. *You do it right, you get a perfect ratio, I mean you can feel both of them. You get the high and then the low and then the high and then low.* But most times, you get one that just overpowers the other and then [it's] pointless for me. So I've tried to do it separate[ly]." –Participant 7, Non-Hispanic, White Male, 20's, Nevada. [emphasis added]

Some people liked the feeling of combining the drugs but preferred to smoke the methamphetamine immediately after a heroin injection, rather than injecting both. For example,

> "I always said my favorite high would be shooting heroin and then smoking speed because you had energy, but you felt the effects of the heroin which I have always really liked." –Participant 14, Non-Hispanic, White Female, 70's, Nevada.

Injecting Heroin and Smoking Methamphetamine Separately

Others specifically sought to *avoid* the effects of combining the drugs simultaneously, describing the undesirable effects of using goofballs. For example,

> "I kind of feel like [a goofball] kills the euphoria from the heroin, so I would rather shoot the heroin and smoke the meth, like, something like that. [A goofball] just seems dangerous too. It's just consuming anything is bad enough, but shooting something, the two polar opposites. One's going up and down, your heart doesn't know what to do with it. I don't know which way to go. In my experience, they send me into kind of a psychotic break where I'm kind of screaming and lose all control." –Participant 8, Non-Hispanic, multi-racial Male, 20's, Nevada.

For participants like this man, injecting heroin and smoking methamphetamine at separate times was preferred. He goes on to describe how he moderates his methamphetamine use over time:

> "I want to say I control my limits with meth. It's not a daily thing anymore. After one or two days, I have to take a break because I just don't like going on days without sleep. It's just the mental side effects for me personally or just outrageous if [I'm] not careful with it." –Participant 8, Non-Hispanic, multi-racial Male, 20's, Nevada.

Injection of Both Drugs at Separate Times

Finally, some respondents preferred to inject both heroin and methamphetamine at separate times (i.e., not as a combined shot or 'goofball'). For example, Participant 3 described smoking methamphetamine as a "waste," and explains why he prefers to inject methamphetamine separately:

> "I do heroin and then do the meth and for some reason, it makes the heroin last longer, so you don't have to you know, you know what I mean? I don't know how or what. But that's for me anyways. I'd rather inject it… because when you smoke it, you waste some." –Participant 3, Hispanic/Latino Male, 30's, New Mexico.

Participant 10 usually preferred goofballs, but sometimes injects heroin and methamphetamine separately, depending on his mood (which was also described by others):

> I: Do you always mix them together or do you sometimes use [methamphetamine] separately?
> P: Sometimes, separate. Just depends on my mood.
> –Participant 10, Non-Hispanic, White Male, 30's, Nevada.

Group 2: Methamphetamine and Methadone

Three participants described occasional methamphetamine use while taking methadone as part of an OUD treatment program. These respondents had engaged in several cycles of OUD treatment (including both methadone and buprenorphine) and periods of returning to heroin use. While they were on methadone treatment, their methamphetamine use increased compared to when they were using heroin:

> "*Now, it seems that I've been on the methadone, I smoke so much meth now – more than I ever have.* I kind of think because the methadone gets you so tired, so down." … "What's amazing, to be honest with you, after I went on that trip, now that I smoke [meth], it's a whole different thing. I don't get high like that no more. Now, I'm normal. It just wakes me up a little. That's it. I don't trip. Thank God." –Participant 15, Hispanic/Latina Female, 40's, New Mexico. [emphasis added]

The "trip" that this participant refers to was an experience of injecting methamphetamine that led to undesirable hallucinations. After that experience, she switched to smoking methamphetamine, which for her does not result in the undesired psychiatric effects.

Two respondents also described ongoing and occasional heroin use, in addition to their methadone and methamphetamine use. Participant 16, who is taking methadone as part of a treatment program but also continues to use heroin, methamphetamine, and cocaine, described the circumstances that lead her to choose one stimulant over another:

> "With the coke, I guess, the coke is like if I just wanted a real quick wake up, just to wake up real quick. Then the meth, if I have a few things I have to do for like the next few days, it'll keep me up for the next few days and keep me going. So [meth] kind of gives the energy too a little bit more than the coke." –Participant 16, Hispanic/Latina, Black/African American Female, 20's, New Mexico.

Group 3: Methamphetamine and Prescription Opioids

In one case, a respondent started her drug use with heroin and transitioned to buying prescription opioids on the street once she settled down and started a family with her husband. The switch to prescription opioids (in pill form) was precipitated by a desire to reduce the harms associated with heroin use. Subsequently, her husband introduced her to methamphetamine. They started by

smoking methamphetamine but switched to injecting because it is easier to hide from other family members.

Section 2: Motivations or Rationales: Pain, Pleasure, Function, Social Context, and Drug Availability

We identified three primary groups of opioid and methamphetamine co-users. Within each group, sub-patterns were described based on timing and route of administration of the drugs. Several factors influenced how participants made decisions about their preferred route of administration (i.e., injection vs. smoking) and sequence of co-administration, which we categorize into five themes: avoiding pain or discomfort, seeking pleasure, responding to social context, responding to drug availability, and achieving functional effects.

Avoiding Pain or Discomfort

Strategies to avoid pain or discomfort largely focused on the route and sequence of administration of opioids and methamphetamine, but also included using one drug or another to address specific pains or discomforts. For example, some people combined heroin and methamphetamine into a single goofball injection because they wanted to avoid the vein pain associated with multiple injections. For example, Participant 6 described a burning sensation associated with methamphetamine injection and a desire to "not poke twice":

> "My veins are so sore because I do maybe 5, 10, 15 shots a day. That's the worst part about it. It's the effects on my veins and the bruising. I really use the same site like these over and over if I can, but that only lasts for maybe a day. Then they're off and so I have to go find new ones again. Then it hurts bad. *And meth hurts. It burns bad. It burns. It hurts bad.* My veins are just so raw because of constantly doing it [injections]. Mainly, *I don't want to hit twice. I don't want to poke twice.* They just hurt so bad already. *I just want it [the heroin and meth] all at once.*" –Participant 6, Non-Hispanic, White Female, 30's, Nevada. [emphasis added]

Others who described vein pain and damage that they attributed to injecting methamphetamine switched to smoking methamphetamine to help avoid some of that pain. For example,

> "Well, I shoot up heroin now and I used to shoot up meth until – *I mean [meth] messes up your veins so bad. It's ridiculous how fast it messes your veins up. I just smoke it now.* There's times where people offer me a shot. And if there's nothing else, I'll do it but I guess the chemicals or whatever that's in it. I mean it just – you go from having that vein there to not being able to hit it, it's just not having veins. And I always told myself I wouldn't be that person that was shooting up and taking hours and hours to hit but sometimes, I can't find a vein. *And the methamphetamine messed up my veins a lot. Not that the heroin didn't either but it's just faster – the meth messes with me.*" –Participant 5, Hispanic/Latina Female, 30's, New Mexico. [emphasis added]

Still, others described lung pain or potential for damage associated with *smoking* methamphetamine, and therefore preferred injecting it. For example, this person experienced unpleasant effects from smoking methamphetamine, which made her hesitant to try it again,

> "When I first took a hit of meth, they didn't tell me not to hold it in like you hold in crack. So when I blew it out, my head started pounding. My friend was like, "Oh yeah. By the way, don't hold it in. You'll crystallize your lungs." I was like, "Well, thanks." So I had a migraine for two days after that. I didn't like it. So it took me a long time to try it [methamphetamine] again." –Participant 5, Hispanic/Latina Female, 30's, New Mexico.

When she resumed methamphetamine use, she injected it to avoid the unpleasant effects of smoking that she experienced the first time.

As described earlier by Participant 15, many people mentioned that they experience undesirable psychiatric symptoms from injecting methamphetamine. As a result, they switched to smoking methamphetamine to avoid the adverse effects but still receive the pleasurable effects (e.g., increased energy). For example,

> "I smoke it [meth]. I've only injected it a couple of times. It was too intense. When you inject it, it's more extreme. It hits you harder and it's more intense. Much faster and much harder. It hits you hard. Being almost erratic. It's just too much – breaking out in a cold sweat. *It's much better – smoking it – for me.*" –Participant 12, Non-Hispanic White Male, 50's, Nevada. [emphasis added]

Heroin-using respondents also described using methamphetamine to alleviate the pain and discomfort of opioid withdrawal:

> "If you're doing meth, you're sort of up and running around. If you get sick on heroin [i.e., experience withdrawal symptoms] and you do meth, you really don't feel sick on heroin anymore for quite a bit. So you can get a lot of shit done like walk around and do whatever you're going to do." –Participant 11, Hispanic White Male, 30s, Nevada.

Seeking Pleasure

A second theme concerned modifying the route or sequence of administration to enhance the pleasurable effects of one drug or the other. For those who prefer goofballs, the experience of injecting the drugs together was intensely pleasurable:

> "I was doing it with meth and heroin. It's like, I don't know, it's a disgusting sort of pleasure. I don't know but it's hard to describe. But yes, I mix the two. Once you get to the point where you're like, and especially since I struggled, the pullback and you see the blood go back in the barrel and you know you're in a vein and when you press down, you're going to get a rush, nothing in this world will ever compare to that." –Participant 11, Hispanic White Male, 30's, Nevada.

Participant 10, who also prefers goofballs, said:

> I: So, the stuff that you're getting right now, how does it make you feel? In your body, what does it feel?
> P: Oh, man. It's good. I do really large hits… But anyways, you fucking slamming here and then you flag it. The blood draws

up back up in it. That's the fucking first time that I'm going to get fucking high as fuck. You feel it coming up your throat, you'll cough maybe, [inaudible] really good. It's fucking really good. It's really good. –Participant 10, Non-Hispanic, White Male, 30's, Nevada.

Several people reported that injecting methamphetamine results in the most intense effects. Although some people considered that intensity to be unpleasant (e.g., Participant 12 and 15, above), others actively sought out the intense pleasure. For example,

"It was bad, like, intense, like, knowing that that was what's supposed to happen. I would love to go back there but I was by myself in an apartment. I thought, "Oh, my god. I'm fucking going to die." Yeah, it was really scary but knowing that that's what's supposed to happen. It's super, like, pleasure that you can never experience. I'm, like, coming to terms with the fact that there will never be a more purely pleasurable experience than that in my life. Orgasm, nothing, will ever compare to that. It's like a warmth and a sort of I don't know, weird headspace where sort of everything – it's strange to say. It's like your environment becomes erotic. Everything is sort of like a very – and later, I've realized, you actually like orgasm in your pants. You have a physical orgasm through injecting which... that sort of happened. I really put two and two together whereas now, I realize it's sort of like it's a sexual drug." –Participant 11, Hispanic, White Male, 30's, Nevada.

Some people found the effects of methamphetamine more pleasurable when they smoked it. Other people simply enjoyed the act of smoking and described smoking methamphetamine to satisfy the urge they have to smoke. For example,

"Just smoking it [meth]. I was craving to smoke something, and cigarettes were – I was craving the smoke." –Participant 2, Hispanic/Latina Black Female, 20's, New Mexico.

Responding to Social Context

Social context (e.g., family, especially partners) was also influential in determining the route and timing of co-administration. Although most people reported a distinct preference when it came to their pattern of co-administration, some people were flexible and would accommodate the preferences of the people they were with, even if it wasn't their preferred method. This was especially evident when people described using drugs with a partner or significant other. As previously mentioned, Participant 17, who used prescription opioids and methamphetamine, was heavily influenced by her husband's preferred drug (methamphetamine) and route of administration (injection), but continued using prescription opioid pills to address underlying issues. She was concerned about hiding her methamphetamine use from family members, so it was easy for her to switch from smoking to injection use (which she believed was easier for her to hide), especially since her husband was there to show her how to inject.

Participant 7, who earlier described the pleasure when a goofball achieves the "perfect ratio," said he would rather do two separate injections of methamphetamine and heroin because, more often than not, that "perfect ratio" is not achieved and, as a result, one drug overpowers the other, rendering the injection "pointless" to him because he cannot feel the effects of the overpowered drug (e.g., too much methamphetamine and he cannot feel the heroin). When this happens, he finds himself spending more money on drugs or being miserable for the rest of the day if he is unable to afford more. Nevertheless, he uses goofballs with his girlfriend because that is her preferred method.

Finally, in the exchange between Interviewer (I) and Participant (P) below, the participant describes how his decisions about how to use were influenced by other members of his drug-dealing network:

I: Yeah. When you first used it, how did you use it? Did you smoke? Did you inject it?
P: I smoked it and I inject it, snort it. I just went all the first time –
I: Okay. Yeah. It's like all the different ones.
P: – because I've been a part of the cartel for a while. I mean when they offer you something, you have to do it. It's not like, "Oh, I don't want it. No, thanks."
I: Yeah, just a little bit of like you've got to prove yourself.
P: Yeah. It's like a disrespect. If you don't do it, they'll think you're a drug or you're a narc or you're something.
–Participant 1, Hispanic Male, 40's, New Mexico.

Responding to Drug Availability

Another theme that influenced decisions about the route and timing of co-administration was drug or supply availability. Several respondents described specific preferences; however, they also described flexibility to adjust to changes in the availability and affordability of drugs and supplies (e.g., syringes). For those who preferred to use goofballs, they used them almost exclusively unless they could not afford it, leading to a hierarchy of drug use. This usually entailed using heroin first to avoid the negative effects associated with heroin withdrawal and then using methamphetamine once it became available. Participant 16 also described the declining quality of heroin, leading to a reduction in her use of that drug (while continuing to use methadone and methamphetamine). For those who preferred injection drug use, some reported resorting to smoking or snorting drugs if no (new, sharp) needles were available.

P: I mean I just smoke [meth], shoot it, it depends… It depends, like, what I have. If I have the syringes.
I: Yeah, okay. If you have syringes, if you have the equipment to inject it. Do you prefer one over the other? Smoking vs. injection?
P: I [would] rather inject it.
–Participant 3, Hispanic/Latino Male, 30's, New Mexico.

Finally, there were some respondents who had familiarity with cocaine, but for whom methamphetamine appeared to be a newer stimulant. For those respondents, they described learning the differences between methamphetamine and cocaine and adjusting their use accordingly (e.g., Participant 5 above describing having to learn not to hold in methamphetamine smoke). Below, Participant 4 describes his first injection of methamphetamine, which he thought would be like cocaine but instead sent him into a "spiral":

> "Methamphetamine, my first time using it was shooting it up, and then *it took me to a spiral.* I had no idea what it would – I thought it would be used like a – *I was told it was going to be the same thing as cocaine*." –Participant 4, Hispanic/Latino, Black/African American Male, 40's, New Mexico. [emphasis added]

This respondent subsequently started smoking methamphetamine, which gave a less intense high, and enjoyed using heroin to help him calm down from the methamphetamine.

Achieving Functional Effects

Finally, participants described using methamphetamine in conjunction with opioids to achieve functional effects. These included "relaxing" with methamphetamine, using methamphetamine to counter the sedation of heroin or methadone, and coping with trauma.

Participant 4, whose primary pattern of co-use was smoking "a steady amount" of methamphetamine on top of his methadone, described the relaxing and calming effects he experiences from using heroin and methamphetamine. Importantly, he experienced undesired psychiatric effects from injecting the methamphetamine, and switched to smoking which gave him the desired effect:

> "Now that I'm smoking [meth] with the bongs and the pipettes [rather than injecting it], I see myself – it does calm me down. It does allow me to – yes, *it does bring me into a calm mode.* It gets me into a place of relaxation, not too deprived of energy, not too deprived of less energy." – Participant 4, Hispanic/Latino, Black/African American Male, 40's, New Mexico. [emphasis added]

Later, he went on to explain that the methamphetamine helps him stay busy, and he also uses heroin to relax and calm down from the busy-ness.

Others described using methamphetamine to "wake up" or "get energy" when they feel overly-sedated from heroin or methadone. For example:

> "I used to inject heroin. It's gotten cut down because of the methadone use." ... "I believe that I use meth with heroin sometimes. Like I said, I get a little bit lazy on the heroin or the methadone and then *I want to come up and I want to start cleaning*, or I got to get energy to deal with stuff and I don't want to just be sleeping. *I'll take a puff to wake up or to get going.*" –Participant 15, Hispanic/Latina Female, 40's, New Mexico. [emphasis added]

Similarly, Participant 9 took heroin to address underlying pain, and used methamphetamine to give her more energy. However, she doesn't use methamphetamine without using heroin:

> "I don't like to use meth without heroin. I don't know if it's because [it's] different nowadays. It is different, but I don't like the—it's like the heroin takes the edge off, because I like to be awake. I don't like to do a bunch of heroin. I don't like to be sleepy and stuff. I just like to—for one thing, I have pain but I don't have to do heroin. But I like doing the meth. It gives me energy"–Participant 9, Non-Hispanic White Female, 40s, Nevada

Participant 17, who started using methamphetamine when she switched from heroin to prescription pills, continued to use methamphetamine and occasional opioid pills because the methamphetamine helped her cope with long-term trauma, increased productivity and focus, and decreased tension with her partner.

> "I would say it [methamphetamine] helped me deal with my trauma, I guess. I mean it's very escaping. I'm not clouded by any trauma that I've had in the past."—Participant 17, Hispanic/Latina Female, 30's, New Mexico.

Finally, as described earlier, when participants had to make decisions about using heroin *or* methamphetamine (e.g., when they couldn't afford both), those who were dependent on heroin typically used heroin first, to ensure that they could avoid experiencing symptoms of heroin withdrawal.

DISCUSSION

We interviewed 21 people who use methamphetamine about their patterns of opioid and methamphetamine use. Notably, the majority (17/21, 81%) engaged in some form of co-administration. While we were able to identify dominant patterns, most respondents had a long history of drug use and had transitioned through many different combinations of timing, drug type, and route of administration. Within each of their preferred patterns of drug use, respondents described sub-patterns that were influenced by a complex set of motivations and rationales that sought to enhance some experiences (e.g., optimize pleasure) and reduce or mitigate others (e.g., avoid pain, counter over-sedation, etc.).

Our findings regarding the rationales underlying patterns of co-use are like those identified in other areas, including Melbourne, Victoria, Australia, and Oregon, USA. Palmer et al. (23) conducted a qualitative study in Melbourne, Victoria, Australia (population 5 million) and identified three main reasons for co-administration: using one drug to balance or manage the negative side effects of the other (in their case, using opioids to treat the effects of coming down from a methamphetamine binge), using one drug to enhance the effects of the other (in their case, using methamphetamine to prolong heroin intoxication or combining the two because it "feels better"), and using methamphetamine to get "high" while using a form of MOUD. Ellis et al. (5) found that 51% of their sample of 145 key informants endorsed the "high seeking" reason for co-administration, 39% endorsed the "balancing" rationale, and 15% reported using methamphetamine as an "opioid substitute." Our findings reflect very similar rationales, with most of our respondents describing co-administration of heroin and methamphetamine as a way to enhance or optimize the desirable sensations of both. Radfar et al. (24) identified a high prevalence of methamphetamine use among methadone maintenance patients in Iran. Many reported that the effects

of methadone and methamphetamine were *better* than the effects of using methamphetamine with other opioids, such as heroin or opium. Our findings extend this knowledge by also describing drug-by-route interactions, such as attempting to avoid pain specifically associated with injecting or smoking methamphetamine to reduce undesirable effects and increase pleasurable ones.

The social context of use is also an important determinant of both drug use patterns and related harms (25). For example, a large body of research describes the outsized influence played by female PWID's male sexual partners in structuring their initiation into and ongoing access to drugs (26, 27). We observed similar situations here, in which women were introduced to methamphetamine use by their male partners. However, this gender dynamic is not unidirectional (28); we also observed a male PWID adjusting his preferred pattern based on his female partner's preferences. Other social considerations included a woman's decision to inject methamphetamine rather than smoking it, as a way to hide her use more effectively from others in her household, and a man's decision that was influenced by members of his drug-selling network.

In terms of availability, sometimes drug availability made one's first choice unobtainable, in which case they would resort to using what they could obtain. In these cases, attending to opioid withdrawal symptoms became a priority, with the stimulant effect of methamphetamine being secondary (but sometimes also an attempt to deal with the opioid withdrawal, if no heroin was available). We also observed discussion of the changing (typically declining) quality of drugs over time, and the influence of quality on consumption patterns. It may be that changes in methamphetamine composition could also underlie some of the experiences described in this study. Specifically, methamphetamine containing *d*-methamphetamine salts without *l*-methamphetamine salts, which can be removed during some manufacturing processes (29), has been associated with stronger and shorter duration effects, a "sleepy" effect (sometimes described as "shutting down") after using methamphetamine (22), and more psychiatric symptoms such as delusions and paranoia (30), some of which were described by our respondents as undesirable effects they sought to mitigate.

Finally, it is important to note the functional nature of the drug use patterns described by our respondents. Several studies have noted that function is a salient dimension of methamphetamine use, with people reporting increased ability to meet everyday tasks, better focus, and increased productivity (31) and to increase income generating ability (32). Others have explored motives for stimulant use using domains such as: enhancement, coping, social, and conformity (33, 34). While these studies did not assess motives for co-administration of methamphetamine with opioids, there are similarities in this study's findings. People described several needs (i.e. to avoid withdrawal symptoms, to wake up, to treat trauma, to counter the sedation from methadone) that were met by their drug use, and opioids and methamphetamine served different functions. Our findings do correlate with a recent examination of co-administration of drugs among methadone maintenance treatment patients, which showed that enhancement (seeking pleasure or to get high) was the primary motive (35). Radfar et al. (24) also identified several reasons for using methamphetamine while on methadone. These reasons include coping with conflict and stress, tolerating undesirable effects of methadone (e.g., lethargy, sexual dysfunction), and self-management of opioid (and other drug) cravings while on methadone maintenance. The overwhelming majority of participants in that study indicated that methamphetamine use is normative among patients and that methamphetamine use is encouraged within social circles as a way to combat the side effects of methadone during the early stages of methadone treatment.

Implications: Harm Reduction and Trauma-Informed Approaches

There are several health-related implications to consider from our research. First, combining stimulants with opioids is a well-established risk factor for opioid overdose death. Not only did our participants describe combining heroin or prescription opioids with methamphetamine, but several also described using heroin, methamphetamine, *and* methadone. Concerningly, a recent study (36) found that most respondents in their study in Dayton, Ohio believed that methamphetamine could be used as a preventive measure to reduce the risk of opioid overdose in a fentanyl-saturated market, or administered as a last resort to reverse the effects of an opioid overdose (especially when naloxone was not available). Combined, these findings reinforce the ongoing imperative to ensure that PWUD are properly trained in overdose recognition and response, and have naloxone available at every drug use event. Overdose prevention efforts should cast their net broadly and include people who use methamphetamine. Another risk factor for overdose is changing the route of administration (i.e., moving from smoking to injection). We found that people transitioned between smoking and injection for several reasons, including pain, vein damage, social context, and to increase or decrease the effects of the drug. Incorporating messages about how the route and sequence of administration can impact overdose risk and providing lower-risk options for administration could be an important addition to existing overdose prevention efforts.

Injection drug use is also a risk factor for transmission of HIV, hepatitis C virus, and other bloodborne and soft tissue infections if a sterile syringe is not used. Importantly, respondents in our sample nearly always described drug use in a social context. While using drugs in the presence of others is protective against overdose death (because someone will be there to observe and respond to the overdose), it can elevate the risk for pathogen transmission if people do not have access to enough sterile injection supplies. While some respondents in our sample reported smoking (rather than injecting) when sterile supplies were unavailable, it is important to note that our respondents were recruited from communities with fairly robust syringe services programs. This may not be the case for communities throughout the Mountain West, and overall, the US has not yet achieved sufficient syringe supply to allow PWIDs to use a new, sterile syringe for each and every injection.

Our findings suggest the potential importance of employing theoretical frameworks that can capture the functional (often ameliorative or protective) motivations for drug use, as well as associated risks and harms. The Trauma-Informed Theory of Individual Health Behavior (TTB) provides such a lens (37). Instead of conceptualizing drug use as inherently and exclusively harmful, it suggests that drug use can confer both protection and harm, dependent on context. TTB highlights that individuals make the best effort to address the most immediate harms that they are facing, and that attempts to change health behaviors must address an individual's focus on these immediate concerns before attempting to change future behavior (26). While we have identified some health harms (e.g., the risk for overdose and bloodborne pathogen transmission), our findings also support the idea that individuals use different drugs to alleviate or otherwise address specific sources of harm they are exposed to (e.g., untreated pain, income instability). Intervention and treatment efforts should consider that people who use drugs may have underlying needs that are currently being addressed via their drug use—therefore identifying and helping PWUDs address those underlying needs must precede attempts to change other health behaviors. For example, the use of methamphetamine to counter the sedative effects of methadone suggests that PWUDs on methadone maintenance might benefit from conversations with healthcare providers about the appropriateness of their methadone dose, and TTB would suggest that this needs to happen before efforts to reduce methamphetamine use. While only described by one of our respondents, the use of methamphetamine to self-medicate underlying trauma suggests that individuals with histories of trauma would benefit from comprehensive behavioral health care. Indeed, other research has shown that motivations for the co-administration of methamphetamine and opioids are complex and multifaceted, influenced by an abundance of personal and social factors that have an influence on drug use behaviors (5, 38). A recent study by Silverstein et al. (39) conducted in Ohio supports the idea that methamphetamine use among people who use opioids depends not only on individual and social factors, but also historical and pharmacological contexts that have implications for health outcomes and drug use trajectories. A TTB-informed approach would make explicit and address those underlying factors before attempting to change other health behaviors.

Limitations

Our results should be considered in light of the study's limitations. Qualitative methods are designed to elicit a diversity of narrative descriptions, rather than generalizable conclusions, and therefore the findings from this study may not be transferable to other regional, cultural, or social settings. Specifically, both New Mexico and Nevada have experienced a high prevalence of methamphetamine use for decades, which may suggest that co-use patterns in these states differ from the Eastern US and other regions where methamphetamine use is more novel. However, the similarity of our findings with other quantitative and qualitative studies suggests that our conclusions are robust to such variation. We arranged people into their respective groups based on either their stated preferences or their most predominantly discussed patterns of use. However, this does not encapsulate the whole picture because people engaged in several patterns of polysubstance use over time. Responses may be subject to social desirability bias, in which respondents alter their responses based on what they believe is acceptable to the interviewers. Interviewers for this study were trained to mitigate such bias, and were embedded within the harm reduction infrastructure in each community to enhance relationships and facilitate open and honest dialogue with respondents.

CONCLUSION

We identified dominant patterns of opioid and methamphetamine co-use and described motivations that influenced the type of drugs used, timing, and route of administration. Findings suggest that respondents engaged in opioid and methamphetamine co-use to address a number of underlying issues and unmet needs, and their patterns of use changed in response to social conditions and drug availability. Patient-centered models of care and support should seek information from participants about their unique drug use patterns, including their motivations for use and the needs currently being met by their use, and interventions and programs should holistically address participants' concerns. Polydrug use, in particular, is understudied and the motivations for co-administration of methamphetamine and opioids needs further inquiry. One potential theory for the development of more patient-centered understandings of methamphetamine and opioid co-administration is the Trauma-Informed Theory of Individual Health Behavior (TTB) (37), which explicitly addresses the underlying individual, social, and structural drivers of substance use behavior.

DATA AVAILABILITY STATEMENT

Because of the sensitive nature of the information contained in the transcripts (e.g., details about illegal behavior) and potential for severe ethical, legal, and social consequences resulting from broken confidentiality, full transcripts will not be made publicly available. Redacted excerpts of the qualitative transcripts used in the current analysis will be made available to qualified researchers subject to review and approval by the appropriate Institutional Review Board(s). Requests can be made to the University of Nevada, Reno Research Integrity Office by calling +1-775-327-2368.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Nevada, Reno (UNR) Institutional Review Board (IRB). The patients/participants

provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

We use the Contributor Roles Taxonomy (CRediT) refined by the Consortia Advancing Standards in Research Administration (CASRAI) for describing authorship contributions. BR and KDW: formal analysis. CM and KDW: writing—original draft. RH and KTW: project administration and investigation. KP and KDW: funding acquisition and supervision. RH, KTW, KP, and KDW: conceptualization and writing—review and editing. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Are There Neural Overlaps of Reactivity to Illegal Drugs, Tobacco, and Alcohol Cues? With Evidence From ALE and CMA

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Abuses of most illegal drugs, including methamphetamine, marijuana, cocaine, heroin, and polydrug, are usually in conjunction with alcohol and tobacco. There are similarities and associations between the behavior, gene, and neurophysiology of such abusers, but the neural overlaps of their cue-reactivity and the correlation of neural overlap with drug craving still needs to be further explored. In this study, an Activation Likelihood Estimation (ALE) was performed on brain activation under legal (tobacco, alcohol) and illegal drug cues, for identifying the similarities in brain functions between different craving states. A Comprehensive meta-analysis (CMA) on the correlation coefficient between brain activation and craving scores in the selected literatures with subjective craving reports explained the degree of the craving via brain imaging results. In ALE, co-activation areas of the three cue-reactivity (posterior cingulate, caudate, and thalamus) suggest that the three cue-reactivity may all arouse drug-use identity which is a predictor of relapse and generation of conditioned reflexes under reward memory, thus leading to illegal drug relapses. In CMA, the brain activation was significantly correlated with subjective craving, with a correlation coefficient of 0.222. The neural overlap of tobacco, alcohol and most of the prevalent illegal drug cues not only further helps us understand the neural mechanism of substance co-abuse and relapse, but also provides implications to detoxification. Furthermore, the correlation between brain activation and craving is low, suggesting the accuracy of craving-based quantitative evaluation by neuroimaging remains unclear.

Keywords: neuroimaging, cue-reactivity, tobacco, alcohol, drug

INTRODUCTION

Substance abuse is a major culprit damaging human physical and mental health and can even lead to death. Tobacco, alcohol, and illegal drug abuse are particularly serious. Alcohol and tobacco use cause the loss of more than 250 million disability-adjusted life years to humans, and illegal drugs cost tens of millions (1). Alcohol and tobacco are the most commonly abused legal drugs, but the legalization of common drugs of abuse is arbitrary and there is a lack of scientific and systematic criteria for classifying drugs of abuse (2). This may lead to misconceptions about the harm of each drug, and people may simply assume that the abuse of legal drugs is less important than the abuse of illegal drugs, which may not be the case. Nutt et al. (3) developed a nine-category matrix of harm to

classify drugs based on physiological impairment, drug dependence, and social impact, and found that tobacco and alcohol were more harmful than some Class A drugs (the most harmful class according to the UK Misuse of Drugs Act) and that their co-abuse with illegal drugs exacerbated the damage.

Tobacco and alcohol abuse can cause damage to the human body in multiple ways. Alcohol abuse causes impairment in executive function, memory, emotional function, and is also a major risk factor for traumatic brain injury (4). Nicotine abuse is strongly associated with the occurrence of sleep disorders, depression, schizophrenia, and anxiety disorders (5). The abuse of illegal drugs has even more serious consequences, as it can lead to acute or subacute leukoencephalopathy, as well as vascular complications, including vasoconstriction, vasculitis, and hypertension (6); it can also severely impair prospective memory—the higher the frequency of cocaine use, the stronger the degree of memory deficit (7).

Illegal drug abuse is often accompanied by tobacco and alcohol abuse (8). Research has found evidence of co-abuse of alcohol, tobacco and illegal drugs. Smoking rates among methamphetamine abusers typically exceed 80% (9). 86.4% of cocaine abusers reported co-abusing tobacco, 99.4% co-abusing alcohol and 95.1% co-abusing cannabis. In a dire co-substance abuse situation, it cannot be ignored that both tobacco and alcohol abuse have significant effects on illegal drug abuse, and alcohol abuse serves as a mediating factor between tobacco and illegal drug use (10). Some studies have found that simultaneous abuse of alcohol and psychostimulants can lead to neurophysiological dysfunctions, such as decreased antioxidant enzymes in the brain, disruption of learning and memory processes, inadequate brain perfusion, and neurotransmitter depletion; as well as increased heart rate, blood pressure, myocardial oxygen consumption, cellular stress, and increased risk of different types of cancer (11). Joint abuse of cocaine and nicotine enhances co-induced locomotor activity, as well as the induction and expression of locomotor sensitization, making each other mutually reinforcing abuse (12). Thus, the concurrence of tobacco, alcohol and illegal drug abuse is highly harmful.

Since abusers' cravings for tobacco and alcohol increase their cravings for drugs, it is proposed that smoking and drinking cessation should be performed simultaneously with detoxification (13–18). But institutional issues and individual health care providers often skip providing concomitant treatment to tobacco and alcohol abusers. Despite evidence that co-abuse of alcohol and cocaine produces unique neuroadaptations, their concomitant treatment needs are far from being met (19). Among alcohol abusers, methamphetamine is the most commonly co-abused illegal drug, but there is no effective treatment for this methamphetamine addiction comorbidity (20). Exploring the exact relationship between tobacco and alcohol abuse and illegal drug abuse can shed light on this dilemma.

Strong genetic and neurophysiological correlations among tobacco abuse, alcohol abuse and drug abuse have been identified. Research on the genetics of co-drug abusers could help develop more effective treatment programs (21–23). By measuring genetic variation, people initially found a certain genetic correlation between nicotine and marijuana (24). Drug abuse can lead to drug addiction. The widespread changes in hippocampal gene expression in both cocaine dependents and alcohol dependents may reflect neuronal adaptation common to both addictions (25). In terms of neurophysiological changes, when both illegal and legal drugs are abused, their interactive effects on neurophysiological mechanisms exacerbate the damage. After co-abuse of tobacco, alcohol and illegal drugs, the brain and biological mechanisms of abusers will have abnormal changes. It has been found that alcohol will increase the concentration of different psychostimulants and their active metabolites in the blood (26). When alcohol is used in conjunction with these drugs, the pharmacokinetics of methamphetamine, cocaine, and nicotine may change (11). Drinking alcohol alone did not affect the levels of dopamine and serotonin in the striatum and prefrontal cortex, but injecting methamphetamine after previously consuming alcohol somehow enhances methamphetamine-induced dopamine and serotonin (27). It can be seen that the abuse of tobacco and alcohol will aggravate the neurophysiological damage of illegal drugs. In addition, the three drug abuses have a common neurophysiological mechanism, such as the reward circuit of abnormal dopamine release (28). Are there overlaps between different cue-induced craving state?

Exploring the neurophysiological mechanism of craving can not only provide theoretical guidance for the "regression model of craving," but also provide enlightenment for considering whether the craving for one drug triggers the intake of another addictive substance while solving concomitant drug use. In previous studies, methods of "induction under cues" or "physical withdrawal" are generally used to induce subjects' craving for psychoactive substances (29, 30). The measurement of brain changes under cue induction in neuroimaging only proves that the neurophysiological mechanisms caused by the two inducing conditions are different but cannot prove the exactly differences in craving. Therefore, the accuracy of neuroimaging to assess drug craving is often illustrated by the correlation coefficient between its results and subjective self-evaluated craving scores (31). However, the degree of correlation between drug craving scores and activated brain regions was different in different studies. Therefore, in this meta-analysis, we need to clarify the degree of correlation between cue induction and craving.

In a word, Tobacco, alcohol, and drugs are often abused jointly. They have a certain mutual predictive relationship and a common biological mechanism (32). Since craving is a major cause of relapse, research on the impact of tobacco and alcohol craving on drug relapse is critical. Presently, the similarities between the brain mechanisms of legal drug (tobacco and alcohol) cravings and illegal drug cravings are unclear. This study employed activation likelihood estimation meta-analysis (ALE meta-analysis) to conclude similarities in activated brain areas in drug-dependent patients under induction by legal drug (tobacco, alcohol) and illegal drug cues. We hypothesize that these three cues induce some co-activated brain regions. In addition, a Comprehensive Meta-Analysis (CMA) was performed for the correlation coefficients between the brain activation levels and

self-reported scores of the cravings. The level of activation of co-activated brain regions may to some extent represent the degree of craving. The results of this study are expected to provide enlightenment for the treatment sequence of tobacco, alcohol, and drugs and the effectiveness of neuroimaging measurements of drug cravings.

METHODS

Literature Search

After determining the issue for investigation, three sets of search keywords were determined (each set separated by "or"): (1) related words for craving induction by cues—craving/cue; (2) words related to drug addiction—addiction/drug use/ drug abuse/drug dependence/substance use/substance abuse/ substance dependence/alcohol/ heroin/cocaine/opiate/cannabis/ marijuana/nicotine/smoke/tobacco/MDMA/polydrug; and (3) words related to brain/imaging—fMRI/functional Magnetic Resonance Imaging/BOLD/blood oxygen level dependent/ neuroimaging/PET/Positron Emission Computed Tomography/ fNIRS/ functional near-infrared spectroscopy. Data bases including Web of Science, PubMed, PsycINFO, CNKI, and others were searched. The publication time was set from January 1975 to March 2021, and the search contents were three sets of search terms connected by "AND." Supplemental screening was conducted for the included literature.

Literature Screening

The downloaded literature was screened according to the inclusion criteria: (1) the coordinates of the enhancement point of the drug cue-neutral cue were reported; (2) it uses the statistics contrasts(drug cue > Neutral cue); (2) it was a whole brain study, not a specific brain area study; (3) the drug craving was induced by the cue; (4) it adopted an in-group design—the brain activation areas of drug-dependent patients under drug and neutral cues were compared; (5) research subjects were substance abusers; (6) fMRI, PET, or fNIRS was used; (7) literature review and meta-analysis were excluded; and (8) subject had no mental illness.

Implementation of Meta-Analysis

ALE Meta-Analysis

The final coordinates were organized into text, and GingerALE 2.3.6 was used to convert the coordinates based on Talarich template to the coordinates based on Montreal Neurological Institute (MNI) template; to be conservative, according to the recommendations of the ALE instruction manual, the threshold of the diagram of activation likelihood estimation was set to $p < 0.001$ and corrected by the method of Uncorrected P (33). The minimum cluster size was 250 mm^3 (34), and the default preferences were set. The following meta-analysis was performed: (1) meta-analyses were performed for legal drug-related (tobacco-related and alcohol-related) and illegal drug-related literature separately; (2) a conjunction meta-analysis was performed between legal drug-related (tobacco-related and alcohol-related) literature and illegal drug-related literature, separately (see **Figure 1**). Each meta-analysis produced their respective activation area pictures and cluster files. Mango4.1 (http://rii.uthscsa.edu/mango/) was used to cover the activation area on the MNI standard brain (http://www.brainmap.org/ale/) (35).

Comprehensive Meta-Analysis

Effect Size

Of the 49 included articles, two papers reported the correlation coefficient between an activated brain area (drug cue > neutral cue) and craving score; seven papers reported the correlation coefficients between several activated brain areas (drug cue > neutral cue) and craving score. Ultimately, we obtained a total of 26 correlation coefficients as effect sizes.

Selection of Models

Current meta-analyses mainly use fixed-effect models or random-effect models. The fixed-effects model assumes that there is only one true effect size behind all studies in the meta-analysis, and that the difference in effect size for each study is due to sampling error. The random effects model assumes that the true effect size is different for each study and that the difference in effect size for each study is due to a combination of the difference in true effect size and sampling error (36). If the total effect sizes from the meta-analysis are not only for the included studies but need to be extended to other groups, we should use a random-effect model (36). Since the age, gender, occupation, etc. of the subjects in the meta-analysis varied, the effect sizes obtained from our meta-analysis could not be limited to just one, so we chose a random-effect model.

Test for Publication Bias

Publication bias means that the published research literature does not systematically and comprehensively represent the total body of research that has been done in the field (37). The most effective way to remove publication bias is to increase the sample size (including published and unpublished studies), as a lack of representative sample, particularly of dissertations with insignificant or unpublished findings, may affect the reliability of the meta-analysis results. To address this issue, firstly, we obtained as many unpublished papers as possible during the literature search stage; secondly, in the specific meta-analysis process, we used three methods including funnel plot, Rosenthal's Classic Fail-safe *N*-test, Egger's test to further evaluate publication bias.

Comprehensive Meta-Analysis Process

CMA (comprehensive meta-analysis) is a commercial software package dedicated to meta-analysis (www.meta-analysis.com), developed by Borenstein et al. (36). It was released in 2007 with Version 2.0 and above, and is now available in Version 3.0. In our experiments, we used CMA version 2.2. The software has a user-friendly interface, is easy to operate, can import more than 100 kinds of data structures, and can implement advanced statistical analysis functions such as subgroup analysis, meta regression and cumulative meta-analysis.

Using correlation coefficient as the effect size, random effects models were used and CMA 2.2 was adopted for meta-analysis.

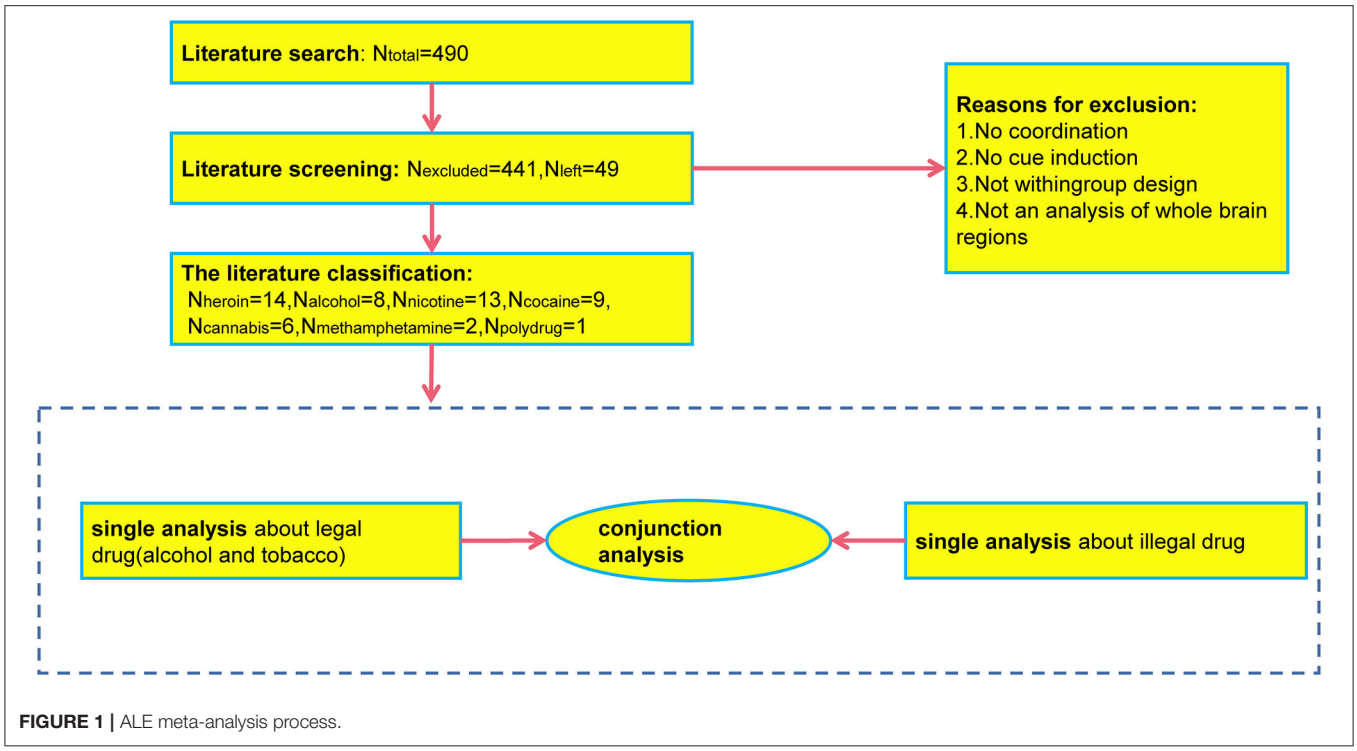

FIGURE 1 | ALE meta-analysis process.

Methods such as funnel plot, Begg's test, Egger's tests and the Trim and Fill method were used to evaluate the publication bias of this meta-analysis.

RESULTS

Description of Included Literature

Of the 49 articles that met the inclusion criteria, one article contained two addiction groups with different lengths of detoxification, one article included two addiction groups with different drug cues and one contained three addiction groups with different addictive substances. There were altogether 53 sub-studies from the above mentioned articles included in this study, and they could be classified by addictive substance, 14 articles explored heroin; 8, alcohol; 13, tobacco; 9, cocaine; 6, marijuana; 2, methamphetamine; and 1, polydrug addiction. With consideration of cue exposure, treatment status of the participants, abstinence of the samples included, and diagnosis modulating the brain reactions to drug cues (38), we collated relevant information from the included literature (See **Table 1** in the additional file).

ALE Meta-Analysis

Single Meta-Analysis Results

There were 32 experiments, 687 subjects, 18 activity enhancement points, and 13 activation clusters with enhanced activity for drug data. The brain regions of drug-dependent patients with enhanced activity after induction by cues were concentrated in the amygdala, hippocampus, middle occipital gyrus, middle temporal gyrus, fusiform gyrus, cingulate gyrus, anterior central gyrus, caudate, middle frontal gyrus, thalamus, and inferior frontal gyrus.

The ALE meta-analysis on alcohol and tobacco included 21 experiments, 687 subjects, 14 activity enhancement points, and 10 activation clusters with enhanced activity. The brain regions of alcohol-dependent patients and tobacco-dependent patients with enhanced activity induced by cues were gathered in the caudate, posterior cingulate gyrus, anterior cingulate gyrus, middle frontal gyrus, thalamus, insula, superior temporal gyrus, and precuneus (see **Table 2** in the additional file).

Conjunction Meta-Analysis Results

Co-activation Area of Nicotine and Drug-Related Data

Regarding the comparative ALE meta-analysis of nicotine and drugs, five activity enhancement points and three activation clusters with enhanced activity were generated. The brain areas co-activated by the two were the posterior cingulate and caudate (see **Table 3**, **Figure 2**).

Comprehensive Meta-Analysis Results

Heterogeneity Test and Publication Bias Test

First, the Heterogeneity test was performed. The *Q*-test result was significant ($P < 0.001$), indicating that the effect sizes of the original research were not similar.

Second, the publication bias of this meta-analysis was checked by a funnel plot (see **Figure 3**).

Regarding the funnel plot, the point on the left is farther from the axis of symmetry than the point on the right. This distribution characteristic indicates the possible occurrence of publication bias. Because the funnel plot is a preliminary check

TABLE 1 | Characteristics of the study.

References	*N*	Male%	Mean age (years)	Diagnostic criteria	Mean time of drug abuse	Daily dose of drug use	Withdrawal time	Comorbidities	Types of cues	Imaging technology	Questionnaire for cravings	Brain regions	Correlation coefficient
Heroin													
Wang et al. (39)	32	53	29.19 ± 7.50	DSM-IV	–	–	–		Picture	fMRI			
Hossein Tabatabaei-Jafari et al. (40)	40	100	32.00 ± 4.40		11.35 ± 4.60 years	-	3 months		Picture	fMRI			
Li et al. (41)	18	100	34.60 ± 6.80	DSM-IV	96.30 ± 69.50 months	0.80 ± 0.40 g	6 months		Picture	fMRI			
Chang (42)	10	100	30.70 ± 5.50	DSM-IV	79.30 ± 47.40 months	0.71 ± 0.25 g			Picture	fMRI			
Wang et al. (43)	14	100	41.00 ± 5.60	DSM-IV	58.14 ± 12.27 months	1.07 ± 0.54 g			Picture	fMRI			
Lou et al. (44)	37	100	32.38 ± 1.40	DSM-IV	7.62 ± 1.05 years	0.70 ± 0.15 g			Picture	fMRI			
Wang et al. (45) (short-term withdrawal group)	17	100	33.20 ± 1.40		7.00 ± 1.00 years	0.60 ± 0.10 g	1.2 ± 0.1 months		Picture	fMRI			
Wang et al. (45) (long-term withdrawal group)	17	100	31.80 ± 1.40		8.40 ± 1.10 years	0.70 ± 0.10 g	13.7 ± 0.4 months		Picture	fMRI			
Song et al. (46)	10	100	37.79 ± 6.46	DSM-III R	58.14 ± 12.27 months	1.07 ± 0.54 g	–		Drug	fMRI			
Yang (47)	12	100	33.20 ± 4.31	DSM-IV	10.00 ± 1.30 years	0.25 ± 0.11 g	≤1 month		Picture	fMRI			
Zijlstra et al. (48)	40	100	44.50 ± 3.90	DSM-IV	16.00 ± 6.80 years	–	8.1 ± 6.1 weeks		Picture	fMRI			
Shao et al. (49)*	30	67	31.00 ± 8.00	DSM-IV	6.00 ± 3.00 years	1.20 ± 0.80 g	9 ± 2 months		Picture	fMRI	11-point Likert scales	Left inferior frontal gyrus	0.554
												Left middle frontal gyrus	0.512
												Left anterior cingulate	0.587
												Right orbitofrontal cortex	0.528
												Right amygdala	0.515
												Right insula	0.509
												Left medial frontal gyrus	0.501
Xiao et al. (50)	14	100	33.2		7.10 years	–	0		Picture	fMRI			
Sun et al. (51)	30	67	30.9	DSM-IV	5.92 ± 3.24 years	1.20 ± 0.80 g	1.90 ± 2.30 months		Video	fMRI			
Totals or samplesize-weighted averages	321	89	34.41 ± 3.81		85.13 ± 30.86 months	0.56 ± 0.23 g							

(Continued)

TABLE 1 | Continued

References	*N*	Male%	Mean age (years)	Diagnostic criteria	Mean time of drug abuse	Daily dose of drug use	Withdrawal time	Comorbidities	Types of cues	Imaging technology	Questionnaire for cravings	Brain regions	Correlation coefficient
Cocaine													
Zhang et al. (52)	23	74	42.20 ± 7.60	DSM-IV	16.00 ± 9.70 years	1.10 ± 0.70 mg			Picture	fMRI			
Ma et al. (53)	15	100	39.10 ± 8.00	DSM-IV	–	–	14.6 ± 10.3 months		Word	fMRI			
Prisciandaro et al. (54)	15	87	27.50 ± 8.00	DSM-IV	–	–	24 h		Picture	fMRI			
Volkow et al. (55)	36	44	–	DSM-IV	–	–	0		Video	PET			
Kilts et al. (56)*	8	50	–	DSM-IV, QMI	–	–			Picture	fMRI	11-point Likert scales	Amygdala, dorsal cingulate cortex	−0.68
Bonson et al. (57)	11	82	32–39	DIS, DSM-IV	6.4	0.33 mg			Picture	PET	Self-report questions	Amygdala, dorsal cingulate cortex	0.74
Kilts et al. (58)*	8	0	–	DSM-IV	–	–	2 days	①	Sound	fMRI	Minnesota craving scale	Right subcallosal cortex	−0.89
												Left anterior insula	−0.74
												Brainstem	−0.71
												Left posterior caudate nucleus	−0.77
Sell et al. (59)	10	100	31.6	–	12.40 years	28.75 mg	<11 days	②	Picture	PET			
Hugh Garavan et al. [Hugh (60)]	24	82	34	DSM-IV	-	-			Video	fMRI			
Totals of sample size-weighted averages	150	72	24.59 ± 3.28		4.21 ± 1.53 years	1.35 ± 0.11 mg							
Cannabis													
Zhou et al. (61)	51	100	22.94 ± 2.71	DSM-IV	–	–				fMRI			
Karoly et al. (62)	41	53	18.83	DSM-IV, ICD-10	–	–	12 h		Picture	fMRI			
Charboneau et al. (63)	16	31	23.77 ± 3.90	DSM-IV	15.17 ± 2.80 years	2.21 g	8 h		Picture	fMRI			
Cousijn et al. (64)	31	65	21.30 ± 2.30	CUDIT, FTND, MCQ	2.50 ± 1.90 years	5.00 ± 1.50 g			Picture	fMRI			
Ray et al. (65)	10	50	–		–	–			Picture	fMRI			
Filbey et al. (66)	38	81	23.74 ± 7.25	SCID	7.00 ± 7.00 years	3.00 ± 2.00 g	3 days		Item (pipe or pencil)	fMRI			
Totals or sample size-weighted averages	187	71	21.39 ± 3.2		2.56 ± 2.01 years	1.53 ± 0.69 g							

(Continued)

TABLE 1 | Continued

References	*N*	Male%	Mean age (years)	Diagnostic criteria	Mean time of drug abuse	Daily dose of drug use	Withdrawal time	Comorbidities	Types of cues	Imaging technology	Questionnaire for cravings	Brain regions	Correlation coefficient
Methamphetamine													
Guterstam et al. (67)	40	100	40.1 ± 10.2	DSM-IV	12.60 ± 7.90 years	–	5.2 ± 4.6 days		Video	fMRI			
Grodin et al. (68)	15	80	36.6 ± 8.82	DSM-IV	–	–	9.58 ± 6.58 days	③	Picture	fMRI			
Totals or sample size-weighted averages	55	95	39.29 ± 9.88		12.60 ± 7.90 years	–							
Polydrug													
Ray et al. (65)	10	50	–		–	–			Picture	fMRI			
Tobacco													
Bi et al. (69)	33	100	19.62 ± 1.89	DSM-V	4.20 ± 1.88 years	15.58 ± 5.53	0		Picture	fMRI	QSU-Brief	Left anterior insula	−0.508
												Right anterior insula	−0.5742
												Left ventromedial prefrontal cortex	−0.494
Zhao (70)*	26	100	–	DSM-V	–	–	9 ∼ 13 h		Picture	fMRI	QSU-Brief; VAS scale	Right anterior cingulate	0.593
												Right insula	0.432
												Orbitofrontal lobe ($p = 0.006$)	0.533
												Orbitofrontal lobe ($p = 0.002$)	0.585
												Right superior frontal gyrus	0.549
												Right auxiliary motor cortex	0.604
Yang (71)*	32	100	26.68 ± 6.28	FTND	8.11 ± 7.02 years	14.41 ± 4.36	0		Picture	fMRI	VAS scale	The PPI between the lDLPFC and the rPHG	0.522
Kathy et al. (72)*	78	60	22.57 ± 1.2	FTND	37.53 ± 33.31 months	8.09 ± 1.51	24 h		Video	fMRI	UTS scale	Dorsolateral prefrontal cortex	0.36
												Nucleus accumbens	0.44
Ko et al. (73)	16	100	25.38 ± 3.36	DCIA, DSM-IV-TR	–	–			Picture	fMRI			
Wilson (74)	60	100	33.6 ± 8.5		–	20.90 ± 6.00			Picture	fMRI			
Wilson (74)	82	85	33.0 ± 8.3		–	20.50 ± 5.60	0		Picture	fMRI			
Hartwell (75)	32	44	33.5 ± 11.5	FTND	–	17.70 ± 6.90			Picture	fMRI			
Goudriaan et al. (76)	18	100	35.3 ± 9.4	DSM-IV	–	17.20 ± 3.80			Picture	fMRI			

(Continued)

TABLE 1 | Continued

References	*N*	Male%	Mean age (years)	Diagnostic criteria	Mean time of drug abuse	Daily dose of drug use	Withdrawal time	Comorbidities	Types of cues	Imaging technology	Questionnaire for cravings	Brain regions	Correlation coefficient
Weinstein et al. (77)	11	0	45 ± 17	DSM-IV	23.00 ± 13.50 months	26.00 ± 10.00			Video	fMRI			
McClernon et al. (78)	18	39	28.6 ± 7.5	-	11.60 ± 6.70 years	17.80 ± 2.80	–		Picture	fMRI			
McBride et al. (79)	20	50	–	FTND	–	22.00 ± 6.00			Video	fMRI			
Totals or sample size-weighted averages	450	78	25.26 ± 5.95		19.85 ± 14.06 months	15.28 ± 4.31 g							
Alcohol													
Bach et al. (80)	115	72	45.6 ± 9.78	DSM-IV	–	–			Picture	fMRI			
Ray et al. (81)	10	70	–	NIAAA	–	6.90 ± 1.90 drinks			Video	fMRI			
Kreusch (82)	12	100	21.30 ± 2.10	AUDIT	–	–			Picture	fMRI			
Courtney (81)	20	70	29.40 ± 9.01	DSM-IV	–	6.42 ± 2.24 drinks			Taste	fMRI			
Vollstädt-Klein (83)	38	0	46.00 ± 9.00	DSM-IV	14.00 ± 10.00 years	120.00 ± 129.00 g	9 ± 5 years		Picture	fMRI			
Vollstädt-Klein et al. (84)*	21	57	49.00 ± 11.00	ICD-10, DSM-IV	–	5.00 ± 1.50 drinks			Picture	fMRI	VAS scale	Mesolimbic system	0.32
Ray et al. (65)	10	50	–	Michigan alcohol screening test, alcohol abuse category of the alcohol dependence scale	–	–	24 h	④	Picture	fMRI			
Park et al. (85)	9	89	23.22 ± 2.48		–	9.16 ± 2.50 drinks			Picture	fMRI			
Myrick et al. (86)	10	80	33.60 ± 11.50	DSM-IV	–	8.17 ± 4.14 drinks	24 h		Picture	fMRI			
Totals or sample size-weighted averages	250	60	36.88 ± 8.1		14 ± 10 years	1.94 ± 0.69 drinks							

** represents included literature; QSU-Brief is "Brief Questionnaire of Smoking Urges;" UTS Scale is "the Urge to Smoke." In the "comorbidities" column, "①" means "One met the criteria for nicotine dependence and one met the criteria for marijuana abuse;" "②" means "two used illicit methadone;" "③" means "Marijuana can be positive;" "④" means "Marijuana can be positive;" each blank space indicates that there are no comorbidities or the presence of comorbidities is not mentioned in the literature.*

TABLE 2 | Single meta-analysis results.

Illegal drug						Alcohol and tobacco					
Cluster #	**Volume (mm^3)**	**x**	**y**	**z**	**Label**	**Cluster #**	**Volume (mm^3)**	**x**	**y**	**z**	**Label**
1	2,072	22.9	−5.2	−20.7	Amygdala, parahippocampal gyrus	1	3,000	−4	14	0	Caudate
2	1,680	−47.9	−66.5	−3.8	Middle occipital gyrus, middle temporal gyrus, fusiform gyrus	2	1,704	−3.7	−47	24.1	Posterior cingulate
3	1,456	−22.2	−6.2	−21.5	Parahippocampal gyrus	3	1,264	−4.4	48.7	−7.2	Medial frontal gyrus
4	1,272	−2	−37.6	28.4	Cingulate gyrus	4	912	−12.3	−14.7	6.6	Thalamus
5	760	47.5	7	26.2	Precentral gyrus	5	904	−4.6	39.8	17.2	Anterior cingulate
6	672	−34.3	−77.4	−24.7	Uvula	6	584	−36.8	11.1	2.2	Insula
7	592	−2.8	16.4	27.7	Cingulate gyrus	7	552	−6	52	−8	Middle frontal gyrus
8	488	7.8	8.9	−10.9	Caudate head	8	408	31.1	−58	48.8	Superior parietal lobule
9	408	−45.6	40.8	14.9	Middle frontal gyrus	9	360	−2.1	−5.2	7.5	Thalamus
10	320	2	−3.2	−15	Hypothalamus	10	256	−28.9	−89.9	10.3	Middle occipital gyrus
11	304	−18.9	−11.2	5.7	Thalamus						

TABLE 3 | Co-activated clusters about alcohol, nicotine, and illegal drug.

Cluster #	Volume (mm^3)	x	y	z	Extrema value	Label
1	472	−1.5	−40.1	28.3	0.020584242	Posterior cingulate
2	32	10	11.5	−8	0.015853202	Caudate
3	16	−16	−12	5.1	0.01629886	Thalamus

from a subjective point of view, we further performed Rosenthal's Failsafe N and Egger's tests to more accurately test the possibility of publication bias (see **Table 4**).

According to the Egger's test, the results suggest that there is no publication bias. From Rosenthal's *N*-value, it is necessary to include 238 (<2,200) articles to neutralize the two total effect sizes, indicating the presence of publication bias in this study.

Of the three publication bias tests described above, two results (funnel plot and Rosenthal's N) indicated the presence of publication bias and one result (Egger's test) indicated the absence of publication bias, and no results were obtained for all three tests. Therefore, further analysis is still required and the Trim and Fill method needs to be employed to examine the effect of publication bias on the results of the meta-analysis.

The Trim and Fill method proposed by Duval and Tweedie was further used to test the influence of publication bias on the results of meta-analysis (87). It was found that after trimming and filling the research literature, the overall effects obtained by using the random effects model were still significant. In addition, our unpublished literature represents 14.3%, which is already a significant proportion. Taken together, these results suggest that although there may be a slight publication bias in this study, the main findings of the meta-analysis are valid. Thus, although there may be publication bias in the two meta-analyses in this study, the main conclusion drawn from the comprehensive meta-analysis is valid.

Main Effect

The relationship between brain imaging data and craving scores was tested from an overall perspective. The results show that there are a total of 26 independent effect sizes, with the total subjects number of 6,663, and the overall correlation coefficient of 0.222 (see **Table 5**).

DISCUSSION

Co-activated Brain Regions

Posterior Cingulate

Findings indicate that the main co-activated brain area of tobacco-, alcohol-, and drug-related data is the posterior cingulate cortex (PCC); its voxel is far more than other co-activated brain areas. The PCC's most common identifier in the addiction field is as the self-function center of the default mode network (DMN), which is mainly responsible for the processing of "self" information such as autobiographical recall, self-evaluation, and reflection of one's own emotional state (88). In general, PCC guides attention to the internal (89), transmitting internal information for further evaluation via the ventromedial prefrontal lobe (mPFC) (90). Previous studies have found that changes in the PCC gyrus of different drug-dependent patients in craving states are often closely related to the DMN (91). In heroin-dependent patients, the PCC→ mPFC pathway is activated in the process of reducing the significance of drug-related cues (92). After 24 h abstinence in alcohol-dependent patients, PCC has high synchronicity with other parts of the DMN (93). PCC damage can even lead to the disappear of drug cravings and its damage causes tobacco-dependent patients to lose interest in smoking tobacco (94). Regarding concomitant

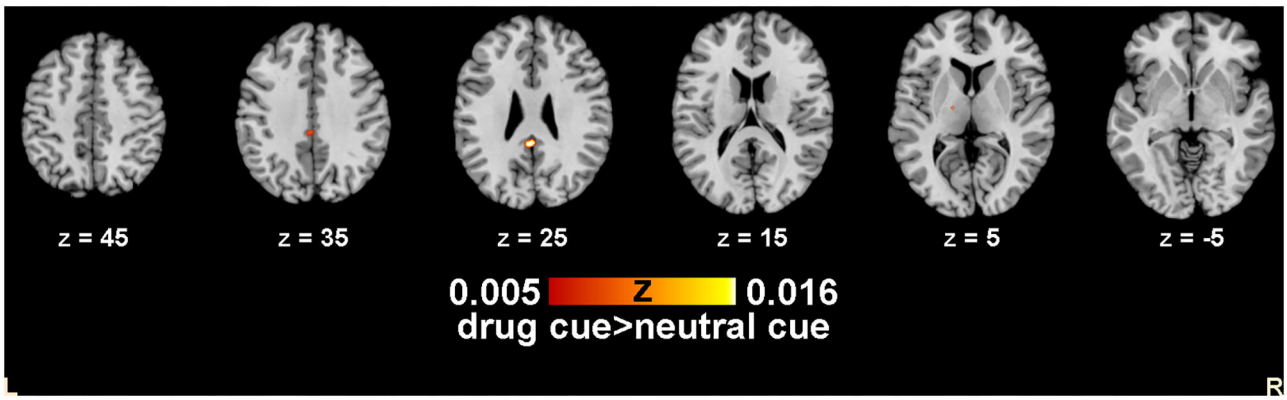

FIGURE 2 | Co-activated clusters about alcohol, nicotine, and illegal drugs. Slices taken at X = 0; Y = −18.

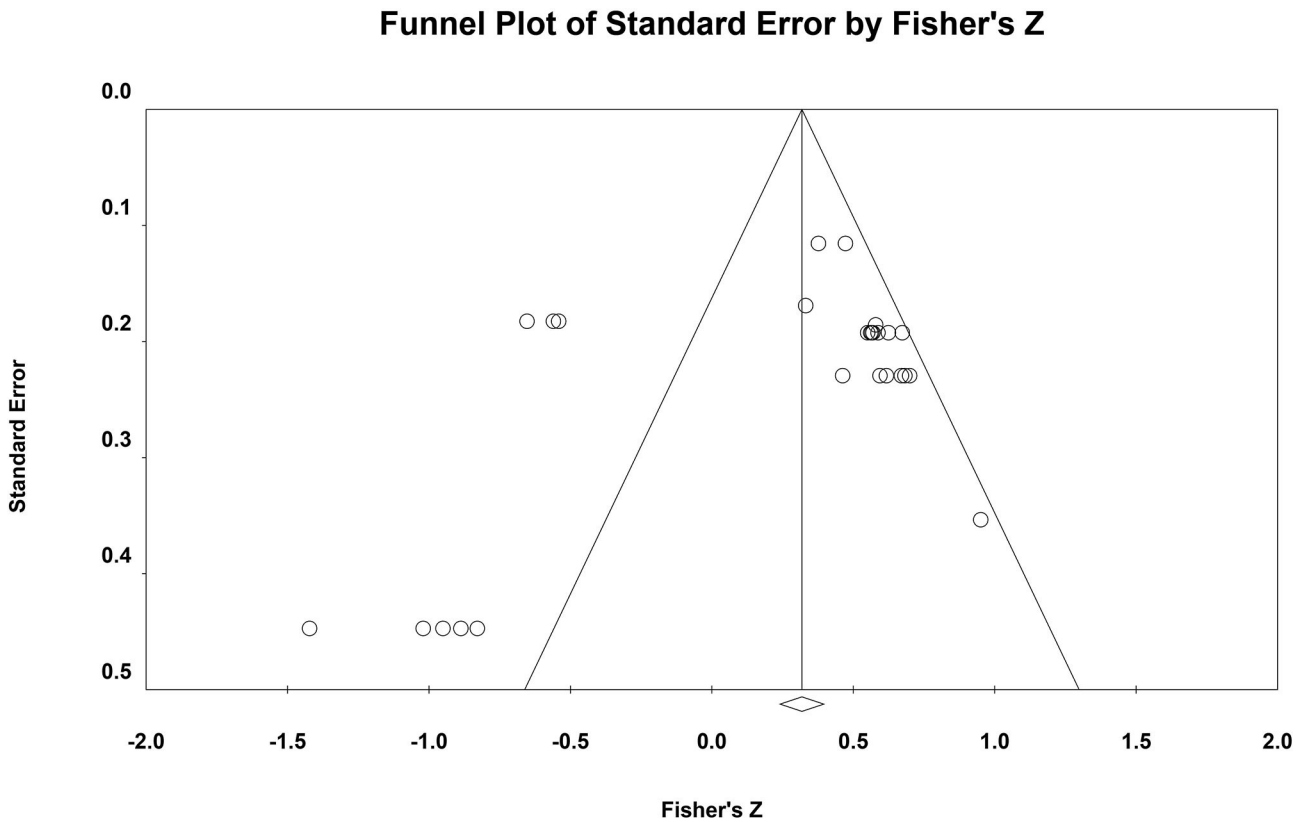

FIGURE 3 | Funnel plot. The vertical axis is the log standard error of the effect size, the horizontal axis is the effect size, the inside of the funnel is the confidence interval, and the central axis is the combined effect size.

substance use, attention should be paid to cultivating patients' positive self-concept to enhance withdrawal motivation and mitigate relapses. Simultaneously, attention should be paid to the self-identity of successful abstainers to allow them to fully integrate into social groups and resume normal work and life.

Caudate

The caudate is the second co-activation area. Habit formation is a cause of substance addiction and, here, the caudate produces neuronal responses (95). Using reward methods for individuals form conditioned reflexes is an effective way to form habits and the caudate and related cortical-striatal loop brain regions

TABLE 4 | Publish deviation test results.

Rosenthal's *N*	Egger's intercept	SE	LL	UL	*p*
238	1.71	01.40	−5.27	0.49	>0.05

LL and UL respectively represent the lower and upper limits of Egger's Intercept's 95% confidence interval.

TABLE 5 | Random effects model analysis results.

N	k	r	LL	UL	Z	*p*
260	26	0.222	0.025	0.402	2.203	<0.05

N represents sample size, K represents number of studies, and LL and UL respectively represent lower limit and upper limit of 95% confidence interval of R.

are crucial parts of the addiction reward loop. This suggests that the caudate may promote the formation of drug-taking habits through the activation of reward loops. Additionally, the caudate participates in the cognitive process of inhibiting control (96, 97). The dual disorders of cognitive control and craving processing can cause addiction. The activation of the caudate in drug craving is beneficial for inhibiting relapse behavior; however, it cannot effectively inhibit the spontaneous activities of DMN in heroin-dependent patients, thus it cannot perform cognitive control on some target-directed activities (e.g., seeking drugs, drug use) (98). Therefore, the caudate, a part crucial to the brain's learning and memory, accelerates the addiction process. Its control function allows it to inhibit individual relapse to a certain extent in the craving state, but abnormal changes in the caudate may explain why patients cannot control relapses or take other drugs to relieve their cravings. Treatment providers should pay more attention to cognitive control training for people who use substances concomitantly, such as high-intensity interval training, mindfulness training, and cognitive behavioral therapy.

Thalamus

The thalamus is the third co-activation area. As a sensory center, thalamus abnormality can cause patients to disassociate themselves from reality (99). After ketamine enters the human body, it inhibits the thalamus-neocortical system, selectively blocks pain, and activates the limbic system leading to excitement; the combination of alcohol with $GABA_A$ receptors in the thalamus makes people unresponsive as they temporarily detach from painful realities (100, 101). Here, the thalamus is also an important part of the memory system and addiction memory often causes relapse (102). The thalamus downstream loop is closely related to addiction-related memory: the PVT→ CeA loop is the key neural pathway for the formation of drug addiction memory and is responsible for connecting rewards produced by opioids with the environment; the PVT→ NAc→ LH loop is important for maintaining addiction-related memory. Through optogenetic and other technical means, the PVT→ NAc or NAc→ LH pathway can be manipulated in the memory extraction stage to eliminate addiction-related memory, for preventing relapse (103). It can be seen that the thalamus is like an eraser that erases the memory of addiction. The two subregions of the thalamus are also involved in cognitive control and craving, revealing the implications of the thalamic subnucleus in the pathology of acute abstinent heroin users (104). Thus, the thalamus has become a new focus for solving drug addiction. Regarding concomitant substance abuse, the "eraser" is a new development proposed for wiping addiction-related memory from patients during detoxification.

Therapeutic Implications From Three Overlaps

Tobacco, alcohol, and drug-dependent patients will process self-information in a craving state. Relevant studies have shown that self-concept is related to drug craving (105). Drug users adopt negative coping mechanisms when facing social pressure or pressure caused by drug withdrawal because of their low self-concept (106). Additionally, self-concept is positively correlated with the motivation of drug withdrawal (107, 108), which is an important factor in the treatment of craving (109). Notably, the self-concept of drug use involves a drug-use identity the degree to which drug use behavior is included in the self-concept by the drug-dependent patients. The higher the level of inclusion, the higher the identity of drug use. Drug-use identity can significantly predict drug craving, as confirmed in alcohol, tobacco, and drug use (110–114). Furthermore, substance users' drug craving has a cross-cue response mode when they try to withdraw from one addictive substance, and continuous exposure to another drug may induce craving for both substances, thus increasing the possibility of treatment failure (115). Therefore, drug-dependent patients may also experience drug cravings under tobacco and alcohol cues, arousing drug-use identity and resulting in a low sense of self-identity and loss of determination to abstain from drug-use.

That said, addiction-related memory (a pathological memory formed by repeatedly associating the pleasure of drugs with the drug-use environment) is activated by patients' craving state. Like other long-term memories, addiction-related memory contains both narrative scenarios and emotional memories such as reward memories, habitual actions, and drug-use techniques that are formed during long-term drug use and belong to procedural memory (116). Therefore, tobacco and alcohol-dependent patients may activate the reward circuit in the craving state, producing conditioned reflexes and abnormal reward circuits that may cause drug abstainers to relapse (117).

Thus, both self-information processing and the arousal of addiction-related memories can trigger relapses. However, in the current social status of addiction treatment, many people mistakenly think that focusing on drug rehabilitation and ignoring tobacco and alcohol withdrawal or using them to replace drugs are effective treatments. In fact, such treatments may cause drug-dependent patients with tobacco and alcohol addiction to give up on themselves because their identity of drug use is induced by craving for tobacco and alcohol after successful drug withdrawal, and they may regard themselves as patients in their mind. At the same time, the reward memory in the addiction-related memory will induce conditioned reflexes and activate the action of drug use. Therefore, drug-dependent patients can

start to abstain from tobacco and alcohol in the early stage of detoxification, so as to avoid the tragedy of "penny wise and pound foolish" at a later stage.

Relationship Between Brain Imaging and Subjective Craving

We found that only nine of the 51 studies reported a correlation between craving scores and activated brain regions. Therefore, this result ($r = 0.222$) does not fully indicate that ALE meta-analysis results can be represented by craving but it suggests to some extent that the accuracy of neuroimaging indirect measurement of craving needs to be improved. Neuroimaging provides a quantitative measurement for the evaluation of drug craving. However, these results can only show that neurophysiological changes are related to craving, and they cannot prove that there is a causal relationship between these factors. Sayette et al. (118) proposes that craving and hunger are both subjective experiences of the desire to ingest a substance, they are not necessarily related to physiological signals, and neither is necessarily related to physiological indicators that express biological needs. However, (for example, the blood sugar level in the circulation when hunger does not necessarily decrease), but both can be stimulated by environmental stimuli (such as stimulated by signals that indicate availability). A study also shows that craving and relapsing do not depend on direct physiological drug effects (119). Furthermore, the ecological validity of the cue-induced paradigm is poor, as the subject may be affected by response tendency and social expectations, which may influence the correlation between brain activation and craving scores.

LIMITATIONS AND FUTURE IMPLICATIONS

There are few published studies on cravings for new drugs, and the proportion of new drugs explored in this study is low, thus further work is needed to improve the representativeness of the current status of drug dependence. Conditions that induce craving are mostly shown in pictures, so the retrieved literature is not enough to conduct a comparative meta-analysis of brain activation induced by different cues.

Future research can examine related unpublished research on new drugs, emerging conditions for induction, and different imaging conditions to supplement the literature and correct the unpublished deviations of meta-analysis. Concerning craving in drug addiction, researchers should consider current social situations and increase research efforts on new drug addiction in future studies. Additionally, scholars should actively explore experimental conditions that can better induce real psychological craving, such as the use of multi-sensory stimulation, and specific conditions for induction should be formulated based on different regions and drugs.

CONCLUSION

The co-activation areas of tobacco, alcohol, and drug-dependent patients induced by cues are mainly the PCC, followed by the caudate and thalamus. The PCC is closely related to the DMN and is the main component of the DMN self-function center; the caudate and thalamus are both related to addiction-related memory. This indicates that the three drug cravings all involve the processing of self-information and the initiation of addiction-related memories.

Because these cravings induce the processing of self-information, including self-concept, drug-dependent patients will stimulate their drug-use identity. As these drug abstainers may induce drug cravings under tobacco and alcohol cues, they may also arouse drug-use identity under these cues, thereby increasing the rate of relapse. Moreover, addiction-related memories evoked under tobacco and alcohol cues include reward memories, which can activate drug abstainers' reward circuits, produce a conditioned reflex, and cause relapse. Therefore, professionals should pay attention to tobacco and alcohol withdrawal in the early stage of drug rehabilitation.

This study found that neuroimaging only mildly represents subjective craving. Thus, researchers should not use neuroimaging results exclusively to represent subjective craving. Furthermore, the ecological validity of the environment for cue-induced craving should be increased in the laboratory to improve the present research.

AUTHOR CONTRIBUTIONS

HL: study concept and design. YL, JX, YQ, and QZ: literature acquisition. HH: data analysis and interpretation. DZ: manuscript preparation and editing. YL: guidance of methodology and language revision. YJ: data curation and editing of writing. All authors contributed substantially and according to Frontiers in Psychiatry guidelines to be recognized as authors. All authors have read and approved the final version of the manuscript.

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REVIEW
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Dopamine Supersensitivity: A Novel Hypothesis of Opioid-Induced Neurobiological Mechanisms Underlying Opioid-Stimulant Co-use and Opioid Relapse

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Emergent harms presented by the co-use of opioids and methamphetamine highlight the broader public health challenge of preventing and treating opioid and stimulant co-use. Development of effective therapeutics requires an understanding of the physiological mechanisms that may be driving co-use patterns, specifically the underlying neurobiology of co-use and how they may facilitate (or be leveraged to prevent) continued use patterns. This narrative review summarizes largely preclinical data that demonstrate clinically-meaningful relationships between the dopamine and opioid systems with direct implications for opioid and stimulant co-use. Synthesized conclusions of this body of research include evidence that changes in the dopamine system occur only once physical dependence to opioids develops, that the chronicity of opioid exposure is associated with the severity of changes, and that withdrawal leaves the organism in a state of substantive dopamine deficit that persists long after the somatic or observed signs of opioid withdrawal appear to have resolved. Evidence also suggests that dopamine supersensitivity develops soon after opioid abstinence and results in increased response to dopamine agonists that increases in magnitude as the abstinence period continues and is evident several weeks into protracted withdrawal. Mechanistically, this supersensitivity appears to be mediated by changes in the sensitivity, not quantity, of dopamine D2 receptors. Here we propose a neural circuit mechanism unique to withdrawal from opioid use with implications for increased stimulant sensitivity in previously stimulant-naïve or inexperienced populations. These hypothesized effects collectively delineate a mechanism by which stimulants would be uniquely reinforcing to persons with opioid physical dependence, would contribute to the acute opioid withdrawal syndrome, and could manifest subjectively as craving and/or motivation to use that could prompt opioid relapse during acute and protracted withdrawal. Preclinical research is needed to directly test these hypothesized mechanisms. Human laboratory and clinical trial research is needed to explore these clinical predictions and to advance the goal of developing treatments for opioid-stimulant co-use and/or opioid relapse prevention and withdrawal remediation.

Keywords: opioid, stimulant, treatment, methamphetamine, relapse, withdrawal, cocaine

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INTRODUCTION

Historically, there have been periods of time in which the co-use of opioids and stimulants has been highly prevalent and of significant public health concern. The frequency of opioid-stimulant co-use has tended to wax and wane over the years and in the past decade the primary public health concern has focused on exclusive opioid use. However, now, amidst the ongoing opioid epidemic, this opioid-stimulant polysubstance use trend has reemerged. Deemed a "Fourth Wave" or "Twin Epidemic," epidemiological evidence now emphasizes a renewed and rapidly increasing public health harm of concurrent stimulant use, particularly methamphetamine use, among people who use opioids (1, 2). National and regional treatment admission data report stark increases in recent methamphetamine use among people entering treatment for opioid use disorder (OUD) (3–5), representing an approximate 5-fold increase in methamphetamine use among primary heroin treatment admissions from 2008 to 2017 (3). Such trends are also evident in national prevalence data (6–8). Data from the nationally representative National Survey on Drug Use and Health (NSDUH), for instance, show that past month methamphetamine use increased five-fold from 9% in 2015 to 44% in 2019 among people who also used heroin in the past month (6). Related surges in methamphetamine-involved overdoses in combination with opioids have been observed (9–13) with greater increases in non-cocaine psychostimulant overdoses in states with a greater prevalence of opioid use disorder (OUD) (12). This concomitant use of opioids and methamphetamine is worrisome beyond this noted overdose risk given other associations with psychiatric comorbidity, infectious disease transmission, and healthcare utilization (6, 14, 15). Moreover, although treatments for opioids and opioid overdose exist, no such treatments are available for stimulants, suggesting that the population of persons with co-use may face significant challenges to recovery.

These emergent concerns underscore broader challenges presented by opioid and dopamine agonist ("stimulant") co-use. While recent public health emphasis has been placed on opioids and methamphetamine, the practice of opioid-stimulant co-use dates back decades with trends observed across diverse subgroups and geographic regions. The co-use of opioids and cocaine, for example, was extensively described throughout the 1980's, 90's, and 00's in the United States [e.g., (16, 17)] and more globally [e.g., (18, 19)]. Reports of simultaneous (i.e., "speedballs") or concurrent co-use of opioids and cocaine motivated intense preclinical and clinical investigation into novel treatments (20). Despite these efforts, opioid and stimulant co-use remains a challenging treatment phenomenon with no FDA approved medication for co-use and weak to negative evidence for those pharmacotherapies that have been tested [e.g., (21)]. Development of effective therapeutics requires an understanding of the mechanisms driving co-use, specifically the underlying neurobiology of co-use and how these neurobiological mechanisms may facilitate (or be leveraged to prevent) continued use patterns.

Goal of This Review

The purpose of this review is to synthesize data collected primarily from preclinical studies dating back to the 1950's that demonstrate clear relationships between the dopamine and opioid systems with direct implications for opioid and stimulant co-use. These data outline a hypothetical but mechanistically-based premise for why opioid and stimulant co-use occurs. Notably, this hypothesis pertains specifically to the onset of stimulant use in persons who have opioid physical dependence. This is not meant to suggest that persons who are co-using these substances were naïve to stimulants prior to using opioids, rather the following conversation focuses on the large proportion of persons whose most recent use period was not characterized by concurrent initiation of opioids and stimulants together but rather is characterized by a new stimulant use episode that begins after opioid physical dependence has developed. This is a relatively common pattern that has been evident for several decades, most notably in persons who are receiving methadone for opioid use disorder treatment (22–25), for which numerous interventions have been evaluated to address new stimulant use (21, 26–29). In effect, this review is proposing a novel mechanistic hypothesis that the development of opioid physical dependence changes underlying neurobehavioral mechanisms in such a way that the experience of stimulants is uniquely different from that prior to opioid dependence development.

This hypothesis also has implications for the treatment of OUD, particularly relapse to opioids, and we have therefore outlined a putative and testable underlying neurobiological mechanism we hypothesize may function as a barrier to the development of effective opioids use disorder treatments. The data reviewed here are primarily drawn from preclinical animal studies; this hypothesis has not been prospectively examined in human subjects. Thus, the limited human laboratory, clinical, and qualitative studies available in this area are also reviewed to provide corroborating preliminary evidence for these mechanistic predictions in support of more focused prospective research.

Specifically, we propose a novel mechanism involving enhanced dopamine D2 receptor-mediated activity of the striatal-ventral mesencephalon-thalamic circuit, which we propose occurs as a function of chronic opioid exposure and results in organisms that are being withdrawn from opioids having a unique dopaminergic experience. We suspect these conformational changes may cause dopamine agonists to take on enhanced reinforcing properties during states of acute or protracted opioid withdrawal, including stimulants that are introduced after opioid physical dependence has been developed. This review is meant to present a novel yet testable hypothesis that has not yet been examined in human subjects and which has the potential to yield insights that could contribute meaningfully to collective efforts to address opioid and stimulant co-use. Thus, this review concludes with directions for future work to address the sustained morbidity and mortality presented by the co-use of opioids and stimulants.

BRIEF OVERVIEW OF OPIOID AND DOPAMINE NEUROBIOLOGY

Prior reviews have discussed the relationship between opioid and dopamine neurobiology and its relevance for opioid use and OUD [see contemporary and classic reviews in (30, 31)], so these concepts are reviewed here only briefly to support interpretation of the summarized results. The opioid system is regarded as the natural analgesia system and is distributed throughout the central and peripheral nervous systems. Opioids, such as morphine, oxycodone, and heroin, function as agonists that bind to the opioid mu, kappa, and delta (as well as ORL-1 and nociception/orphanin) receptors. The strength of conventional opioid effects (e.g., analgesia, euphoria) are primarily related to the strength of activity the opioid confers on the mu opioid receptor. The dopamine system is widely regarded as the primary reward and motivation system that is responsible for producing euphoria and for reinforcing repeated drug use behavior. Dopamine neurons are highly concentrated in the midbrain, which is characterized by projections from the ventral tegmental area (VTA) to the nucleus accumbens in the striatum (i.e., the mesolimbic system) or to the prefrontal cortex (i.e., the mesocortical system). The degree to which this system is activated corresponds generally to the degree of reward experienced. Additional and important nuances also exist with regard to the dopamine receptor system, which are categorized into D1 and D2 families. D1 family receptors (D1 and D5 receptor subtypes) are Gs-coupled receptors that generally produce excitatory signals; D2 family receptors (D2, D3, and D4 receptor subtypes) are Gi-coupled receptors that generally produce inhibitory signals. Moreover, when D2 family receptors are found presynaptically they often function as autoreceptors that regulate (e.g., inhibit) dopamine release and firing (32). The nucleus accumbens contains both D1 and D2 receptor families of receptors.

Although opioids exert their primary effects via agonism of the mu opioid receptor, these drugs also exert indirect effects on the mesocorticolimbic dopamine system (33–35). Mu opioid receptors within the VTA are located on GABAergic interneurons, which reside within the VTA (33–35). Under drug naïve conditions, these GABAergic cells provide inhibitory tone on dopamine neurons, which project to the nucleus accumbens. Within the nucleus accumbens, dopamine provides modulatory tone on GABAergic medium spiny neurons (MSNs), which express either D1 or D2 receptors. In preclinical studies, MSNs within the nucleus accumbens are critical in driving use of drugs, including opioids. Importantly, this has been shown to be driven by D1-expressing and not D2-expressing MSNs, as most of these cells express either D1 or D2 and have been heavily studied for their opposing roles in substance use (36). Thus, the recent literature regarding D1 versus D2 supports an important role of D1-expressing MSNs in regulating stimulant use, whereas D2-expressing MSNs are involved in negative regulation of these behaviors (36–39). As well, there is a large body of literature outlining the output structures of these differential cell populations [e.g., (40–42)]. Although emerging evidence suggests that reinstatement to heroin-associated cues induces synaptic adaptations at D1-expressing MSNs within the nucleus accumbens (43), it is not clear if the outcome measure of matrix metalloproteinase activity surrounding D1 or D2 synapses captures differences in sensitivity of these different dopamine receptor subtypes to subsequent dopamine agonism.

It is important to note that a large number of preclinical studies examining the impacts of D1 vs. D2 pathways on psychostimulant or opioid-related behaviors have generally studied this in animals under protracted withdrawal from these drugs and there may be adaptations specific to drug taking vs. withdrawal. When opioids are present (either systemically administered or locally applied *in vitro*), prior studies show an inhibition of the firing rate of VTA GABA neurons (44, 45), and the canonical pathway would indicate that this then reduces GABAergic inhibition of accumbotegmental dopamine cells (i.e., cells that project from the VTA to the nucleus accumbens), ultimately leading to an increase in dopamine signaling within the nucleus accumbens (44) and, subsequently, an increase of dopamine receptor activation on nucleus accumbens MSNs. It is thought that this neural mechanism contributes to the classic euphoric response produced by opioid drugs. However, one cardinal study showed that selective ablation of dopamine terminals in the nucleus accumbens induced long-lasting reductions in cocaine but not heroin self-administration (46), suggesting that other neurotransmitter systems beyond dopamine signaling are involved in the reinforcing effects of opioids.

In contrast to opioids, stimulant drugs produce their euphoric and reinforcing response by directly activating dopaminergic signaling within the reward pathway. Specifically, they are able to prolong the duration of time that dopamine can exert an effect on receptors by either preventing it from being recycled back into the neuron (e.g., cocaine) and/or by releasing large quantities of dopamine into the synapse (e.g., amphetamine or methamphetamine) (47). Another relatively recent piece of the circuit puzzle regarding stimulants and opioids involves the rostromedial tegmental nucleus (RMTg) or the "tail of the VTA" (tVTA), which project dense inhibitory tone to midbrain dopamine neurons. Importantly, the RMTg projects GABAergic tone into the VTA, and are generally thought to provide a "break" on motivated behavior (48). Bringing this newly charted neural circuit into focus with psychostimulant and opioid use, recent studies have found that the RMTg plays a critical role in aversive responses to cocaine (49), and acute withdrawal from cocaine increases cell firing within the RMTg (50). The RMTg also appears to be a critical mechanism in opioid-induced VTA dopamine disinhibition. As the canonical pathway, described above, typically considered GABAergic interneurons as the primary source of dopamine cell inhibition, one recent study showed that morphine induced a significant inhibition of inhibitory post-synaptic currents (IPSCs) evoked from the RMTg, whereas IPSCs evoked from VTA interneurons were almost insensitive to morphine (51). Taken together, these results support that the GABAergic projection from the RMTg is a critical, and perhaps dominant, neural circuit responsible for opioid disinhibition of dopamine neurons within the VTA.

However, no study to date has examined this more recent circuit in the context of opioid and stimulant co-use. **Figure 1** summarizes these neural circuits involved in opioid use as well as illustrates opioid-induced dopamine disinhibition in the VTA.

CHANGES IN THE DOPAMINE SYSTEM FOLLOWING CHRONIC OPIOID EXPOSURE MAY BE RESPONSIBLE FOR OPIOID-STIMULANT CO-USE AND STIMULANT INITIATION

Dopamine Is Meaningfully Involved With Opioid Effects and Opioid Withdrawal

Evidence that the dopamine system has meaningful interactions with the opioid system or expression of opioid effects have been reported as far back as 1954 (52). However, the manner through which this happens is nuanced. This is evident in a series of studies that revealed opioid agonists produce biphasic effects in animal models whereby low doses of opioids engender stimulant-like behavior, and the expected sedative-like effects of opioids are not elicited until higher doses are administered. In addition, in these studies tolerance to the depressant-like effects of opioids was observed to develop quickly over time, coincident with development of opioid physical dependence, whereas tolerance to the stimulant-like effects was not observed to develop at the same rate. In fact, continuous exposure to opioids was found to increase the emission of stimulant-like behaviors over time. These effects were firmly related to opioid activation because the stimulant-like behaviors produced by opioids can be blocked through administration of the opioid antagonist naloxone, demonstrating a causal relationship with opioid administration and opioid-receptor activity in the expression of behavior. The opioid-induced stimulation observed was only surmounted once large doses of opioids were administered in a repeated fashion (53–56), see also (57). The simulating effects of opioids have also been reported by human subjects, though this has only been examined in a small number of largely non-empirical studies (described below). The mesolimbic dopamine system appears to be a major contributor to the manifestation of opioid-induced stimulating effects (54, 58–60), and a convergence of data has also reliably implicated the dopamine system in the expression of some opioid withdrawal symptoms [see (61) for review], an effect that is especially profound with regard to thermoregulatory behavior (62).

As outlined above, it is well-established that exposure to opioids increases dopamine release in the striatum, and this is often hypothesized to be the mechanistic basis by which opioid-seeking behavior develops. However, there has been less discussion paid to the role dopamine may play during states of acute or prolonged opioid abstinence in animals that have developed opioid physical dependence. Several studies have revealed that when animals are made physically dependent on opioids and undergo withdrawal that is either spontaneous in nature (e.g., discontinuation of opioid agonists) or precipitated by administration of an opioid antagonist (e.g., naloxone, naltrexone), dopamine levels in the striatum decrease. This is evident through multiple different assays, including microdialysis quantification of extracellular dopamine levels (63–67), analysis of striatal brain tissue (68, 69), morphological examination of dopamine-containing neurons (70), *in situ* hybridization quantification of striatal adenylate cyclase levels (71), and 6-hydroxydopamine (6-OHDA) lesioning assays (72). The decrease observed in dopamine signaling during a state of abstinence is not simply a function of having been recently exposed to an opioid agonist because such changes do not occur during periods of acute opioid agonist exposure and the level of dopamine depletion that occurs has been correlated with the somatic expression of withdrawal (63, 66, 67). Moreover, the decrease in dopamine observed in animals that have opioid physical dependence and are put into a state of opioid abstinence is substantial, ranging from 25 to 35% of the level observed in control animals (67, 73). We know of only one human study that has examined this effect. That study used positron emission tomography (PET) to compare dopamine release in persons with OUD during a state of naloxone-precipitated withdrawal vs. a state of satiety. The study found that withdrawal was associated with a rapid and significant release of dopamine in the striatum and that the degree to which subjects reported the withdrawal to be aversive correlated with the strength of the dopamine release (74).

Conformational changes in dopamine signaling are also evident via electrophysiological assays. For instance, neuronal recordings of spontaneous meso-accumbens dopaminergic activity have revealed that rats that are made physically-dependent on morphine and then withdrawn exhibit reduced dopamine firing rates relative to control animals, and that both gross and burst firing rates continue to be low when measured 24-h after the final morphine exposure. The same effect was observed when opioid withdrawal was precipitated with a naloxone injection. The reduction in neuronal firing rates could also be reversed by intravenous administration of morphine, which was found to restore dopamine firing rates to the levels observed in control animals (75). Importantly, these changes in firing patterns only became evident when animals underwent a long period of abstinence (24 h); no such differences were observed when the animal was tested after 2 h of abstinence (75). The fact that this effect is easily reversed through provision of an opioid demonstrates a causal relationship between a state of abstinence and change in dopamine firing patterns. Another study that used microdialysis to examine postsynaptic dopamine levels found a similar effect. In that study, rats that underwent spontaneous withdrawal from opioids for 1 day evidenced levels of striatal dopamine that were 80% lower than control animals, and a dose of morphine was found to decrease this gap in a dose-dependent manner but did not fully restore the levels to those observed in control animals. In contrast, rats that were spontaneously withdrawn from opioids and left untreated continued to demonstrate lower striatal dopamine levels than controls for up to 3 days (the longest time frame examined in this study) (63). A follow-up microdialysis examination of mesolimbic dopamine levels in rats withdrawn from opioids found that extracellular dopamine levels were decreased in animals as far out as 7 days after the final opioid administration (76).

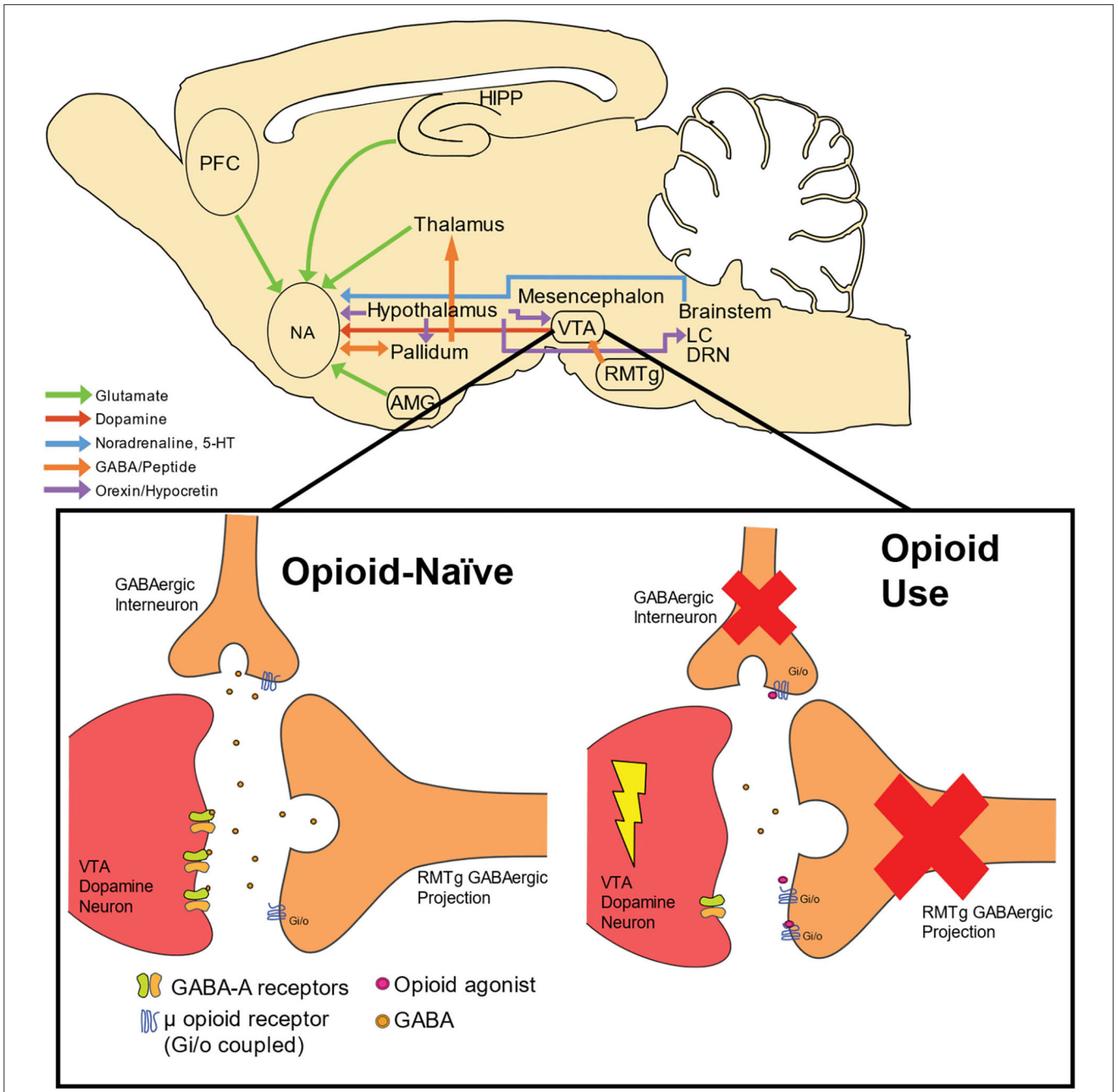

FIGURE 1 | Neural circuitry and dopamine disinhibition by opioid use. Neural circuitry involved in opioid use includes cortical, striatal, thalamic, mesencephalon, and brainstem structures. Dopamine cell bodies residing within the VTA receive GABAergic innervation from both GABAergic interneurons and projection neurons from the RMTg. GABA activates GABA-A receptors located on dopamine neurons, thus providing inhibition of dopamine neuronal activity. Through these terminals, dopamine excitability is maintained in homeostasis within an opioid-naïve system. When opioids are present, these compounds act as agonists at inhibitory ($G_{i/o}$) μ opioid receptors, which exerts inhibitory tone on GABAergic terminals synapsing onto dopamine cells. The net result is an enhancement of phasic dopamine release into terminal structures, including the NA. PFC, prefrontal cortex; HIPP, hippocampus; NA, nucleus accumbens, VTA; ventral tegmental nucleus; RMTg, rostromedial tegmental nucleus; LC, locus coeruleus; AMG, amygdala; DRN, dorsal raphe nucleus; 5-HT, serotonin.

Changes in the Dopamine System Remain Evident Long After the Somatic Signs of Opioid Withdrawal Have Remitted

Changes in dopamine signaling have been observed to persist for several days after the somatic signs of withdrawal appeared to have remitted, suggesting that the animals are continuing to experience an altered dopaminergic state even when overt signs of withdrawal are not apparent. This has been demonstrated with microdialysis, which revealed that animals that were withdrawn from opioids showed reduced rates of striatal dopamine levels

even after the signs of withdrawal remitted (63). A second study reported that rats withdrawn from opioids showed observable somatic signs of withdrawal until around day 3 of abstinence, yet the electrophysiological reduction observed in their dopamine firing rates were pronounced up to day 7 and only showed signs of full resolution around day 14 of abstinence. When morphine was administered to those animals on day 14, their striatal dopamine levels surged well-beyond the levels observed in the control animals, suggesting they had entered a state of dopamine supersensitivity (77).

The D2 Family of Receptors May Be Responsible for Enduring Changes in the Dopamine System Once Opioid Physical Dependence Is Established

Growing evidence has implicated the D2 family of receptors in the altered dopaminergic state that is produced by chronic opioid exposure. For instance, *in situ* hybridization of D1 and D2 receptor mRNA in rats that were made physically dependent on morphine showed that chronic opioid exposure increased only D2 receptor mRNA levels. These changes were specifically observed in the nucleus accumbens and striatum, which increased by as much as 27% relative to controls; no effect was observed with D1 receptors (78). Data from genetically-modified mice provide additional insight into this process by suggesting that the involvement of the D2 receptor becomes relevant only once physical dependence is developed. In this study, mice that were genetically engineered to be D2 (+/+) or D2 (-/-) were both able to develop morphine physical dependence and shows signs of withdrawal following naloxone administration. However, although D2 (+/+) mice showed conditioned place aversion to environments in which naloxone was administered, the D2 (-/-) mice showed no such aversion. Comparisons to opioid naïve mice further suggested that the D2 receptor was crucial for maintaining opioid motivation but only once the animal developed opioid physical dependence and was in a state of withdrawal, and that D2 was not implicated in behavior when the animal was opioid naïve and/or developing opioid-use behaviors (79).

Limited research has empirically examined this concept in humans. One study used a combined positron emission tomography (PET) imaging and drug administration study in adults who did ($n = 16$) and did not ($n = 16$) have a history of heroin use. Data revealed that adults who had used heroin showed reduced D2 family receptor availability and presynaptic dopamine release. However, neither of those outcomes were significantly related to their subsequent choice to self-administer a low or high dose of heroin (measured using a progressive ratio task), relative to healthy controls (80). Another study evaluated D2 receptor availability with and without naloxone administration using PET imaging in people with current DSM-IV opioid dependence and ongoing heroin use ($n = 11$) and controls without this opioid use history ($n = 11$) (81). Persons with opioid dependence showed decreased D2 receptor availability in the striatum compared to controls at presentation to the study. Precipitation of acute withdrawal using the opioid antagonist naloxone was not found to further decrease D2 receptor availability relative to control subjects, though a *post-hoc* analysis did suggest that persons with opioid dependence who received higher naloxone doses (0.02 mg/kg; $N = 7$) demonstrated greater reductions in D2 relative to persons who received a lower naloxone dose (0.01 mg/kg; $N = 2$).

The D2 Family of Receptors May Become Supersensitive Once Opioid Physical Dependence Develops

The evidence described above identifies a potential role for the D2 receptor family in the expression of opioid effects and introduces the notion that receptor quantity is not necessarily the only mechanism through which this occurs. This notion is supported by an abundance of data from animal studies that suggest chronic exposure to opioids leads to functional adaptations in the dopamine system that sensitizes the system to D2 agonists rather than changes in the quantity of receptors. This supersensitivity may, in turn, increase drug seeking by potentiating behavioral responses to D2-like activation or, theoretically, increase the reinforcing effects of D2 agonists. Consistent with changes observed over time in levels of striatal dopamine, supersensitivity also appears to last well-beyond the somatic resolution of withdrawal symptoms, suggesting they are enduring conformational changes.

For instance, doses of the D2 agonist quinpirole that are so low they produce no effect in control rats were shown to increase behaviors that resemble opioid withdrawal as well as stimulant-induced stereotypies in rats that were made dependent and then withdrawn from opioids. Moreover, quinpirole in that study was also shown to increase the rate of dopamine metabolism, an effect that was more pronounced at 48 than 24 h (82). Another study that administered the D2 receptor agonists propylnorapomorphine and quinpirole found they selectively increased locomotor activity in rats only once they had developed opioid physical dependence and were in a state of naltrexone-precipitated or spontaneous withdrawal; those effects were not observed when morphine was acutely administered to non-dependent animals or when the probe was a D1 receptor agonist (83). A comparison of the dopamine agonists apomorphine and dopamine to acetylcholine and prostaglandin E found that rats undergoing naloxone-precipitated withdrawal exhibited increased jumping behavior when apomorphine or dopamine were administered but showed no effect to the other substances; changes in jumping were also not evidence in animals that were not physically dependent on opioids or in animals that were physically dependent but not in a state of withdrawal (84).

Examination with the D2 receptor agonist bromocriptine has revealed similar outcomes. In rats trained to respond for cocaine and heroin, bromocriptine was found to be more potent in reinstating responding for heroin than it was for cocaine, evidenced by its ability to reinstate heroin responding at lower dose ranges than for cocaine. Bromocriptine also revealed a time x dose interaction in which larger doses engendered substantially more responding when administered at later vs. earlier time points; this effect was only observed in the heroin-trained animals

and the cocaine-trained animals showed no such effect (85). An examination of dopamine sensitivity and receptor quantity provides further evidence that these effects are not a byproduct of D2 receptor upregulation. Specifically, administration of the D2-probe [3H] spiroperdiol in rats that were chronically exposed to opioids revealed no differences in the number of D2-receptor binding sites, regardless of whether the rats were receiving opioid agonists, in a state of withdrawal, or were opioid-naïve control animals. In contrast, administration of the selective D2 agonist bromocriptine to animals that had opioid physical dependence increased their locomotor and stereotypic responses relative to control animals (86). Finally, a comparison of morphine and amphetamine in dogs found that initial doses of morphine increased locomotive behavior but did not produce the same type of stereotypies observed following amphetamine exposure; however, after repeated small doses of morphine stereotypies emerged, suggesting a supersensitivity had developed in response to repeated opioid agonist administration (87).

This effect has been rarely studied in humans and it is difficult to know whether the decreased D2 levels reported by the PET studies above reflect acute changes in D2 as a function of chronic opioid exposure (which would suggest it is the mechanism through which opioids may influence stimulant co-use) or whether reduced D2 levels precede the acquisition of opioid misuse. This latter point is supported by several studies that have implicated reduced D2 receptor density as a predictor of the strength of the reinforcing effects of drugs that exert dopaminergic activity (88–90). We know of only one study that examined dopamine supersensitivity in persons as a function of opioid exposure. That study conducted a venotest wherein small test doses of serotonin and dopamine were administered to men ($n = 7$) who had opioid physical dependence to measure changes in their smooth muscle response using orthodromic incanulization. When tested 3–12 h after their last opioid exposure, exposure to small challenge doses of serotonin and dopamine resulted in 100 and 1,000-fold changes in venous pressure, respectively. In contrast, norepinephrine had no effect. The participant with the most proximal exposure to heroin (3 h prior) showed the strongest response to dopamine, a 1,000-fold change. Naloxone administration reversed the direction of effects and decreased levels by 100 and 1,000-fold, and re-administration of morphine was able to restabilize levels (demonstrating causal relationships) (91). These data support the preclinical data presented and indicate that supersensitivity may at least play a role in the human experience.

Supersensitivity of the Dopamine System Continues to Intensify as the Opioid Withdrawal Syndrome Transitions From Acute to Protracted

Several studies that have examined the time course of dopamine supersensitivity have found that mild supersensitivity is evident almost immediately after the last opioid exposure in physically dependent animals and that supersensitivity continues to increase in strength over time, such that sensitivity peaks several days after the final opioid exposure. For instance, during a period of spontaneous opioid withdrawal, rats trained to nose-poke for heroin that received the D2 receptor family agonist quinpirole emitted a sensitized locomotor response around day 4 of withdrawal (with effects resolving by 21-days) (92). This outcome was also observed in rats that were withdrawn from morphine and followed over an 8-week protracted withdrawal period. These animals exhibited relatively low rates of lever pressing in response to morphine during the protracted withdrawal period but increased responding for the D2 agonist apomorphine. Moreover, the ability of apomorphine to elicit responding increased during the protracted period relative to when rats were physically dependent on opioids (93). Microdialysis studies have also found that although extracellular dopamine levels are increased by 35% in response to a morphine dose in animals that have been withdrawn from opioids for 2 days, administering morphine on days 3 and 5 of opioid abstinence increased dopamine levels by as much as 160% and this potentiation of dopamine release only began to resolve by day 7 of abstinence (the final day evaluated in this study) (76).

Another method for evaluating dopamine supersensitivity is through unilateral lesioning of dopamine neurons either through electrolysis or administration of the 6-OHDA dopamine-neurotoxin. In animals that have received a unilateral striatal lesion, dopaminergic agonism and antagonism produces ipsilateral and contralateral turning behaviors, respectively (94). Evidence suggests that rats with 6-OHDA lesions will elicit ipsilateral turning behavior in response to opioid agonists but not antagonists and that this behavior can be blocked by naloxone; these data support the notion that opioids confer dopaminergic effects and suggest this assay is useful for detecting opioid-induced changes in behavior (72, 95, 96). Consistent with the aforementioned evidence, 6-OHDA-related turning behavior is not evident when a single acute opioid dose is examined; it only emerges following chronic opioid exposure and then increases in frequency as opioid tolerance develops (96). In addition, once animals have developed a physical dependence on opioids, naloxone administration produces contralateral (e.g., antagonistic) turning behavior (72) which can be reversed by provision of the stimulant D2 agonists apomorphine and d-amphetamine (95). Co-administration of apomorphine and morphine in non-tolerant rats has also been found to increase ipsilateral (e.g., agonist) circling behaviors in an additive manner, signifying a dopamine agonist effect. Moreover, once an animal that has developed opioid physical dependence has been withdrawn from opioids, morphine will no longer elicit a turning response; however, apomorphine will continue to elicit the ipsilateral (e.g., agonist) turning response in animals during a period of withdrawal, and the intensity of the turning behavior has been found to increase as a function of time since last opioid exposure (96).

Finally, a series of behavioral assays provide additional evidence that the D2 receptor family becomes sensitized with extended opioid exposure. One study found that rats that were withdrawn from opioids exhibited excessive locomotor behavior on a rotometer during the withdrawal period that did not decrease to normal rates for 2-months (97). This effect has also been examined using aggression as a behavior

metric of dopaminergic activity and supersensitivity. One such study found that rats that received d-amphetamine while undergoing spontaneous opioid withdrawal exhibited pronounced enhancement of aggression that was evident immediately and increased in severity when d-amphetamine was administered at various points during the 70-h post-withdrawal observation period (98). A second study that withdrew rats from morphine and followed them for a 30-day period found that aggressive behaviors that were observed during opioid withdrawal could be blocked entirely by lesioning the nigrostriatal bundle (demonstrating a causal effect of the dopamine system in this behavior) and restored in lesioned animals through administration of the D2 receptor agonist apomorphine. Moreover, the dopamine turnover rate in the rats undergoing withdrawal, a measure of dopamine sensitivity, was also not found to differ between control and opioid-dependent animals prior to withdrawal but was significantly reduced in animals that had been withdrawn from opioids at a 30-days observation (99).

WHAT HUMAN EVIDENCE DO WE HAVE?

The preponderance of evidence for hypotheses concerning dopamine supersensitivity has been generated in preclinical studies; only a limited number of human studies are able to contribute to this discussion and none of them were prospectively designed to evaluate these specific hypotheses. Thus, the data presented below, comprised of correlational, retrospective, or secondary analyses, should be considered as preliminary evidence to support more focused research. Nevertheless, we present them here to provide some evidence that the dopamine system is both integral to opioid-based effects and becomes disrupted following extended opioid exposure and/or abstinence in humans.

Evidence That Opioids Produce Stimulating Effects in Humans

Only a few studies have examined the role of the dopamine system in the opioid physical dependence syndrome in humans. However, these studies do provide some preliminary evidence that corroborate the reviewed preclinical data by suggesting that supersensitivity to dopaminergic effects can be observed in humans following chronic opioid exposure as well as during periods of opioid abstinence. Two companion studies retrospectively assessed the experience of opioids in populations of individuals who were exposed to opioids for pain management and either did or did not continue on to develop opioid misuse or OUD. The first found that the initial subjective experience of opioids in persons who developed misuse behaviors ($n = 20$) was remembered as producing more opioid and stimulant-like effects, as determined by Addiction Research Center Inventory (ARCI) ratings, than was experienced by persons who did not continue on to develop misuse behaviors ($n = 20$) (100). A subsequent retrospective study by this group replicated the same ratings on the ARCI in a larger sample, and also found that persons who ultimately developed OUD ($n = 39$) were more likely to remember their first experience as producing effects consistent with increased dopaminergic activity, including feeling happy and experiencing greater activation than did persons who did not develop OUD ($n = 40$) (101). This effect has also been reported in laboratory studies. The first was a within-subject laboratory study that administered ascending doses of d-amphetamine and hydromorphone to individuals who had a history of opioid and stimulant co-use ($n = 5$) who then rated their subjective experience on the ARCI. The two highest doses of d-amphetamine administered (15 mg, 30 mg) produced scores on the morphine scale of the ARCI that exceeded the level produced by highest dose of hydromorphone (12 mg); in addition, 8 and 12 mg of hydromorphone produced a rating on the amphetamine scale consistent with 15 and 30 mg of d-amphetamine (102). The second was a within-subject human laboratory study that administered cocaine, hydromorphone, and cocaine/hydromorphone to persons with a history of cocaine and opioid use ($n = 8$). This study reported that cocaine (20, 40 mg) produced higher ratings on the morphine ARCI scale than did hydromorphone (1.5 mg, 3.0 mg) and that hydromorphone 3.0 mg produced higher ratings than cocaine on the ARCI amphetamine scale (103). Collectively these data provide evidence that opioids can produce a stimulating effect in humans, consistent with the preclinical work cited in the section above.

Evidence That Individuals With Opioid Physical Dependence Experience Positive Effects From Stimulants

The limited number of studies that have investigated the experience of stimulants in persons who have opioid dependence collectively suggest stimulants confer unique effects in that population. Several of these studies have been conducted in the context of the emergent twin epidemic of opioids and methamphetamine co-use and present qualitative descriptions of rationales for this co-use from people with lived experience. The first collected semi-structured interviews from people in Appalachian Kentucky who had a history of non-medical opioid and methamphetamine use (104). That study identified key person-level motives to use that include: (1) suppressing withdrawal and craving for opioids, (2) achieving an attractive or desirable high, and (3) addressing underlying mental or physical health needs. These motives are not selective to this population; similar themes have been consistently observed across demographically and geographically diverse groups of people such as people who inject drugs or use opioids in rural Oregon (105) and those entering treatment across admission sites in the United States (4) and more globally (106).

Additional studies provide more concrete evidence that the dopamine system is activated during opioid withdrawal in humans. The first was a human laboratory study that evaluated naloxone-precipitated opioid withdrawal in persons with opioid physical dependence that did ($n = 19$) or did not ($n = 33$) also report using cocaine (107). Withdrawal severity was observed to be lower in patients who had concurrent cocaine use relative to those who had exclusive opioid use across the full-time course examined. An accompanying preclinical experiment in

that paper reported that acute cocaine (20 mg/kg) was also able to reduce the severity of naloxone-precipitated withdrawal in rats. However, these data contrast with a survey study wherein people ($n = 89$) who had opioid physical dependence indicated that stimulating drugs (cocaine, amphetamine, nicotine, caffeine) were perceived as being less useful than depressants (e.g., benzodiazepines and alcohol) or cannabis at treating their opioid withdrawal. The majority of those patients felt that cocaine (62% of patients) and amphetamine (62%) increased the severity of the withdrawal syndrome, the highest for all drugs queried (108). This conflicting evidence may relate to the period when these stimulant drugs are administered (e.g., early or preempting withdrawal vs. during peak withdrawal period), duration of opioid use, or the stimulant dose administered; more systematic work is needed to evaluate these possibilities.

A third study used data from a 24-week randomized clinical trial comparing participants ($n = 125$) who were randomly assigned to varying doses of methadone (35 or 65 mg) or buprenorphine (2 or 6 mg buprenorphine) and found that subjects who received low doses of methadone or buprenorphine reported lower withdrawal in weeks wherein they had co-occurring cocaine use vs. weeks where they did not have co-occurring cocaine use (109). In contrast, patients who received high doses of buprenorphine reported higher withdrawal in weeks with co-occurring cocaine use. A dual model was proposed in which high maintenance doses of opioid drugs may result in a sensitivity to stimulant-induced withdrawal expression, a hypothesis consistent with some of the preclinical literature reviewed above, whereas low dose maintenance may result in a context where stimulant drugs alleviate low-level persistent withdrawal symptoms.

Evidence of Dopamine Supersensitivity in Humans With Opioid Physical Dependence

The small number of studies that have evaluated outcomes related to dopamine supersensitivity in persons with OUD can provide some evidence of this effect. Here we conceptualize reports of a desirable subjective high following stimulant administration to be suggestive of an increased sensitivity to the effects of dopaminergic compounds following a period of chronic opioid exposure and during acute (and possibly prolonged) abstinence. The first was a double-blind study that compared the subjective effects of intravenous cocaine (0, 12.5, 25, and 50 mg) in patients receiving methadone treatment (50 mg/day) to persons who had a history of non-medical opioid use without any current opioid physical dependence. In that study cocaine was observed to produce greater positive subjective effects (e.g., good effect, like drug) for participants maintained on methadone compared to those who did not have opioid physical dependence (110). A second double-blind, human laboratory study administered varying doses of intravenous cocaine (0, 8, 16, 32, and 48 mg/70 kg) to patients maintained on methadone. Patients maintained on the highest dose range of methadone (90–100 mg) showed greater ratings of positive subjective effects to acute cocaine administration compared to those maintained on lower dose ranges, although these findings were limited by the small sample ($n = 16$) and lack of randomization to methadone dose (111). In contrast to these studies however, a third study reported no effect of buprenorphine maintenance on subjective effects produced by intravenous cocaine (30 mg) using a within-subject pre (before maintenance) post (after maintenance) design (112). It is possible that differences in the intrinsic efficacy between methadone and buprenorphine contributed to this discrepancy or that participants had already achieved high levels of opioid exposure resulting in a ceiling effect.

HYPOTHESIZED NEURAL CIRCUIT OF DOPAMINE D2 HYPERSENSITIVITY DURING OPIOID WITHDRAWAL

Above, we described in detail preclinical and clinical data which suggests that D2 receptor hypersensitivity occurs specifically following opioid dependence and during states of acute or protracted opioid withdrawal, and that this change deviates from what is understood about stimulants alone and appears unique to stimulants in the context of opioid physical dependence. It is critical to understand how neural circuit changes due to chronic opioid use may differ from those that have been defined following use of chronic use of stimulants, which may also explain the emergence of psychomotor stimulant use among persons with OUD without premorbid chronic stimulant use. Preclinically, several studies have shown that withdrawal from cocaine induces a D1-driven mechanism, which drives cocaine seeking via disinhibition of the dopaminergic ventral mesencephalon, which in turn disinhibits the thalamus (113). Previously, it was thought that D1- and D2-expressing MSNs uniquely define the "direct" and "indirect" pathways projecting out of the striatum, originally from the dorsal striatum (114) and then later applied to the ventral striatum in the context of reward learning and cocaine use [e.g., (37, 115)]. However, more recent evidence suggests this dichotomy is inaccurate (36) as both D1- and D2-expressing MSNs project to the striatomesencephalic pathway and the striatopallidal pathway (116). Notably, in some of this work, none of the D2 MSNs identified appeared to project to the ventral mesencephalon (116). Moreover, another study found neurons projecting from the nucleus accumbens to dopamine neurons within the VTA that were inhibited by dopamine acting on D2 receptors (51). Collectively, these data indicate it is possible for a subpopulation of D2-expressing MSNs to project directly from the nucleus accumbens to the VTA. Despite the desegregation of D1 and D2 from the "direct" and "indirect" pathways, it has been repeatedly shown that D1-expressing MSNs are critical in driving cocaine seeking behavior (117–119), with a potential impairment in D2 inputs to the ventral pallidum to promote D1-driven cocaine seeking (120).

We now propose a novel neural circuit mechanism through these pathways, one that is uniquely consequential to chronic opioid use and withdrawal. It should be noted that the entirety of this circuit is based on hypotheses derived from neuroanatomical literature, and each of the steps within the proposed pathway need to be empirically tested. Although stimulants may strengthen D1 innervation of terminal fields,

we hypothesize that it is through strengthening of D2s that opioid withdrawal enhances the reinforcing effects of dopamine agonists, as well as alter other behaviors such as locomotor activity as described above. This hypothesis is supported by the fact that D1 agonists do not appear to have enhanced locomotor activity or show greater reinforcing efficacy following withdrawal from opioid use as well-one study finding that D2 receptors can suppress lateral inhibition from indirect MSNs to direct MSNs, which enhances the D1 output pathway in cocaine's stimulant actions [although, this suppression was specific to the collateral transmission, and did not impact transmission to the ventral pallidum; (121)]. This study specifically examined mechanisms relevant to cocaine, and it is not clear if collateral transmission would be enhanced or decreased following opioid use. Thus, in our hypothesized circuit (**Figure 2**), we have grayed the D1 projections from the nucleus accumbens to the ventral mesencephalon and the ventral pallidum. However, we acknowledge that this pathway may play a critical role in dopamine disinhibition in output structures, and thus we have included dopamine input from the ventral mesencephalon into the ventral pallidum and thalamus. Here we will systematically describe a potential novel circuit which we derived both from the relevant opioid and cocaine literature, and from a large body of neuroanatomical literature that has defined neurocircuitry in detail.

In **Figure 2**, we show a complex multi-step circuit, beginning in the nucleus accumbens (there are numerous glutamatergic projections into the nucleus accumbens as well, which we acknowledge may play a role in modulating nucleus accumbens circuit activity but are not included here). We propose that D2 receptors expressed on accumbens MSNs (122) originating in the nucleus accumbens and projecting to the ventral pallidum show enhanced functional activity (1). Given that D2 receptors are $G_{i/o}$ coupled inhibitory receptors (123, 124), they function as autoreceptors (32) and their activation would reduce GABAergic tone into terminal regions. Thus, hypersensitivity of D2 receptors located on accumbens MSNs would result in inhibition of GABAergic MSNs (2) projecting to the ventral pallidum (3) (113, 116). Importantly, it has been previously shown that inhibition of ventral striatal terminals into the ventral pallidum via upregulation of D2 receptors in the nucleus accumbens enhances motivation (125), thus supporting this potential mechanism in the proposed circuit. Importantly, ventral striatal projections from the nucleus accumbens to the ventral pallidum include cells the express mRNA of both glutamate decarboxylase [GAD; a rate-limiting enzyme that catalyzes the conversion of glutamate to GABA and is thus used as a marker for GABA-containing cells; (126)], and the peptide enkephalin (127, 128), which comprise 46% of projecting neurons (129). Although it is unclear if there are enkephalin-containing neurons that do not co-express D2, there are studies showing that a third neuronal subtype exists which contain both D1 and D2 mRNA (130, 131), and which express D1-D2 heteromers (132, 133). Although unknown, it is possible that D2 hyperactivity through this subset of neurons disinhibits enkephalin input into the ventral pallidum. This is premised on prior data showing that enkephalin indirectly exerts excitatory tone on hippocampal pyramidal cells via blockade of spontaneous and evoked inhibitory potentials, and inhibitory pathways are depressed by enkephalin (134). Thus, the ventral pallidum may be disinhibited by cells projecting from the nucleus accumbens via enkephalin (4). It is also possible that D1/D2 co-expressing MSNs comprise a third subpopulation of cells, which project GABAergically to the ventral mesencephalon (51). These neurons may play a critical role in opioid withdrawal and enhancement of dopamine sensitivity following chronic opioid use, because it has been previously shown that disinhibition of dopamine neurons induced by chronic opioid use involves multiple GABA inputs, and these pathways are selectively sensitive to μ opioid receptor agonists (51).

The next step in this circuit involves ventral pallidum projections to the mediodorsal thalamic nucleus, which is a primary terminal region of the ventral pallidum (135). Although this early study unsuccessfully determined the neurotransmitter system(s) of the ventral pallidum-mediodorsal thalamic nucleus projection, later studies determined that this projection contains both GABAergic (GAD-positive; 53%) and cholinergic (ChAT-positive; ∼16%) neurotransmitters (136, 137). Importantly, one prior study showed that both feeding and d-amphetamine administration enhanced extracellular acetylcholine in the medial thalamus, identifying a possible role of acetylcholine in this region in reward (138). Thus, although a much smaller proportion of cells as compared to GABA, it is possible that activation of the ventral pallidum may enhance cholinergic input into the mediodorsal thalamic nucleus, thus driving drug use during opioid withdrawal (5). Next, we describe potential dopaminergic modulation of the thalamus in our hypothesized circuit. Given that the ventral pallidum sends GABAergic projections to the dopaminergic mesencephalon (128, 139), we hypothesize that this may be disinhibited as a consequence of chronic opioid use, leading to enhanced dopaminergic tone into output structures of the mesencephalon including a loop back to the ventral pallidum and also to the thalamus, as it has been previously shown that dopaminergic neurons of the ventral mesencephalon project bilaterally to the thalamus (140). As well, it is possible that D1-MSNs do not send strong GABAergic tone into the ventral mesencephalon after chronic opioid use, given that D1 receptors do not appear to be involved in hypersensitivity to dopamine agonists.

The net result may be enhanced dopaminergic signaling due to dopamine agonists during withdrawal from chronic opioids. It has been previously established that the ventral pallidum receives dopaminergic innervation from the ventral mesencephalon (141). Because the mesencephalon contains a mix of A9 and A10 midbrain dopamine neuron subtypes (142, 143), we hypothesize that this group of midbrain structures projects dopaminergically into the thalamus (6) and enhances its activity following opioid use (7). We also hypothesize that this projection, along with the accumbens-pallidal-thalamic projection [steps 1–5], plays a potential role in driving enhanced sensitivity to dopamine agonists during opioid withdrawal (8). Recently, there has been an interest in the role of thalamic nuclei in addiction (144), and thus we hypothesize that this is a critical output structure involved in opioid withdrawal-induced enhancement of dopamine agonists.

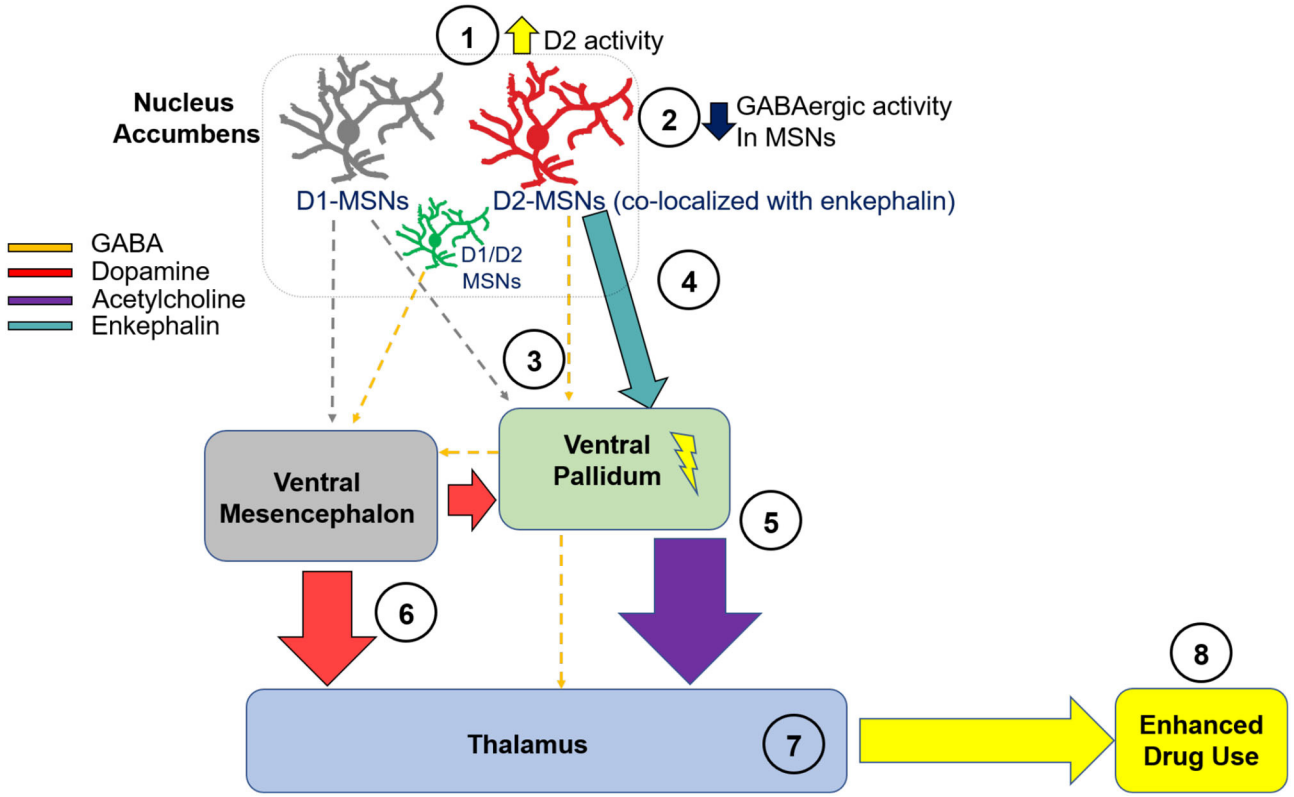

FIGURE 2 | Hypothesized Neural Circuit of D2 Hypersensitivity in Opioid Withdrawal. We hypothesize that D2 receptor activity is during withdrawal from chronic opioid use (1), which leads to decreased activity of GABAergic MSNs within the NA (2). This leads to a reduction in GABAergic inhibitory tone from the NA to the VP (3). Through the direct projection to the VP, disinhibition of the VP from reduced NA-derived GABAergic innervation leads to enhanced excitability of cells residing in the VP. It is also possible that MSNs co-expressing D1 and D2 receptors project from the NA to the VM, and play a critical role in enhancing dopaminergic signaling from the VM to output structures. As well, enhanced enkephalin activity may enhance neuronal excitability within the VP (4). This excitation leads to enhanced acetylcholine release into the MD (5), which may enhance reward. Through the direct GABAergic projection from the VP to the mesencephalon, there is less inhibitory tone and consequently, enhanced dopaminergic activity in cells residing in the VM and projecting back to the VP or to the MD (6). The net result of these neural adaptations is enhanced excitability of thalamic nuclei including the MD (7), and, consequently, enhanced use of dopamine agonists during opioid withdrawal (8). NA, nucleus accumbens; VP, ventral pallidum; VM, ventral mesencephalon; MD, mediodorsal thalamic nucleus; D2, dopamine receptor D2; D1, dopamine receptor D1; MSN, medium spiny neuron.

HOW CAN THESE DATA INFORM TRANSLATIONAL RESEARCH

Collectively, these data suggest that following chronic exposure to an opioid and development of opioid physical dependence, the dopamine system appears to operate in a typical manner when an opioid agonist is concurrently present. However, the absence of an opioid agonist causes a disruption of dopaminergic signaling that is evident very shortly after the final opioid exposure occurs, and that disruption grows in severity and intensity as the acute withdrawal period extends into the protracted withdrawal period. Studies that examined long-term changes in functioning suggest that alterations in dopaminergic signaling may not resolve for several weeks. Although some data have been collected in human laboratory and clinical settings that may inform this hypothesis, the specific degree to which dopamine supersensitivity intensity occurs and the time course over which it develops and resolves in humans is uncertain. Moreover, differences in how opioid withdrawal is expressed, as well as its normal time course, between animals and humans makes it challenging to directly translate the preclinical evidence to the human clinical condition. Nevertheless, a few noteworthy conclusions from this review can be made, each of which point toward critical translational steps for future research with broader implications for the stimulant-opioid co-use epidemic as well as opioid relapse (see also **Table 1**):

(1) Changes in the dopamine system occur only once physical dependence to the opioid develops and the chronicity of opioid exposure is associated with the magnitude of changes.
(2) Opioid withdrawal leaves the organism in a state of substantive dopamine deficit.
(3) Changes in dopamine levels and signaling persist long after the somatic or observed signs of opioid withdrawal appear to have resolved (thus, organisms that appear to have

TABLE 1 | Notable conclusions, clinical implications, and future research directions.

Notable conclusions	
1	Changes in the dopamine system occur only once physical dependence to the opioid develops and the chronicity of opioid exposure is associated with the magnitude of changes
2	Opioid withdrawal leaves the organism in a state of substantive dopamine deficit
3	Changes in dopamine levels and signaling persist long after the somatic or observed signs of opioid withdrawal appear to have resolved (thus, organisms that appear to have resolved the acute withdrawal syndrome may be continuing to function in a dysregulated state, suggesting continued sensitivity to acute withdrawal consequences)
4	Once physical dependence occurs, a state of dopamine supersensitivity develops very soon after abstinence from opioids begins
5	Supersensitivity to drugs that function as dopamine agonists (including low doses of opioids and otherwise subthreshold doses of dopamine agonists) increases as the abstinence period continues and is evident several weeks into the protracted withdrawal period
6	Changes appear to be driven by conformational changes in the sensitivity but not quantity of the D2-family of receptors
Clinical implications	
1	Stimulant-opioid co-use may confer euphoric effects that are greater than what is produced by either drug alone or what may be experienced by persons who do not have opioid physical dependence
2	Stimulants may partially remediate symptoms of opioid acute withdrawal, thus reinforcing stimulant-opioid co-use
3	Opioid acute and protracted withdrawal may be characterized by a hypo-dopaminergic state during which an individual may experience an enhanced motivation to restore dopamine function that can manifest as craving and/or opioid relapse
Future research directions	
1	Evaluate presence and time course of dopamine supersensitivity in humans with opioid physical dependence during periods of opioid maintenance and withdrawal
2	Evaluate new and/or repurposed D2 agonists or antagonists for stimulant-opioid co-use treatment, opioid withdrawal remediation, and/or opioid relapse prevention/craving remediation

resolved the acute withdrawal syndrome may be continuing to function in a dysregulated state, suggesting continued sensitivity to acute withdrawal consequences).

(4) Once physical dependence occurs, a state of dopamine supersensitivity develops very soon after abstinence from opioids begins.

(5) Supersensitivity to drugs that function as dopamine agonists (including low doses of opioids and otherwise subthreshold doses of dopamine agonists) increases as the abstinence period continues and is evident several weeks into the protracted withdrawal period.

(6) Changes appear to be driven by conformational changes in the sensitivity but not quantity of the D2-family of receptors.

Implications for Increased Reinforcing Effects of Stimulants

Stimulant-Opioid Co-use for Euphoric Effects

Supersensitivity of the dopamine system that develops following chronic opioid exposure would presumably increase the reinforcing effects of dopaminergic agonists (such as cocaine and methamphetamine) beyond what might be experienced in people who are using opioids but have not yet developed opioid physical dependence and at levels that could possibly be greater than what is experienced in non-tolerant, opioid-naïve individuals. If true, this hypothesis would suggest that exposure to a stimulant during a state of opioid physical dependence would produce a unique and robust reinforcing effect, which theoretically could increase the likelihood the drugs would be co-used.

Preclinical evidence already partly supports this suggestion. One experiment evaluating cocaine and the opioid agonist remifentanil in rodents showed increased sensitivity to cocaine (i.e., increased hedonic setpoints and reduced sensitivity to increasing response cost) among animals that had a greater prior exposure to the opioid remifentanil (145). This effect was not reciprocal; prior exposure to cocaine was not associated with later remifentanil use motivation. These data suggest that exposure to opioids prior to cocaine administration increased cocaine reinforcement in a manner that was directionally and pharmacologically-specific. Another study found that among non-human primates, motivation to use cocaine was higher during periods of morphine withdrawal and that this period of increased use extended four-to-five weeks after chronic opioid exposure ended (146). The human laboratory data reviewed above similarly partly support this notion, for example, with greater subjective effects of intravenous cocaine observed among those with a history of opioid physical dependence (110). Systematic and controlled studies to this end are needed.

Stimulant Use for Opioid Withdrawal Remediation

Another pathway through which co-use could be reinforced is by remediation of the acute opioid withdrawal syndrome. The daily pattern of opioid use is generally characterized by frequent administration of a short-acting opioid several times a day. Functionally, this means that during the inter-dose interval an individual will start moving into a state of acute opioid withdrawal several times throughout the day. The data reviewed here suggest acute withdrawal is associated with both a dopamine depletion and development of dopamine receptor supersensitivity that can emerge following even a short period of opioid abstinence and whose magnitude is at least somewhat related to the chronicity of prior opioid exposure. Thus, exposure to a dopamine agonist during a period of

transition into acute withdrawal could theoretically produce a reinforcing effect that is enhanced relative to its administration in a non-opioid dependent state, and which might engender additional co-use behavior. Although these effects have not been systematically evaluated in humans, the data reviewed here reveal a putative mechanism through which dopaminergic agonists could produce extra-stimulating effects and some evidence for mitigation of this withdrawal syndrome that might strongly maintain co-use behavior. However, evidence also suggest a possibility for precipitation of opioid withdrawal-like symptoms following stimulant administration among a subset of patients. These findings emphasize the need for parametric evaluation of factors that impact the precipitation vs. alleviation of opioid withdrawal by stimulants drugs to include history of use, timing of administration, and type of dopamine agonist.

Implications for Opioid Relapse

In clinical practice, the period of time after an individual is fully withdrawn from opioids is characterized by excessively high rates of opioid relapse, particularly during the first 30 days. Relapse during this period is also extremely dangerous; the lack of opioid tolerance following withdrawal raises the risk of fatality due to overdose to a level higher than at any other point during a person's opioid use history. It is recognized that people who have been withdrawn from opioids experience a protracted withdrawal syndrome, and while the actual composition of that syndrome has not been sensitively characterized it is generally believed to consist of persistent mood disruptions, craving, and sleep disturbance. The clinical importance of the protracted withdrawal symptoms is often overshadowed by the more visible and better characterized acute withdrawal syndrome, around which most of our opioid-related treatments are organized.

The data reviewed here provide evidence that the resolution of observable and/or somatic withdrawal symptoms does not reflect a resolution of the acute withdrawal syndrome and that the organism is likely still in a state of dopamine deficit even once overt signs of physical withdrawal symptoms have abetted. Dopamine deficits have themselves been independently associated with mood impairments, suggesting this state could be responsible for some of the mood-related symptoms generally characterized as protracted withdrawal. Moreover, the fact that dopamine signaling is not only dysregulated, but may become super-sensitized during the immediate protracted period, provides a putative mechanism through which the excessively high rates of relapse to opioids in early abstinence may occur. Specifically, the collective data reviewed suggest that during a state of dopamine supersensitivity, exposure to a drug that produces a stimulating effect (a low dose of an opioid or of a stimulant) may produce a more robust and reinforcing effect than it would have produced during a state of opioid satiety (prior to withdrawal). Data further suggest that this effect will become stronger over time before eventually stabilizing several weeks later. Although hypothetical, this supersensitivity could manifest to the individual as a general "urge" or "craving" to use a substance, particularly something that they have previously associated with the restoration of dopamine levels (147). This is supported by evidence that craving for opioids also increases in severity following withdrawal from opioids (148), a phenomenon referred to in the preclinical field as "incubation of craving" (149). It is therefore plausible that the dopamine deficit and resultant supersensitivity that is present following opioid withdrawal could be driving increases in opioid-related craving. In a state of dopamine deficit and supersensitivity, exposure to even low doses of opioid or stimulant could theoretically produce a reinforcing effect that is higher than what had been recently experienced and precipitate a relapse to regular opioid use.

COMPETING HYPOTHESES

The collective data reviewed here support a novel and testable hypothesis that (if true) would advance our understanding of why stimulant and opioid co-use occurs, as well as inform risk for opioid relapse during periods of acute abstinence. As this hypothesis remains untested, it is important to acknowledge competing hypotheses that may also explain these same behaviors. One example is the Reward Deficiency Syndrome (RDS), which hypothesizes that chronic opioid exposure produces a hypodopaminergic state that leads to compulsive drug seeking [see (150–152) for review of RDS]. The reward deficiency syndrome posits that genetically-mediated (e.g., trait) differences between individuals underlie differential dopamine function and subsequent drug use behavior. Our hypothesis posits that the same individual could move in and out of a state of dopamine supersensitivity as their opioid physical dependence changes over time (e.g., state-based differences). It is therefore possible that these two theories could be operating in parallel. However, it is also possible for these theories to be competing with each other, and some of the data reviewed here support both potential theories. For instance, the clinical PET imaging data reviewed do not strongly support our current hypothesis, though they were also not designed to examine D2 supersensitivity and were conducted with small and selective samples (e.g., predominately male); thus, the degree to which they support or refute this theory is uncertain. We also did not uncover any preclinical studies that examined receptor function in the context we described, namely a period of acute abstinence from opioids in animals that had established opioid physical dependence. It is also possible that the effects we describe are driven by neuroadaptations in other non-dopamine substrates or circuits. The vast majority of studies reviewed in support of this hypothesis were conducted several decades ago and reported outcome measures that do not reflect current techniques or a contemporary understanding of neural architecture and function, so these questions remain untested.

CONCLUSIONS AND CALL FOR FUTURE RESEARCH

Collectively, this existing evidence base outlines putative mechanisms to understand how conformational changes to the dopamine system in persons with opioid physical dependence may contribute meaningfully to opioid-stimulant co-use as well as opioid-relapse behavior. This hypothesis is based almost exclusively on animal research models, which are highly rigorous but challenging to translate to the human condition. More research is needed in human models to examine

dopamine supersensitivity following development of opioid physical dependence. These data also provide potential pathways for medication development. A variety of D2 receptor family medications exist on the market for other indications that could be repurposed as treatments for new onset stimulant use in persons with opioid use disorder and/or opioid relapse prevention or opioid withdrawal remediation. This may include a dopamine agonist replacement approach using D2 agonists such as bromocriptine, pergolide, lisuride, ropinirole, risperidone, and prampipexole or D2 partial agonists aripiprazole and brexpiprazole. Additional work may also focus on D2 receptor antagonism using medications such as buspirone, metoclopramide, tiapride, or raclopride. It is acknowledged that several prior attempts to utilize agonist replacement or D2-specific treatments for stimulant use disorder have been ineffective, and that several of these medications are also recognized as producing somewhat low or minimal effects for their indicated conditions (153, 154). However, since the data presented here indicate these medications may exert more potent effects in persons with opioid physical dependence than the general population and that these effects may be especially relevant during withdrawal from opioids, these approaches should not be ruled out on the basis of those prior studies. These data suggest that the population of people who have developed opioid physical dependence will likely have a unique response to dopaminergic medications. Importantly, the fact that these FDA-approved medications are largely unscheduled means that, if effective, there would be few barriers to their clinical adoption. Such an approach could help dramatically scale up treatment access and provide a method to combat the growing co-use epidemic, as well as provide an empirically-supported method to augment existing opioid treatment paradigms. In the context of an ever growing and evolving opioid crisis, with increasing morbidity and mortality, innovative approaches are needed, and the data reviewed here provide a pathway for exploration that is worth pursuing.

AUTHOR CONTRIBUTIONS

All authors conceptualized the topic, drafted the manuscript, and reviewed and approved the final version.

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