Methadone treatment and associated health and social outcomes after a national manufacturing closure in Mexico: a longitudinal observational cohort study in Tijuana

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Summary

Background Medications for opioid use disorder (MOUD) are key to the prevention of drug overdose and bloodborne infections among people with OUD while also improving psycho-social wellbeing. From February to August 2023, following government orders, *Psicofarma*, Mexico's primary methadone production facility remained closed, interrupting its supply nationwide. We aimed to explore associations between the time periods during and after the closure and prevalence of methadone treatment, drug use, mental health and social harms among methadone treatment patients.

Methods We examined these associations among 200 MOUD clinic patients in Tijuana, using log-binomial regressions via generalized estimating equations (GEE) over three six-month response periods during and post-closure (Period 1, during and post: 07/2023–01/2024, Period 2, post, limited availability: 02/2024–07/2024 and Period 3, post, restored availability but fewer clinics open: 08/2024–12/2024). We ran three sets of GEE models to test for potential mediation effects of methadone treatment on associations between response period and deleterious outcomes.

Findings Time period was associated with methadone treatment (i.e., significant decline from 36% in Period 1–13% and 26% in Periods 2 and 3, respectively), and with drug use (opioids, methamphetamine, benzodiazepines, injection use), and mental health (anxiety symptoms) outcomes.

Interpretation Methadone treatment often suppressed the strength of the associations between time periods during and after the *Psicofarma*'s closure and drug use/mental health outcomes, which was consistent with a partial mediating role, but formal causal mediation could not be established due to data limitations. Although other unmeasured changes may have occurred during the study period, these findings suggest that the methadone shortage may have contributed to prolonged adverse effects on patients and highlight the need for policies that ensure consistent MOUD provision in Mexico, including the authorization of buprenorphine for the treatment of OUD.

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Keywords: Methadone; Opioid use disorder; People who use drugs; Medication shortage; Mexico

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Research in context

Evidence before this study

Medications for opioid use disorder (MOUD), including methadone and buprenorphine, are considered Essential Medicines by the World Health Organization (WHO). Stable MOUD use is positively associated with patients' psychosocial and physical well-being. However, disparities in MOUD availability and consistent provision persist globally. In Mexico, like in other Latin American countries, access to MOUD is hampered by limited local production (and no imports) of the medications and by regulatory barriers (e.g., buprenorphine is not classified as a MOUD). In the past decade, Mexico has experienced several long-term, policy-related national methadone shortages. The latest and most severe occurred in 2023 due to the government ordered closure of Psicofarma, the national methadone production facility. Understanding the impact of involuntary MOUD treatment interruption among patients is important, both to promote accountability around MOUD shortages and to design interventions that mitigate associated harms. We recently published a qualitative study investigating experiences during Psicofarma's closure among former methadone patients in Tijuana, which revealed a range of impacts across multiple life domains. Our current study aimed to ascertain and quantify those impacts in a larger sample of patients. To identify relevant evidence on this topic, we searched Google Scholar, PubMed, ResearchGate, and ScienceDirect from January 1st, 1965 up to November 1st, 2025, for peer-reviewed journal articles assessing the health, psychological, and social harms of MOUD shortages and disruptions. We used the following sets of search terms: ("methadone" OR "buprenorphine" OR "opioid agonist therapy" OR "opioid substitution therapy" OR "medication* for opioid use disorder*") AND (shortage or interruption or disruption) AND (impact or harm) AND (overdose or death or psychological or social or financial). Our review of the available literature showed that among patients receiving MOUD treatment, 1) MOUD shortages or disruptions can lead to severe anxiety, use of other drugs (e.g., benzodiazepines, alcohol) to mitigate withdrawal symptoms, resumption of street opioid use and engagement in associated riskier drug use behaviors (e.g., injection drug use), fatal overdose, and long-term disengagement with MOUD treatment; 2) emergency planning and policy changes to address MOUD shortages and disruptions can prevent negative impacts.

Most literature focused on MOUD shortages in the context of the COVID-19 pandemic, and a few papers addressed disruptions in the context of natural disasters, war, and policy changes. Though the duration and severity of pandemic-induced MOUD shortages differed by country, both Canada and the US implemented a variety of mitigation strategies, including take-home dosing, telehealth prescribing, and regulatory waivers. The true impact of changes in MOUD access are unclear, as their effects are difficult to disaggregate from regional changes in the street opioid supply and shifts in drug use behaviors. Natural disasters—hurricanes Rita, Sandy, and Katrina—similarly impacted MOUD provision in the US and Puerto Rico. Even after the implementation of multiple emergency measures, many MOUD patients reported returning to street opioid use. War-induced shortages have been studied in both the Russian invasions of Crimea in 2014 and wider Ukraine beginning in 2022. The 2014 invasion led to a Russian ban on methadone provision in occupied territory. A minority of relocated patients were able to re enroll in treatment in unoccupied Ukraine. During the recent war, Russian attacks forced the closure of two methadone production facilities, causing a wider disruption in treatment access, which the Ukrainian government has attempted to address via emergency measures. Many patients, however, returned to street opioid use or alternatives like alcohol to manage the sudden reduction in their treatment regimens. While not strictly about the supply of MOUD, several studies in Canada linked regulatory changes in MOUD formulations and delivery services to increased withdrawal experiences and returns to injection drug use.

Added value of this study

Our study is one of the first to demonstrate, quantitatively, how a sustained disruption to a country's methadone supply was associated with multiple drug use, behavioral, and psychosocial outcomes among former patients. Specifically, it was significantly associated with increased opioid use, injection drug use, receptive drug use paraphernalia, anxiety symptoms, and depression symptoms. It was not significantly associated with having a stable job, arrest, and homelessness, but prevalence of these outcomes was low. Together, our qualitative and quantitative studies call for both expansion of Mexico's MOUD options, production and procurement capacity, and development of standard operating procedures in the event of further supply disruptions.

Implications of all the available evidence

In regions impacted by worsening drug overdose incidence and drug toxicity, it is critical to maintain stable provision of MOUD. Available evidence indicates that disruptions in this supply are harmful to patients' physical and psychosocial health and limit the establishment of a treatment infrastructure. Expansion of MOUD provision and protection via complementary supply lines are necessary to prevent harm to this patient population. The WHO has recently developed guidelines to prevent MOUD service disruptions that provides a road map for countries like Mexico to protect the health of people with opioid use disorders.

Introduction

People using medications for opioid use disorder (MOUD) use illicit opioids less frequently and engage less in drug use behaviors that put them at risk, such as sharing syringes or other drug use supplies.[1] Broad availability and prescribing of MOUD is known to reduce incidence of overdose and bloodborne infections.[2–4] Individual benefits conferred by MOUD can thus offer a population-level protective effect, reducing the likelihood of bloodborne pathogen spread and decreasing overdose incidence.[5,6] Consistent engagement in MOUD treatment can, under some treatment regimens, also have long-term benefits for overall health, quality of life, social and familial relationships, employment and productivity, and reductions in criminal behavior.[7–10] These beneficial outcomes however, rely on ease of treatment access, treatment adherence among patients, and a consistent supply pipeline of MOUD to clinics.

Despite stated government goals to scale-up prescribing, recent data rank Mexico in the lowest WHO MOUD coverage category.[11,12] Buprenorphine is not classified as MOUD in Mexico, and while methadone is the only widely available evidence-based opioid agonist treatment for opioid use disorder (OUD), few public clinics exist. Treatment options are geographically dispersed, have strict dosing limits, may be unaffordable, and experience shortages in methadone availability.[13–15] In Tijuana, a city that shares a border with the United States (US) and the setting for this study, only four clinics offered methadone in 2022, three of which were privately owned and operated. At this time, an estimated 500–1000 patients were enrolled in methadone treatment for OUD at one of these clinics.

Populations of people who use drugs in Mexico, like the US, have been experiencing social and structural changes that put them at increased risk for overdose and/or bloodborne infections.[16] While national level data on drug use outcomes in Mexico are sparse, a recent study indicated steep increases in drug overdose death rates, largely concentrated in cities along the Mexico-US border.[17] Local harm reduction and overdose reversal programs in border cities have been attempting to respond to this crisis that remains hard to demonstrate due to limited overdose surveillance infrastructure.[18] Research suggests that increases in fatal opioid overdose in border cities may be partly driven by changes in illicit drug markets including the distribution of fentanyl, and trafficking ties to US cities.[19,20] In Tijuana and Mexicali, studies testing drug samples and paraphernalia over the past five years have shown fentanyl becoming a prominent opioid on the illicit market, in some cases replacing both powder and black tar heroin.[16,20] While often based on relatively small samples, this work has highlighted the spatial heterogeneity of fentanyl in the drug supply, creating added risk for people who may not fully know what they are purchasing.[20,21] While almost certainly a substantial underestimate, in Tijuana, a recent study reported 1.75 overdose deaths per 100,000 people in the period from 2020 to 2021, an increase from 1.34/100,000 the year prior and continuing a trend since 2005.[17] Another recent study reported that 14% of a sample of people who use drugs from Tijuana had experienced a nonfatal overdose in the prior six months.[21]

After initial inspections in November 2022 and concerns with quality control, in February 2023 the Mexican government issued a production stoppage notice for the *Psicofarma* production facility, Mexico's main supplier of methadone.[22] The plant remained closed for nearly seven months, leading to methadone shortages at clinics in Tijuana and other sites across the country. Our qualitative research with MOUD patients in Tijuana previously enrolled at these clinics revealed a number of psychosocial, economic, and potential health harms related to the abrupt closure and subsequent shortage.[23] Studies of other methadone supply interruptions in Ukraine and the US similarly point to potential health harms.[24,25] Here, we further address this topic to explore an important gap in the literature: how MOUD supply chain disruptions caused by a factory closure can impact patients.

Based on the available literature and our previously published qualitative work on the *Psicofarma* closure, we hypothesized that the closure would be associated with decreased prevalence of methadone treatment engagement and in turn increased prevalence of illicit drug use and drug use risk behaviors, mental health symptoms consistent with anxiety and depression, and social harms, including arrest, homelessness, and unstable employment. We used a longitudinal sample of MOUD patients and aimed to investigate the association between the *Psicofarma* closure, methadone treatment, and individual substance use and psycho-social outcomes.

Methods

Data collection

Between July 2023 and April 2024 (Visit 1), we enrolled and administered questionnaires to 200 patients previously receiving methadone in Tijuana, Mexico. To be eligible, participants must have been over 18 years old and enrolled in a methadone program within the six months preceding the *Psicofarma* closure. While all participants reported methadone program enrollment six months prior to the closure, at the time of the Visit 1 survey, only 46% had received methadone in the past 6 months. We recruited new participants at clinics, via flyers, word of mouth, and via referral. This recruitment was highly targeted, and almost all of those approached were eligible and enrolled. Of the 200 participants, 22 (11%) were enrolled out of a larger cohort of people who

use drugs in Tijuana. After determining eligibility, participants were provided with written informed consent documentation in Spanish. Consent was entirely voluntary, following principles in the Declaration of Helsinki, and obtained via written signature. We administered structured questionnaires on secure study laptops in a private location to protect participants' privacy. We recontacted participants for a second, follow-up questionnaire which they completed approximately six months later, between May and December 2024 (Visit 2). All participants received $20 USD for completing each questionnaire.

Variables

Questionnaires at both visits queried multiple domains, including participant *demographics*, *drug use history*, *drug use behaviors*, *drug treatment history*, *sexual history and behaviors*, *mental and physical health history*, *justice involvement history*, *housing history*, *employment history*, and *infectious disease history*. At Visit 1, behavioral items included both ever and past-six-month variants. At follow-up, we only queried participants on past-six-month behaviors. For this study, we selected eleven binary, past-six-month, outcome variables that correspond with three key domains identified by participants in our previous qualitative study: illicit drug use and related risk behaviors, mental health symptoms, and social harms.[23]

Outcome variables

Drug use and related risk behaviors during the past six months included: at least weekly opioid use, at least weekly benzodiazepine use, at least weekly methamphetamine use, at least weekly drug injection, any receptive syringe sharing, and any receptive drug paraphernalia (cookers, cotton filters) sharing. Opioid use was defined as use of heroin or fentanyl via any modality and in any combination with other drugs. Pharmaceutical opioid use was not included as no participants reported any use in the past six-months. Methamphetamine use and benzodiazepine use were similarly defined. *Mental health symptoms* included depression symptoms (as defined by score of ten or greater on the CESD-10)[26] and moderate to severe anxiety symptoms (versus none or mild, as defined by score of ten or greater on the GAD-7).[27] *Social harms* included unstable employment, unstable housing, and arrest.

Exposure variable

To examine changes in participant outcomes during and after the methadone shortage, we sorted observations chronologically and divided them into three "survey periods" (categorical). We used three criteria to determine cutoffs for these periods. Frist, we assumed that it would take several months for clinics to run out of methadone stocks and several more months to reestablish those stocks when production resumed. Second, we confirmed that cutoffs did not result in any participant having both Visit 1 and Visit 2 data in the same period. And third, we examined the probability of reporting methadone treatment by month and attempted to split periods along observed changes in prevalence (Supplemental Fig. S1).

Survey periods correspond to the dates July 27, 2023 to February 27, 2024 (Period 1, n = 150), February 28, 2024 to July 29, 2024 (Period 2, n = 114), and July 30, 2024 to December 9, 2024 (Period 3, n = 136). All 200 participants contributed data to both visits, and thus two of the three survey periods (Periods 1 and 2, 1 and 3, or 2 and 3) created for this analysis. Response recall includes time spanning the factory closure (Period 1), the five months after production resumed but when availability was highly limited (Period 2), and nearly a year after production resumed (Period 3) but when availability was still limited as one of the private methadone clinics never reopened.[28,29] A timeline of the shutdown, timing of survey visits, response periods, and approximate duration of the methadone shortage is presented in Fig. 1. Depending on when participants

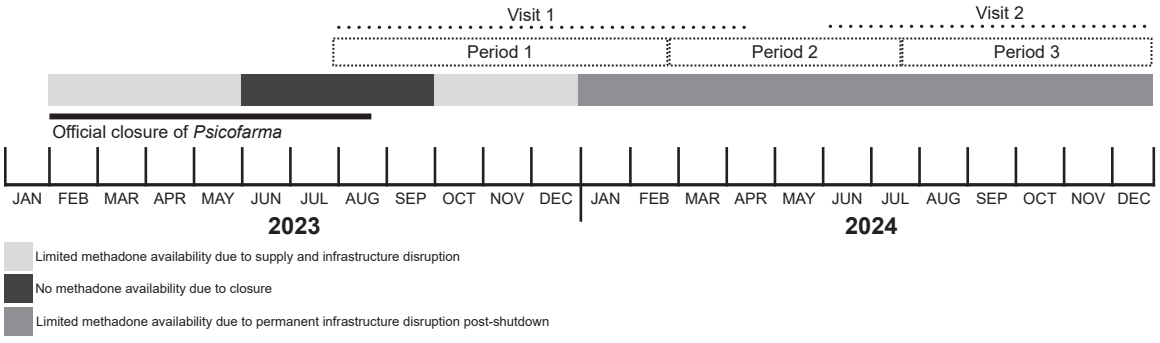


Fig. 1: Study closure and timelines.

were surveyed, response recall may include some of previous period.

Mediator variable

The hypothesized mediator for this study is any past six-month enrollment in methadone treatment (binary).

Covariates

Covariates included participant gender (binary), years of education (continuous), and years since first heroin use (continuous).

Analysis

All 200 participants were included in the analysis. We used descriptive statistics (mean and standard deviation for continuous variables and frequencies for categorical variables) to describe the Visit 1 characteristics of the participant sample both overall and stratified by outcome of interest. We conducted chi-square, t-tests, and fisher exact tests to compare groups predetermined by each outcome at Visit 1. We examined the prevalence of each of the eleven outcomes across survey periods. We then analyzed these outcomes in the total sample longitudinally using log-binomial regressions with robust variance estimation via generalized estimating equations (GEE). This method enabled us to estimate more reliable prevalence ratios, prevalence differences, and confidence intervals by accounting for within-subjects correlations induced by repeated measurements.[30] An unstructured covariance matrix estimating unique correlations for each pair of repeated observations was specified for all models.

To examine the potential mediation effect of methadone treatment on the association between response period and outcome variables, we constructed and evaluated three sets of regression models. First, we tested the effect of survey period (X) on methadone treatment (M) and all outcome variables (Y). Second, we tested the effect of methadone treatment (M) on outcome measures (Y). Finally, we fit a set of models that tested the effects of both survey period (X) and methadone treatment (M) on outcome variables (Y). While we controlled for repeated measurements and used survey period as our exposure variable, we did not test longitudinal mediation. All mediation models are cross-sectional, and results cannot be interpreted as causal. All models controlled for a number of sociodemographic and drug use history characteristics. We assessed all models for multi-collinearity.

To address structural missingness introduced by dividing observations into three survey periods, we also conducted a sensitivity analysis. We imputed data for each participant's missing survey period and reconstructed all GEE modes using this new data.

Data cleaning, variable creation, and descriptive statistics were conducted in R 4.4.2 statistical software, while GEE regressions were performed using Stata SE 19.5.

Role of funding source

Funders had no role in the study design, data collection, data analysis, interpretation, or writing of this study.

Ethics approval

This study was given ethical approval by the Institutional Review Boards at University of California San Diego (IRB #191390, Approval: 07/25/2023) and at the University of Xochicalco, Tijuana (Approval: 08/08/2023). The University of California San Diego and Xochicalco University IRB (Office of IRB Administration) integrates the ethical principles of the Declaration of Helsinki into its core policies. They require all human subjects research to undergo thorough review and comply with these international medical research ethics.

Results

Associations between sociodemographic and outcome variables

Demographic characteristics of the participant sample are shown in Table 1. Participants were majority male (n = 139, 70%), had a mean age of 43.9 years (sd = 7.9), had 10.6 mean years (sd = 2.7) of education, and began injecting heroin 24 years ago on average (sd = 9.1). At Visit 1, most of the groups predetermined by our outcome variables were not found to differ with respect to sociodemographic characteristics. Those participants reporting past six-month methadone treatment were significantly older on average than non-users (46.1 vs. 43.1) and had fewer average years of total education (9.6 vs. 11.0). Among participants reporting at least weekly opioid use in the past 6 months at Visit 1 (n = 106, 53%), 76% were males, as compared to a corresponding 62% of those not reporting opioid use. Similarly, males made up 86% of participants reporting a stable job (n = 62, 31%) as opposed to 62% of those reporting no stable job.

Outcome prevalence

Prevalence of all outcome variables across survey periods is shown in Fig. 2. Methadone utilization and street opioid use show inverse trends, with methadone treatment decreasing from 36% (n = 54) to 13% (n = 15), then increasing to 26% (n = 35), and opioid use increasing from 38% (n = 57) to 69% (n = 79), then decreasing to 47% (n = 64) across all three survey periods. Heroin was the predominant opioid reported by participants, with prevalence moving from 37% (n = 55), to 63% (n = 72), to 41% (n = 56) across the three survey periods. Reported fentanyl use was low at 1% (n = 2), 7% (n = 8), and 7% (n = 10) over the three survey periods.

Benzodiazepine prevalence decreased from 25% (n = 37) in Period 1–20% (n = 23) and 11% (n = 15) in Periods 2 and 3, respectively. Similarly,

	Total	Methadone treatment			Illicit opioid use		
	n (%) or Mean (sd)	No	Yes	p	No	Yes	p
		n (%) or Mean (sd)	n (%) or Mean (sd)		n (%) or Mean (sd)	n (%) or Mean (sd)	
Age	43.9 (7.9)	43.1 (7.6)	46.1 (8.2)	0.019	43.0 (9.0)	44.7 (6.7)	0.14
Gender							
Male	139 (69.5)	104 (71.2)	35 (64.8)	0.48	58 (61.7)	81 (76.4)	0.036
Female	61 (30.5)	42 (28.8)	19 (35.2)		36 (38.3)	25 (23.6)	
Years of education	10.6 (2.7)	11.0 (2.6)	9.6 (2.7)	0.001	10.5 (2.6)	10.7 (2.8)	0.68
Years of heroin use	24.0 (9.1)	23.4 (8.3)	25.8 (10.8)	0.14	23.6 (9.7)	24.5 (8.6)	0.50

	Methamphetamine use			Benzodiazepine use		
	No	Yes	p	No	Yes	p
	n (%) or Mean (sd)	n (%) or Mean (sd)		n (%) or Mean (sd)	n (%) or Mean (sd)	
Age	45.3 (7.7)	43.6 (7.9)	0.22	43.8 (7.7)	44.4 (8.4)	0.67
Gender						
Male	26 (70.3)	113 (69.3)	1	107 (68.6)	32 (72.7)	0.73
Female	11 (29.7)	50 (30.7)		49 (31.4)	12 (27.3)	
Years of education	10.0 (3.2)	10.7 (2.6)	0.23	10.7 (2.8)	10.2 (2.4)	0.25
Years of heroin use	25.0 (9.5)	23.8 (9.0)	0.49	23.8 (9.3)	24.9 (8.6)	0.47

	Any injection use			Receptive syringe sharing		
	No	Yes	p	No	Yes	p
	n (%) or Mean (sd)	n (%) or Mean (sd)		n (%) or Mean (sd)	n (%) or Mean (sd)	
Age	43.1 (9.0)	44.6 (6.7)	0.12	43.9 (7.9)	45.3 (7.2)	0.76
Gender						
Male	59 (42.4)	80 (76.2)	0.045	136 (69)	3 (100)	0.56
Female	36 (37.9)	25 (23.8)		61 (31)	0 (0)	
Years of education	10.5 (2.6)	10.6 (2.8)	0.77	10.6 (2.7)	11.0 (1.7)	0.72
Years of heroin use	23.6 (9.6)	24.4 (8.6)	0.55	24.0 (9.2)	25.7 (5.1)	0.64

	Receptive paraphrenalia sharing			Depression		
	No	Yes	p	No	Yes	p
	n (%) or Mean (sd)	n (%) or Mean (sd)		n (%) or Mean (sd)	n (%) or Mean (sd)	
Age	43.8 (7.9)	45.2 (7.8)	0.46	43.6 (8.1)	45.4 (6.2)	0.18
Gender						
Male	124 (68.5)	15 (78.9)	0.50	116 (68.2)	23 (76.7)	0.48
Female	57 (31.5)	4 (21.1)		54 (31.8)	7 (23.3)	
Years of education	10.5 (2.7)	11.3 (3.0)	0.31	10.6 (2.6)	10.6 (3.2)	0.97
Years of heroin use	24.0 (9.3)	24.4 (7.5)	0.81	23.8 (9.2)	25.6 (8.5)	0.29

	Anxiety			Stable Job		
	No	Yes	p	No	Yes	p
	n (%) or Mean (sd)	n (%) or Mean (sd)		n (%) or Mean (sd)	n (%) or Mean (sd)	
Age	43.7 (8.0)	44.3 (7.6)	0.60	43.9 (7.9)	44.0 (8.0)	0.95
Gender						
Male	91 (65.9)	48 (77.4)	0.14	86 (62.3)	53 (85.5)	0.002
Female	47 (34.1)	14 (22.6)		52 (37.7)	9 (14.5)	
Years of education	10.5 (2.7)	10.8 (2.8)	0.52	10.4 (2.9)	11.0 (2.3)	0.091
Years of heroin use	23.9 (9.2)	24.4 (8.9)	0.67	23.9 (9.2)	24.3 (8.9)	0.80

	Arrest[a]			Homelessness[a]		
	No	Yes	p	No	Yes	p
	n (%) or Mean (sd)	n (%) or Mean (sd)		n (%) or Mean (sd)	n (%) or Mean (sd)	
Age	43.9 (7.9)	NA (NA)		43.9 (7.9)	49 (NA)	
Gender		NA (NA)				
Male	139 (69.5)	0 (0)		138 (69.3)	1 (100)	
Female	61 (30.5)	0 (0)		61 (30.7)	0 (0)	
Years of education	10.6 (2.7)	NA (NA)		10.6 (2.7)	12 (NA)	
Years of heroin use	24.0 (9.1)	NA (NA)		24.0 (9.1)	30 (NA)	

[a]Not enough observations among "Yes" group to for statistical tests of differences.

Table 1: **Participant demographic comparisons by outcome variables at visit 1 (N = 200).**

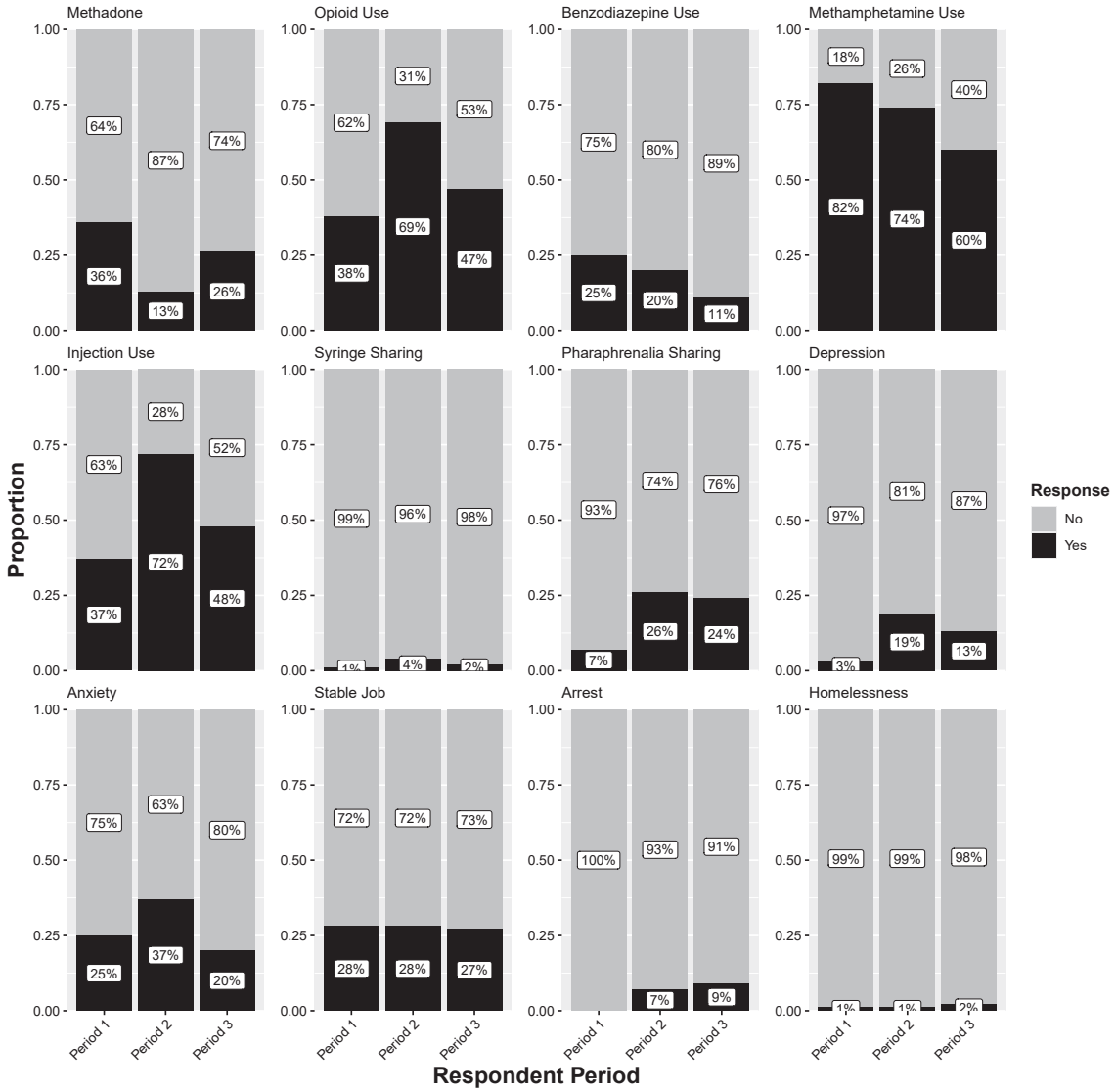


Fig. 2: Outcome measure prevalence by survey period.

methamphetamine use prevalence decreased from 82% (n = 123) in Period 1, to 74% (n = 84) and 60% (n = 81) in Periods 2 and 3, respectively. Prevalence of injection of any drug at Visit 1 was 37% (n = 56), peaked in Period 2 at 72% (n = 82), and decreased to 48% (n = 65) in Period 3. Anxiety symptom prevalence was 25% (n = 37) in Period 1 and 37% (n = 42) and 20% (n = 27) in Periods 2 and 3 respectively. Prevalence of stable employment was 28% (n = 42) in Periods 1 and 2 (n = 32), and 27% (n = 37) in Period 3.

Assessing mediation

Table 2 through Table 8 (Tables 2–8) present parameter estimates (adjusted prevalence ratios [aPR] and adjusted prevalence differences [aPD]) and the corresponding 95% confidence intervals (CI) from regression equations used to test whether methadone treatment acted as a mediator of the relationship between time since factory closure and main outcomes of interest. These outcomes included: illicit opioid use, benzodiazepine use, methamphetamine use, any injection drug use, moderate to severe anxiety symptoms, and stable employment. Additional outcome variables that we explored (receptive syringe sharing, receptive paraphernalia sharing, depression, arrest, and homelessness) had extremely low prevalence in at least one period or were correlated with main outcomes, leading to difficulties with statistical test interpretation and

	Association between X and M	
	aRR (95% CI)	aRD (95% CI)
Period		
Period 1	Reference	Reference
Period 2	0.35 (0.21, 0.59)	−0.223 (−0.317, −0.131)
Period 3	0.73 (0.50, 1.04)	−0.087 (−0.197, 0.024)
Gender		
Male	Reference	Reference
Female	1.17 (0.85, 1.62)	0.037 (−0.055, 0.130)
Education (years)	0.94 (0.90, 0.99)	−0.008 (−0.021, 0.006)
Heroin use (years)	[a]	[a]

aPR: adjusted Prevalence Ration. aPD: adjusted Prevalence Difference. CI: Confidence Interval. [a]Removed from model due to convergence failure.

Table 2: **Association between survey period (X) and methadone treatment (M).**

model convergence. Results for these five outcomes, as well as results for sensitivity analyses, are presented in the Supplemental file.

Association between survey period and methadone treatment

Compared to Period 1, methadone treatment prevalence was significantly reduced in Period 2 (aPR = 0.35, 95% CI: 0.21–0.59) and period 3 (aPR = 0.73, 95% CI: 0.50–1.04).

Illicit opioid use

Participants engaged in methadone treatment had significantly lower prevalence of illicit opioid use (aPR = 0.22, 95% CI: 0.13–0.35). Without controlling for methadone treatment, illicit opioid use prevalence was significantly higher in Period 2 (aPR = 1.81, 95% CI: 1.44–2.27) as compared to Period 1. After accounting for methadone treatment, illicit opioid use prevalence was still significantly higher in Period 2 (aPR = 1.62, 95% CI: 1.32–1.98) as compared to Period 1.

Benzodiazepine use

Participants engaged in methadone treatment had significantly higher prevalence of benzodiazepine use (aPR = 2.34, 95% CI: 1.57–3.49). Without controlling for methadone treatment, benzodiazepine use prevalence was significantly lower in Period 3 (aPR = 0.49, 95% CI: 0.28–0.84) as compared to Period 1. After accounting for methadone treatment, benzodiazepine use prevalence was still significantly lower in Period 3 (aPR = 0.54, 95% CI: 0.31–0.93) as compared to Period 1.

Methamphetamine use

Participants engaged in methadone treatment had significantly lower prevalence of methamphetamine use (aPR = 0.58, 95% CI: 0.47–0.70). Without controlling for methadone treatment, methamphetamine use prevalence was significantly lower in Period 3 (aPR = 0.74, 95% CI: 0.62–0.87) as compared to Period 1. After accounting for methadone treatment, methamphetamine use prevalence was still significantly lower in Period 3 (aPR = 0.78, 95% CI: 0.68–0.90) as compared to Period 1.

Any injection use

Participants engaged in methadone treatment had significantly lower prevalence of any injection drug use (aPR = 0.21, 95% CI: 0.13–0.33). Without controlling for methadone treatment, any injection drug use prevalence was significantly higher in Period 2 (aPR = 1.87, 95% CI: 1.50–2.33) as compared to Period 1. After accounting for methadone treatment, any injection drug use prevalence was still significantly higher in Period 2 (aPR = 1.65, 95% CI: 1.35–2.00) as compared to Period 1.

Anxiety symptoms

Participants engaged in methadone treatment had significantly lower prevalence of moderate to severe anxiety symptoms (aPR = 0.23, 95% CI: 0.12–0.46). Without controlling for methadone treatment, anxiety symptom prevalence was significantly higher in Period 2 (aPR = 1.50, 95% CI: 1.05–2.14) as compared to Period 1. After accounting for methadone treatment, anxiety symptom prevalence was not significantly higher in either survey period as compared to Period 1.

Stable employment

Neither engagement in methadone treatment nor survey period were significantly associated with prevalence of stable employment in any model.

Discussion

This study provides preliminary quantitative evidence that the time periods coinciding with the *Psicofarma* plant closure and the year after were correlated with negative health and behavior changes among methadone clinic patients in Tijuana, Mexico. Observed changes in prevalence of methadone treatment, opioid use, other drug use, anxiety, largely align with our previously reported qualitative results and add to the limited literature on the impact of prolonged methadone shortages.[23,31,32] Available studies from Ukraine[31] and the US[25,33] indicated that disruptions to the methadone supply or to clinic operations have the potential to permanently change the course of patient treatment and retention. While these previous studies were in the context of war (Ukraine) or disasters (US), our study provides evidence that policy-induced shortages can potentially have long-lasting impacts among a highly vulnerable population of people who use drugs in a low-resource setting. As noted in our prior work, shortages of this type are preventable and represent a source of harm for this population.[23]

	Association between X and Y		Association between M and Y		Association between X and Y accounting for M	
	aPR (95% CI)	aPD (95% CI)	aPR (95% CI)	aPD (95% CI)	aPR (95% CI)	aPD (95% CI)
Period						
Period 1	Reference	Reference			Reference	Reference
Period 2	1.81 (1.44, 2.27)	0.325 (0.215, 0.434)			1.62 (1.32, 1.98)	0.155 (0.053, 0.258)
Period 3	1.20 (0.91, 1.57)	0.098 (−0.020, 0.216)			1.23 (0.95, 1.58)	−0.061 (−0.155, 0.033)
Methadone treatment						
No			Reference	Reference	Reference	Reference
Yes			0.22 (0.13, 0.35)	−0.483 (−0.565, −0.400)	0.23 (0.14, 0.37)	−0.464 (−0.543, −0.386)
Gender						
Male	Reference	Reference	Reference	Reference	Reference	Reference
Female	0.70 (0.55, 0.89)	−0.168 (−0.275, −0.060)	0.77 (0.61, 0.97)	−0.109 (−0.202, −0.015)	0.75 (0.61, 0.92)	[a]
Education (years)	0.98 (0.95, 1.01)	−0.007 (−0.022, 0.007)	[a]	[a]	[a]	[a]
Heroin use (years)	1.00 (0.99, 1.01)	0.000 (−0.005, 0.006)	1.00 (0.99, 1.02)	0.002 (−0.003, 0.007)	[a]	[a]

aPR: adjusted Prevalence Ration. aPD: adjusted Prevalence Difference. CI: Confidence Interval. [a]Removed from model due to convergence failure.

Table 3: **Association between survey period (X), methadone treatment (M), and opioid use (Y).**

	Association between X and Y		Association between M and Y		Association between X And Y accounting For M	
	aPR (95% CI)	aPD (95% CI)	aPR (95% CI)	aPD (95% CI)	aPR (95% CI)	aPD (95% CI)
Period						
Period 1	Reference	Reference			Reference	Reference
Period 2	0.84 (0.54, 1.29)	−0.034 (−0.127, 0.058)			1.10 (0.71, 1.71)	0.001 (−0.096, 0.098)
Period 3	0.49 (0.28, 0.84)	−0.130 (−0.217, −0.043)			0.54 (0.31, 0.93)	−0.122 (−0.202, −0.041)
Methadone treatment						
No			Reference	Reference	Reference	Reference
Yes			2.34 (1.57, 3.49)	0.185 (0.087, 0.283)	2.40 (1.57, 3.67)	0.196 (0.093, 0.299)
Gender						
Male	Reference	Reference	Reference	Reference	Reference	Reference
Female	0.72 (0.43, 1.22)	−0.061 (−0.133, 0.012)	0.68 (0.40, 1.15)	−0.052 (−0.130, 0.026)	0.67 (0.40, 1.13)	[a]
Education (years)	0.97 (0.90, 1.04)	−0.003 (−0.016, 0.010)	0.99 (0.92, 1.05)	−0.006 (−0.019, 0.007)	0.99 (0.93, 1.06)	[a]
Heroin use (years)	1.00 (0.98, 1.03)	0.001 (−0.003, 0.005)	1.00 (0.98, 1.03)	−0.002 (−0.006, 0.003)	1.00 (0.98, 1.02)	[a]

aPR: adjusted Prevalence Ration. aPD: adjusted Prevalence Difference. CI: Confidence Interval. [a]Removed from model due to convergence failure.

Table 4: **Association between survey period (X), methadone treatment (M), and benzodiazepine use (Y).**

	Association between X and Y		Association between M and Y		Association between X and Y accounting for M	
	aPR (95% CI)	aPD (95% CI)	aPR (95% CI)	aPD (95% CI)	aPR (95% CI)	aPD (95% CI)
Period						
Period 1	Reference	Reference			Reference	Reference
Period 2	0.91 (0.80, 1.04)	−0.069 (−0.167, 0.030)			0.92 (0.82, 1.04)	−0.090 (−0.188, 0.007)
Period 3	0.74 (0.62, 0.87)	−0.216 (−0.327, −0.105)			0.78 (0.68, 0.90)	−0.228 (−0.327, −0.128)
Methadone treatment						
No			Reference	Reference	Reference	Reference
Yes			0.58 (0.47, 0.70)	−0.342 (−0.442, −0.242)	0.59 (0.49, 0.71)	−0.365 (−0.458, −0.271)
Gender						
Male	Reference	Reference	Reference	Reference	Reference	Reference
Female	0.97 (0.87, 1.09)	−0.021 (−0.102, 0.061)	0.95 (0.85, 1.06)	−0.036 (−0.113, 0.041)	0.98 (0.88, 1.08)	−0.013 (−0.087, 0.060)
Education (years)	1.02 (1.00, 1.04)	0.015 (0.002, 0.028)	[a]	[a]	[a]	[a]
Heroin use (years)	1.00 (1.00, 1.01)	0.001 (−0.003, 0.006)	[a]	[a]	[a]	[a]

aPR: adjusted Prevalence Ration. aPD: adjusted Prevalence Difference. CI: Confidence Interval. [a]Removed from model due to convergence failure.

Table 5: **Association between survey period (X), methadone treatment (M), and methamphetamine use (Y).**

	Association between X and Y		Association between M and Y		Association between X and Y accounting for M	
	aPR (95% CI)	aPD (95% CI)	aPR (95% CI)	aPD (95% CI)	aPR (95% CI)	aPD (95% CI)
Period						
Period 1	Reference	Reference			Reference	Reference
Period 2	1.87 (1.50, 2.33)	0.349 (0.243, 0.455)			1.65 (1.35, 2.00)	0.185 (0.085, 0.284)
Period 3	1.21 (0.92, 1.58)	0.097 (−0.019, 0.212)			1.22 (0.96, 1.57)	−0.051 (−0.144, 0.043)
Methadone treatment						
No			Reference	Reference	Reference	Reference
Yes			0.21 (0.13, 0.33)	−0.496 (−0.576, −0.417)	0.23 (0.14, 0.36)	−0.461 (−0.540, −0.383)
Gender						
Male	Reference	Reference	Reference	Reference	Reference	Reference
Female	0.74 (0.59, 0.94)	−0.150 (−0.262, −0.039)	0.81 (0.64, 1.01)	−0.096 (−0.196, 0.004)	0.79 (0.64, 0.97)	[a]
Education (years)	0.97 (0.95, 1.00)	−0.010 (−0.025, 0.006)	[a]	[a]	[a]	[a]
Heroin use (years)	1.00 (0.99, 1.01)	0.001 (−0.004, 0.007)	1.01 (1.00, 1.02)	0.002 (−0.003, 0.008)	1.01 (1.00, 1.01)	[a]

aPR: adjusted Prevalence Ration. aPD: adjusted Prevalence Difference. CI: Confidence Interval. [a]Removed from model due to convergence failure.

Table 6: **Association between survey period (X), methadone treatment (M), and any injection use (Y).**

All participants had been clinic patients at the time of the plant closure. Even during Period 3, when the plant had been fully operational for nearly a year, reported methadone enrollment had not recovered, indicating potential continuing issues with treatment access. At the time of writing, one clinic remains permanently closed. Given the already-constrained nature of methadone access in Tijuana, permanent closure of even a single clinic may represent a treatment barrier for many former patients and thus adds population-level risk for negative health outcomes. The reduced volume of MOUD treatment provision in the city also presents a barrier to prospective patients, lowering the potential preventative effects of treatment engagement. It is also possible that lower methadone treatment prevalence long after production resumed is due to changes in cost or dosing that might be prohibitive for some former patients. Further, patients who had gone nearly a year without treatment may not have felt compelled to resume.

In our previous study, interviewees reported symptoms of intense anxiety at the loss of treatment, and fear that without methadone they would resume street opioid use and lose socio-economic stability.[23] Our results quantitatively lend credence to these fears. Access to methadone was associated with reduced prevalence of opioid use, methamphetamine use, any injection drug use, and anxiety. These results align with literature that indicates access to MOUD helps patients reduce risk of negative health outcomes and maintain stability.[23] However, neither methadone treatment nor survey period were associated with stable

	Association between X and Y		Association between M and Y		Association between X and Y accounting for M	
	aPR (95% CI)	aPD (95% CI)	aPR (95% CI)	aPD (95% CI)	aPR (95% CI)	aPD (95% CI)
Period						
Period 1	Reference	Reference			Reference	Reference
Period 2	1.50 (1.05, 2.14)	0.115 (0.006, 0.225)			1.28 (0.90, 1.82)	[a]
Period 3	0.78 (0.50, 1.20)	−0.055 (−0.152, 0.041)			0.77 (0.50, 1.16)	[a]
Methadone treatment						
No			Reference	Reference	Reference	Reference
Yes			0.23 (0.12, 0.46)	−0.252 (−0.328, −0.175)	0.25 (0.13, 0.48)	[a]
Gender						
Male	Reference	Reference	Reference	Reference	Reference	Reference
Female	0.72 (0.48, 1.07)	−0.068 (−0.159, 0.022)	0.79 (0.54, 1.15)	[a]	0.77 (0.53, 1.13)	[a]
Education (years)	1.02 (0.96, 1.09)	0.007 (−0.008, 0.022)	1.01 (0.95, 1.08)	[a]	1.01 (0.96, 1.08)	[a]
Heroin use (years)	1.01 (0.99, 1.03)	0.001 (−0.004, 0.007)	1.01 (0.99, 1.03)	0.001 (−0.004, 0.006)	1.01 (0.99, 1.03)	[a]

aPR: adjusted Prevalence Ration. aPD: adjusted Prevalence Difference. CI: Confidence Interval. [a]Removed from model due to convergence failure.

Table 7: **Association between survey period (X), methadone treatment (M), and anxiety symptoms (Y).**

	Association between X and Y		Association between M and Y		Association Between X and Y Accounting for M	
	aPR (95% CI)	aPD (95% CI)	aPR (95% CI)	aPD (95% CI)	aPR (95% CI)	aPD (95% CI)
Period						
Period 1	Reference	Reference			Reference	Reference
Period 2	0.96 (0.87, 1.06)	−0.035 (−0.120, 0.050)			0.97 (0.87, 1.07)	−0.027 (−0.115, 0.060)
Period 3	0.94 (0.86, 1.04)	−0.049 (−0.130, 0.033)			0.95 (0.87, 1.04)	−0.040 (−0.120, 0.040)
Methadone Treatment						
No			Reference	Reference	Reference	Reference
Yes			1.06 (0.98, 1.15)	0.046 (−0.025, 0.118)	1.04 (0.96, 1.13)	0.037 (−0.034, 0.109)
Gender						
Male	Reference	Reference	Reference	Reference	Reference	Reference
Female	1.00 (0.92, 1.09)	0.001 (−0.069, 0.071)	1.01 (0.93, 1.10)	0.008 (−0.063, 0.079)	1.01 (0.93, 1.09)	0.007 (−0.063, 0.077)
Education (years)	1.00 (0.99, 1.02)	0.002 (−0.011, 0.015)	1.00 (0.99, 1.02)	0.003 (−0.010, 0.015)	1.00 (0.99, 1.02)	0.003 (−0.009, 0.016)
Heroin use (years)	1.00 (0.99, 1.00)	−0.003 (−0.006, 0.001)	1.00 (0.99, 1.00)	−0.002 (−0.006, 0.002)	1.00 (0.99, 1.00)	−0.002 (−0.006, 0.001)

aPR: adjusted Prevalence Ration. aPD: adjusted Prevalence Difference. CI: Confidence Interval.

Table 8: **Association between survey period (X), methadone treatment (M), and stable employment (Y).**

employment—something our prior qualitative participants expressed fear of losing.

This seeming return to opioid use for methadone treatment patients, peaking during Period 2, presents a greatly heightened risk for overdose, both because fentanyl may be becoming a prominent illicit opioid in cross-border drug markets,[20] and due to the limited availability of naloxone in Mexico.[34] Many people who use drugs in Tijuana, especially those who have been enrolled in and adherent to methadone programs for multiple years, may not be aware that new opioids sold as heroin contain fentanyl.[21] Given their time spent enrolled in treatment, their reduced tolerance may put them at increased overdose risk in the presence of highly potent illicit opioids. Prevalence of both methamphetamine and benzodiazepine use was significantly decreased in Period 3, but not Period 2, as compared to Period 1. Methadone treatment was associated with increased prevalence of benzodiazepine use and decreased prevalence of methamphetamine use. Given our prior qualitative findings, this result was unexpected. However, these associations may be explained by the commonality of co-prescription of benzodiazepines and methadone, common in Mexican clinics as a means of reducing anxiety and cravings.[35]

The association between methadone treatment and decreased methamphetamine use prevalence might be explained by the commonality of methamphetamine and opioid co-use in Tijuana.[36] Period 2 was associated with increased prevalence of injection drug use, an outcome correlated with opioid use, indicating a risk for blood-borne infections like HIV and Hepatitis C.[37] This infection risk is may be higher given the Mexican government's failure to scale-up both harm reduction and treatment services, alongside medical infrastructure that cannot always adequately serve vulnerable populations of people who use drugs.[38]

The effect of survey period on four of the six outcomes remained significant even in the presence of methadone treatment, suggesting that methadone treatment may partially mediate the relationship between survey period and those outcomes. This partial mediation further indicates that factors beyond methadone may have been changing over time, including unmeasured changes in local drug markets, criminal enforcement, or other social and economic factors. After controlling for methadone treatment, survey period was not significantly associated with anxiety symptoms, indicating that methadone treatment engagement may fully mediate this relationship.

The most critical limitation of this analysis is the timing of data collection. Given the lack of advance warning of the *Psicofarma* closure, data collection for this study did not begin until the end of July 2023, five months after the notice for production stoppage was issued. This created a threefold issue. First, the lack of data from before the factory closure made it impossible to conduct comparisons between the pre- and post-closure periods as well as to establish temporality between the predictor, potential mediator, and the selected outcomes. This precluded us from conducting causal analyses of the factory closure effect on methadone treatment and the selected outcomes. Instead, we examined cross-sectional associations. Second, since recruitment started 5 months after the factory closure, most of our participants were recruited and surveyed once the plant had resumed operations, making our ability to accurately assess conditions close to the initial time of the shutdown limited. Nonetheless, our findings indicate that methadone receipt was still high for a few months following the closure, likely due to remaining stocks at clinics. It then declined abruptly and remained very low several months after production resumed. This suggests that methadone shortages at

clinics in Tijuana lagged behind the factory closure, and that our study captured changes in methadone availability despite this delayed onset.

Third, the study participants have had two study visits, and while all of them completed both visits, for analytic purposes, we divided the data into three consecutive time periods. While there was no missing data in the traditional sense, dividing data into three time periods structurally created one missing data point for each study participant, with participants who enrolled earlier in the study being more likely to contribute analytically to Periods 1 and 2 and participants enrolled later to Periods 2 and 3. While we found no differences with regard to baseline sociodemographics between participants who contributed to different study periods, there is still a chance that the missing data may not be missing completely at random (MCAR) and instead is missing at random (MAR). That might have introduced bias into the GEE analyses, which assume the data to be MCAR. We attempted to address this by conducting a sensitivity analysis in which we reran all mediation models after imputing the missing data for each participant. While the pooled values after imputation shifted estimates towards the null and narrowed associated confidence intervals, the significance and directionality of associations remained largely consistent with our primary analysis. These results should be interpreted with caution, as multiple imputation of longitudinal data tends to perform better for later time points. In this case, it is likely the imputation performed better for participants originally without Period 3 data than for those without Period 1 data.

Another limitation is that as with all self-report survey research, our data are subject to both recall and participant desirability biases. Without access to toxicological data, participants' reporting of their drug use should be viewed with care, especially in the context of a changing illicit drug market. We were unable to assess the closure's potential impact on nonfatal overdose due to its low reported prevalence in the sample.

We also recognize the potential for Type 1 error in the results of this analysis given that we modeled eleven total outcomes. Although we believe the chosen outcomes are justified by our previously published qualitative manuscript on the effects of the methadone shortage, given the increased risk of error our results should be interpreted with this limitation in mind. Additional caution is warranted due to wide confidence intervals around coefficients present in model results for low-prevalence outcomes, as seen in the Supplemental results. Due to data sparsity and a relatively small sample size, we were unable to conduct principal components analysis to reduce the number of correlated outcome variables.

Data sparsity and sample size also limited our ability to both conduct statistical tests to quantify and evaluate the significance of any indirect effects of mediation and to assess or account for potential time varying confounding in this analysis. Other unaccounted-for environmental factors and participant characteristics may have changed over time and influenced both mediator and outcome variables. Our use of GEE may have produced biased effect estimates in the presence of time varying confounders. Given that our assessment of mediation effects is both cross-sectional and incomplete, our results should be viewed as exploratory. Nonetheless, it is important to note that recruiting recent methadone patients in the midst of a methadone supply disruption in Tijuana was challenging, especially given the temporary or permanent closure of some clinics, and that investigating patients' experiences during and long after the methadone factory closure across a range of behavioral, health and social outcomes represents a strength. To our knowledge, no other studies were conducted in other parts of the country to document this event.

These results, though exploratory, add to a growing body of research indicating the necessity for expanded MOUD treatment availability and stable procurement of essential medications in Mexico and broader Latin America.[39] This is especially important as opioid use—and its contribution to the overall burden of drug-related morbidity and mortality—is increasing in the region.[40] Opioid overdose incidence continues to increase, although sparse data and inaccuracies in official mortality registries in many Latin American countries make it difficult to ascertain the magnitude of this change. Prescription opioid availability remains low and medication shortages persist.[41] Ensuring evidence-based treatment availability, including prescribing and provision of buprenorphine for OUD treatment, is key to preventing overdose outcomes.[42] Given the centrality of *Psicofarma* to distribution of methadone across Mexico, we believe that the Mexican government should have ensured supplemental supply lines of the medication to clinics. Though notoriously difficult, this could have been accomplished via foreign importing of methadone into the country. In addition, regulations around the use of buprenorphine for OUD treatment should have been lifted to expand MOUD options.

In the case of future disruptions, poor patient outcomes could be prevented by developing national-level emergency plans and stockpiling emergency supplies of methadone and buprenorphine. Further, changing the regulatory status of naloxone to make it more easily available would reduce potentially fatal overdose among patients who return to using illicit opioids. At the local level, clinics should be encouraged to establish standard operating procedures that support patients who may be cut off from MOUD treatment. This could include provision of continued counseling, medications to address withdrawal symptoms and related insomnia, as well as harm reduction education and supplies to prevent potential bloodborne infections.

People with OUD in other Latin American countries may experience similar hardships to those in Mexico if reforms are not implemented. Recent WHO guidelines further emphasize the necessity of preventing and mitigating the harms of unplanned disruptions.[43] Prevention involves ensuring MOUD procurement pipelines are stable, programs are well-stocked, and services are fully integrated into existing healthcare systems. In unplanned disruptions, WHO recommends mitigating by ensuring continuity of medication via other medical and public health service organizations, considering take home dosing, provision of psychosocial, withdrawal, and overdose support, and crisis-initiated budget reallocation if necessary.

Contributors

JLG–conceptualization, data validation, formal analysis, methodology, writing–first draft, writing–review and editing.

AHV–data curation, investigation, writing–review and editing.

GR–funding acquisition, investigation, writing–review and editing.

DA–data curation, data validation, methodology, writing–review and editing.

NKM–funding acquisition, writing–review and editing.

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MEMM–funding acquisition, writing–review and editing.

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All authors have accessed, read, and approved the final version of this manuscript.

Data sharing statement

Data underlying this project have not yet been shared and are not available to access publicly due to participant privacy considerations but can be made available upon request to those researchers with a methodologically rigorous proposal. Data available includes participant-level data following deidentification. All requests for data access should be directed to Steffanie Strathdee (sstrathdee@health.ucsd.edu). Requestors will be required to file a proposal and sign a detailed data access agreement.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2026.101577.

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