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Naloxone-induced Withdrawal in Individuals with and without Fentanyl-positive Urine Samples

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Abstract

Background and Objective: This retrospective analysis of data from heroin users screening for clinical research, sought to determine if more naloxone is needed to precipitate opioid withdrawal among those who regularly use heroin with fentanyl, as opposed to those who use heroin without fentanyl.

Methods: Over the course of 3–5 screening visits, participants completed assessments of drug use, along with urine toxicology tests at each visit. To test for opioid dependence, participants completed a modified Wang Test (score: 0–150) during which an intramuscular dose of naloxone (0.2mg - 0.4mg) was administered and the severity of withdrawal was quantified.

Results: The severity of opioid withdrawal was compared between individuals whose urine toxicology regularly tested positive for fentanyl (N=15), and those only positive for other opioids (N=14). No significant differences were found in demographic or drug use between the Fentanyl Positive (mean: age 41.1 years, 9.1 bags heroin/day) and Fentanyl Negative (42.0 years, 10.0 bags heroin/day) groups. Intramuscular naloxone precipitated robust withdrawal in both samples ($p < 0.01$) with no significant difference ($p = 0.8$) in the severity [Fentanyl + (100.6 ± 13.4); Fentanyl - (82.7 ± 9.6)].

Conclusions and Scientific Significance: These data suggest that a standard naloxone dose can be equally effective at precipitating withdrawal in individuals using heroin with fentanyl compared to heroin without fentanyl. These data contribute to our understanding of how naloxone antagonizes the effects of fentanyl and may have significant implications for the clinical laboratory and opioid overdose. A prospective clinical laboratory study with the proper opioid maintenance controls is needed to provide a more definitive finding.

Keywords

Naloxone; Heroin; Fentanyl; Precipitated-Withdrawal; Naloxone Challenge

Introduction

The naloxone challenge procedure involves the administration of the opioid-receptor antagonist, naloxone, to assess for and quantify the degree of physiologic opioid dependence based on the presence or absence of physiological and subjective indicators of opioid withdrawal¹. The naloxone challenge paradigm has been utilized in various clinical capacities for over 40 years². In the clinical laboratory, this paradigm is often a critical screening tool to verify chronic opioid use³. This diagnostic tool is also important for the management of opioid use disorder (OUD). The naloxone challenge is recommended as a method of antagonist-assisted detoxification⁴. Additionally, the test is recommended as a part of induction procedures onto antagonist-based OUD pharmacotherapy (i.e., naltrexone), where it is used to avoid medication-precipitated opioid withdrawal⁵. Finally, the severity of naloxone-precipitated withdrawal, as assessed using in this paradigm, has been shown to predict opioid use disorder treatment response⁶. However, the changing face of non-medical opioid use may have a significant impact on the efficacy and generalizability of this assessment.

The Centers for Disease Control and Prevention (CDC) has attributed the most recent wave of opioid overdose deaths to the increased use of the illegally manufactured, synthetic opioid, fentanyl and its related analogs⁷. Medically, fentanyl is used for anesthesia and to treat severe pain, however, in the illicit drug market, fentanyl is often mixed with heroin in order to increase its potency⁸. Fentanyl is generally estimated to be 100 times more potent than morphine, and some analogs like carfentanil are up to 10,000 times more potent than morphine⁹. The higher potency of fentanyl in comparison to other opioids and its increased prevalence in the street drug market may have important implications for the utility of the naloxone challenge paradigm. The stronger affinity of fentanyl for the μ -opioid receptor may make it more difficult for naloxone to displace it from the receptor. Therefore, a fentanyl-dependent individual may not as show somatic opioid withdrawal, in response to naloxone administration. A better understanding of naloxone's ability to antagonize fentanyl is important for this clinical laboratory assessment and may also have important implications concerning the use of naloxone to reverse fentanyl-related overdoses. The current study utilized clinical laboratory screening data from several ongoing studies in order to assess whether more naloxone is needed to precipitate withdrawal among opioid-dependent individuals who regularly use heroin with fentanyl compared to those who do not use fentanyl.

Materials and Methods

Participant Screening:

This study is a secondary analysis that utilized data from current non-medical opioid users (primarily heroin) screening for clinical research studies ([ClinicalTrials.gov](https://clinicaltrials.gov) IDs: , ,) at the

New York State Psychiatric Institute (NYSPI)/Columbia University Irving Medical Center (CUIMC). These studies all aim to recruit opioid-dependent participants who are not actively seeking treatment for OUD. Following a telephone screen, potential participants were scheduled for additional screening procedures at NYSPI/CUIMC. Screening consisted of various self-report assessments, along with clinical interviews concerning drug use, medical and psychiatric history.

Participants are generally required to be physically healthy users of heroin (or non-medical use of opioid analgesics) between the ages of 21 and 60 years. Participants were excluded for psychiatric symptomatology that may have impaired their ability to provide informed consent (e.g., active bipolar disorder or schizophrenia) or make participation hazardous (e.g., a significant history of violence). Screening typically necessitated 3–5 visits to determine eligibility. Rapid urine drug toxicology tests were conducted at each visit using a standard 11-panel drug urine test (amphetamine, barbiturate, benzodiazepine, buprenorphine, cocaine, methamphetamine, methadone, opiates, oxycodone, PCP, and THC), along with an individual test for fentanyl. The One Step Fentanyl Test Dipcard provided qualitative analytical results for fentanyl above the detectable level of 200ng/ml. This test also has specificity for the following analogs: norfentanyl (>40ng/ml), sufentanyl (>50,000 ng/ml) fenfluramine (>50,000 ng/ml).

Naloxone Challenge:

The final screening procedure was a naloxone challenge test to verify opioid dependence. The naloxone challenge procedure we use is a slightly modified version of the Wang test. Participants were asked not to change their pattern of drug use in order to prepare for the challenge. The challenge began with pre-naloxone measurements of pupil diameter (using a NeurOptics™ Pupillometer under ambient lighting conditions), vital signs (heart rate, blood pressure, and pulse oximetry), and symptoms of opioid withdrawal (gooseflesh, vomiting, tremor, sweating, restlessness, lacrimation/nasal congestion, yawning, warming/cooling sensations, stomach pain, and muscle ache). A trained research nurse performed the naloxone challenge test. Symptoms of opioid withdrawal were rated as being either “absent” or “present.” Points were added to the outcome score for “present” symptoms, while no points were added for “absent” symptoms. After pre-test assessments, the nurse began with a 0.2 mg intramuscular dose of naloxone. Some naloxone challenge procedures begin with a larger naloxone dose (0.4 – 0.8 mg)^{1,5}. Though our procedure begins with a lower dose, if no withdrawal signs were present after 10 minutes (score = 0), an additional 0.2 mg was administered. If no withdrawal signs were present after an additional 10 minutes, another 0.4 mg dose was administered. Separating the naloxone administrations in this manner provides a more sensitive assessment of the degree of physiological opioid dependence. In order to accommodate this variability in the amount of naloxone that could have been administered, the scoring of the Wang Test was modified. To calculate the final score, the total score across the entire testing period was multiplied by 4 if only 0.2 mg of naloxone was used, and by 2 if a total dose of 0.4 mg was used (Range: 0–150). No participants in the current analysis needed more than 0.4 mg of naloxone to induce withdrawal. For participants who exhibited significant withdrawal symptoms (score > 10) after the 20-minute assessment, a rescue dose of oral morphine (30 mg) was administered. Following the morphine rescue, participants are

monitored/assessed for an additional 30 minutes. The primary outcome measures were the severity of naloxone-precipitated withdrawal and pupil diameter, a measure of μ opioid receptor activation¹⁰. For safety, vital signs (heart rate, blood pressure, pulse oximetry) were monitored throughout the testing period.

Data from the naloxone challenge screening sessions were collected from December 2016 to December 2018 for the current analysis. For this analysis, naloxone challenge testing sessions were compared between individuals whose screening urine samples regularly tested positive for the presence of fentanyl (or tested positive for fentanyl the day of the challenge procedure) and those who did not. Challenge data from participants whose urine samples were opioid-free at any point during screening, or tested positive for buprenorphine on the day of the naloxone test session were excluded from the current analysis. All procedures were approved by the NYSPI Institutional Review Board, and this study was conducted in accordance with federal regulations (i.e. 45 CFR 46)..

Statistical Analyses:

Continuous and categorical demographic variables were summarized descriptively. Naloxone test session comparisons between fentanyl positive and fentanyl negative groups were made using chi-square (X^2) tests (w/ Yates correction) for nominal variables. For continuous demographic variables, between-samples T-tests were used. Naloxone challenge data were assessed using a repeated-measures analysis of variance (ANOVA) with Group (Fentanyl Positive vs. Fentanyl Negative) and Time as factors. In cases where a significant main effect or interaction was found, T-tests were used to identify group differences. The distributions of all continuous variables were checked for normality before applying parametric tests. All statistical comparisons were two-sided, and the critical level for rejection of the null hypothesis was a p of < 0.05 . All data analyses were performed using SPSS Version 25¹¹. As this study was a secondary analysis that relied on existing data, a power analysis was not performed.

Results

Participants:

Data from 29 naloxone challenge sessions were analyzed, 15 from subjects who tested positive for fentanyl and 14 from those who only tested positive for other opioids (hereinafter referred to as the “Fentanyl Positive” and “Fentanyl Negative” groups, respectively). On average each participant provided 3.7 urine samples. Urine toxicology results from the day each participant completed the naloxone challenge are shown in Table 1. Urine samples taken on the day of the naloxone challenge procedure were collected under close observation by a research assistant.

No significant differences were found in demographics or drug use outcomes between the two groups (Table 2).

Naloxone-Precipitated Withdrawal:

Outcome data were examined as a function of absolute values and percent shift from baseline (pre-naloxone administration). Since no substantive differences were found between these analyses, for the sake of brevity, only absolute values are presented. The mean dose of naloxone administered did not significantly differ between the Fentanyl Positive ($0.26 \pm .09$ mg) and Fentanyl Negative ($0.27 \pm .10$ mg) groups. Following naloxone administration, withdrawal scores significantly increased for both the Fentanyl Positive and Fentanyl Negative groups (p 's < 0.01 ; Figure 1). No significant differences in the severity of withdrawal scores were observed between the Fentanyl Positive and Fentanyl Negative groups at any individual time point, or in the total sum score. All participants required morphine reversal of naloxone-precipitated withdrawal.

Pupil Diameter:

Pupil diameter increased following the administration of naloxone, though this increase only reached statistical significance for the Fentanyl Positive group ($p < 0.05$; Figure 1). Pupil diameter did not differ significantly between the two groups at any point assessed.

Discussion

The current pilot study found no significant difference in the degree of naloxone-precipitated withdrawal among heroin users whose urine toxicology results indicated recent or regular use of fentanyl. These data suggest that the standard naloxone doses used in naloxone challenge procedures may be equally effective among individuals using fentanyl compared to less potent μ opioid receptor agonists. In this study a relatively small dose of intramuscular naloxone was used, therefore, is unlikely that we are observing a withdrawal ceiling effect and that no difference in sensitivity was found.

None of the participants in our sample reported being primarily fentanyl users, and only one actively sought heroin adulterated or "cut" with fentanyl. Therefore, our findings are limited to heroin users whose heroin supply is being cut with fentanyl by drug dealers and may not be generalizable to a fentanyl dependent population. Nevertheless, heroin users without specific intentions to use fentanyl are an important population to study, given the changing face of the illicit opioid market. Though these findings are provocative, there are several limitations to the present study.

The primary limitation of this trial is that urine toxicology tests cannot provide quantitative information concerning fentanyl use and our urine toxicology screen is unable to detect many fentanyl analogs. Thus, this trial had no controls for the amount, duration, or type (specific analog) of fentanyl that was detected among our Fentanyl Positive group. Furthermore, a lack of objective information about the subjects' opioid regimen is also a concern for our Fentanyl Negative group. In addition, the purity and other drug adulterants (e.g., benzodiazepines) of street heroin may have varied among the participants. Additionally, the severity of physical dependence is also dependent upon patterns of drug consumption (e.g., duration of action, frequency of use, duration of use, etc.). Finally, naloxone is often used clinically intramuscularly and intranasally. The impact of differential

absorption based on the route of administration may be relevant to future studies. As such, a prospective clinical laboratory study with the proper opioid maintenance controls is needed to provide a more definitive answer concerning the efficacy of naloxone to precipitate withdrawal in individuals using fentanyl.

A better understanding of how naloxone antagonizes the effects of fentanyl may have significant implications for the opioid overdose epidemic. Multiple investigations have noted the increased fentanyl-related overdose deaths in several states across the U.S.,^{12, 13}. Expanded availability of naloxone has become a principal opioid overdose harm reduction effort^{14, 15}. Anecdotal reports suggest that a greater amount of naloxone is needed to reverse an overdose event in which fentanyl is a contributing drug^{16,17}. The ability of naloxone to antagonize fentanyl-induced respiratory depression deserves carefully controlled extensive investigation, as it may have important implications for overdose mortality. In conclusion, the interaction between naloxone and fentanyl deserves further study and could have significant implications for the study of physiological opioid dependence in the clinical laboratory as well as an opioid overdose in the field.

Declaration of Interest and Sources of Funding

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Figure 1:

Mean ($\pm$ standard error) withdrawal severity score and pupil diameter before and after the administration of intramuscular naloxone (NLX). * indicates significant difference from pre-NLX baseline (* $p < 0.05$; ** $p < 0.01$). There were no significant differences between Fentanyl Positive and Fentanyl Negative groups. To calculate the final score, the sum score across the time points is multiplied by 4 if only 0.2 mg of NLX was used, and by 2 if a total dose of 0.4 mg was used.

Table 1:

Testing Day Urine Toxicology

FEN - Subject ID:	Amphetamine > 300 ng/mL	Barbiturate > 300 ng/mL	Benzodiazepine > 300 ng/mL	Buprenorphine > 10 ng/mL	Cocaine > 300 ng/mL	M-amphetamine > 1000 ng/mL	Methadone > 300 ng/mL	Opiates > 300 ng/mL	Oxycodone > 100 ng/mL	PCP > 300 ng/mL	THC > 50 ng/mL
001					+			+			
002					+			+			
003								+			+
004					+			+			
005								+			
006					+		+	+			
007					+			+			+
008			+				+	+			
009								+			
010								+			
011					+		+	+			
012							+	+			
013								+			
014								+			+
FEN + Subject ID:	Amphetamine > 300 ng/mL	Barbiturate > 300 ng/mL	Benzodiazepine > 300 ng/mL	Buprenorphine > 10 ng/mL	Cocaine > 300 ng/mL	M-amphetamine > 1000 ng/mL	Methadone > 300 ng/mL	Opiates > 300 ng/mL	Oxycodone > 100 ng/mL	PCP > 300 ng/mL	THC > 50 ng/mL
015								+			+
016							+	+			
017					+		+	+			
018								+			
019								+			
020								+			+
021					+		+	+			+
022					+			+			+
023					+			+			
024			+		+			+			
025							+	+			
026					+		+	+			
027			+					+			+
028								+			
029						+		+			

Table 2:

Sample Demographics and Naloxone-Precipitated Withdrawal Severity

Demographics			
	# Participants (%) or Mean (Std. Dev.)		
	<i>Fentanyl Positive (n=15)</i>	<i>Fentanyl Negative (n=14)</i>	<i>Statistic (p-value)</i>
Age	41.1 (12.1)	42 (7.3)	$t = -0.2, p = 0.4$
Sex			
Male	14 (100)	13 (87.5)	$\chi^2 = 0.1, p = 0.8$
Female	0 (0)	2 (12.5)	
Self-Reported Heroin Use			
Heroin Use (bags/day)	9.1 (7.0)	10.0 (7.3)	$t = -0.4, p = 0.4$
Years of Use	16.2 (8.8)	16.0 (9.3)	$t = 0.05, p = 0.5$
Current Route of Administration			
Intranasal	6 (40)	7 (50)	
Intravenous	6 (40)	6 (43)	$\chi^2 = 0.03, p = 0.9$
Both (50–50)	2 (20)	1 (7)	
Self-Reported Concomitant Substance Use in the Past 30 Days: # Participants (%)			
Nicotine	14 (93)	13 (92)	$\chi^2 = 0.1, p = 0.8$
Mean Cigarettes per Day (Std. Dev.)	10.7 (6.1)	10.4 (5.2)	$t = 0.1, p = 0.5$
Cocaine	8 (53)	6 (43)	$\chi^2 = 0.3, p = 0.6$
Benzodiazepines	3 (20)	4 (28)	$\chi^2 = 0.1, p = 0.8$
Marijuana	6 (40)	4 (28)	$\chi^2 = 0.6, p = 0.4$
Prescription Opioids	1 (6)	1 (7)	$\chi^2 = 0.3, p = 0.6$
Final Severity Withdrawal Score (0–150)			
	Mean (Std. Dev.)		
	100.4 (50.5)	82.7 (36.0)	$t = 1.1, p = 0.8$