

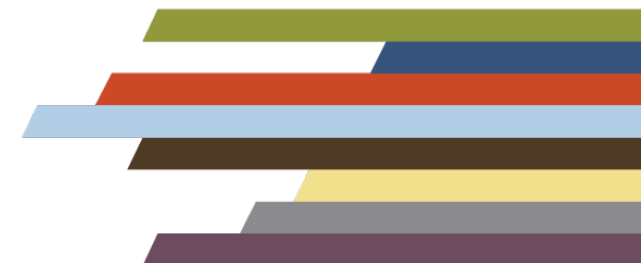


The Northwest & Pacific Southwest ATTCs and the CTN Western States Node present:

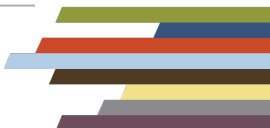
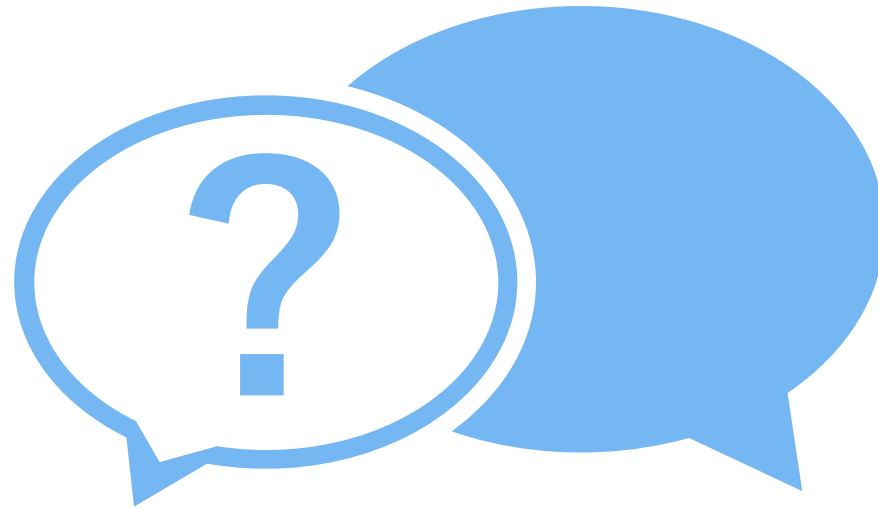
Problems Initiating Buprenorphine Treatment Among Patients Using Fentanyl

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Problems Initiating Buprenorphine Treatment Among Patients Using Fentanyl: The Results of CTN-0135

Western States Node Webinar

February 25, 2026



Erin L. Winstanley, Ph.D.
Professor of Medicine with Tenure, Division of General Internal Medicine

Disclosures

None

Presentation Objectives

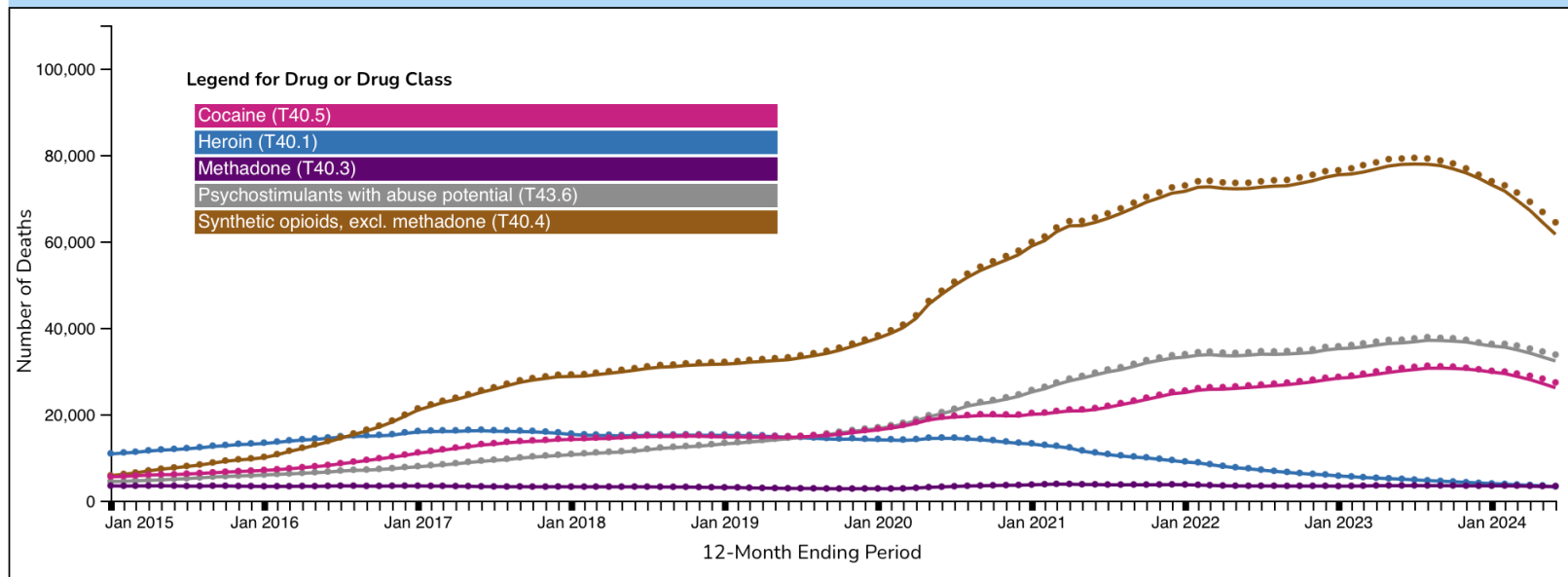
1. Summarize challenges to initiating buprenorphine treatment among patients using fentanyl
2. Review the methods and primary findings of a national survey of clinician-reported problems initiating buprenorphine treatment among patients using fentanyl
3. Differentiate strategies clinicians are using to improve engagement in buprenorphine treatment

CTN-0135 Aim 1

Background – Fentanyl Availability

- The majority (76%) of overdose deaths in the United States (US) continue to involve opioid compounds, specifically synthetic opioids like fentanyl
- There is limited regional data on fentanyl availability which was believed to be more widely available east of the Mississippi River (Hedegaard et al. 2019), but there are reports of fentanyl on the west coast (Shover et al. 2020)

Figure 2. 12 Month-ending Provisional Number of Drug Overdose Deaths by Drug or Drug Class: United States



SOURCE: <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>



SOURCE: J of Studies on Alc & Drugs

CTN-0135 Study Aim 1

- **Aim 1:** To estimate the national prevalence of fentanyl positive urine drug screens (UDS) in 2021 and determine whether there were regional differences.

Hypothesis 1a: Fentanyl positive UDS are ubiquitous in that every geographic unit will have at least one specimen positive for fentanyl.

Hypothesis 1b: There are geographic variations in fentanyl use and fentanyl hotspots occur more frequently in geographic areas east of the Mississippi River.

Aim 1 Methods

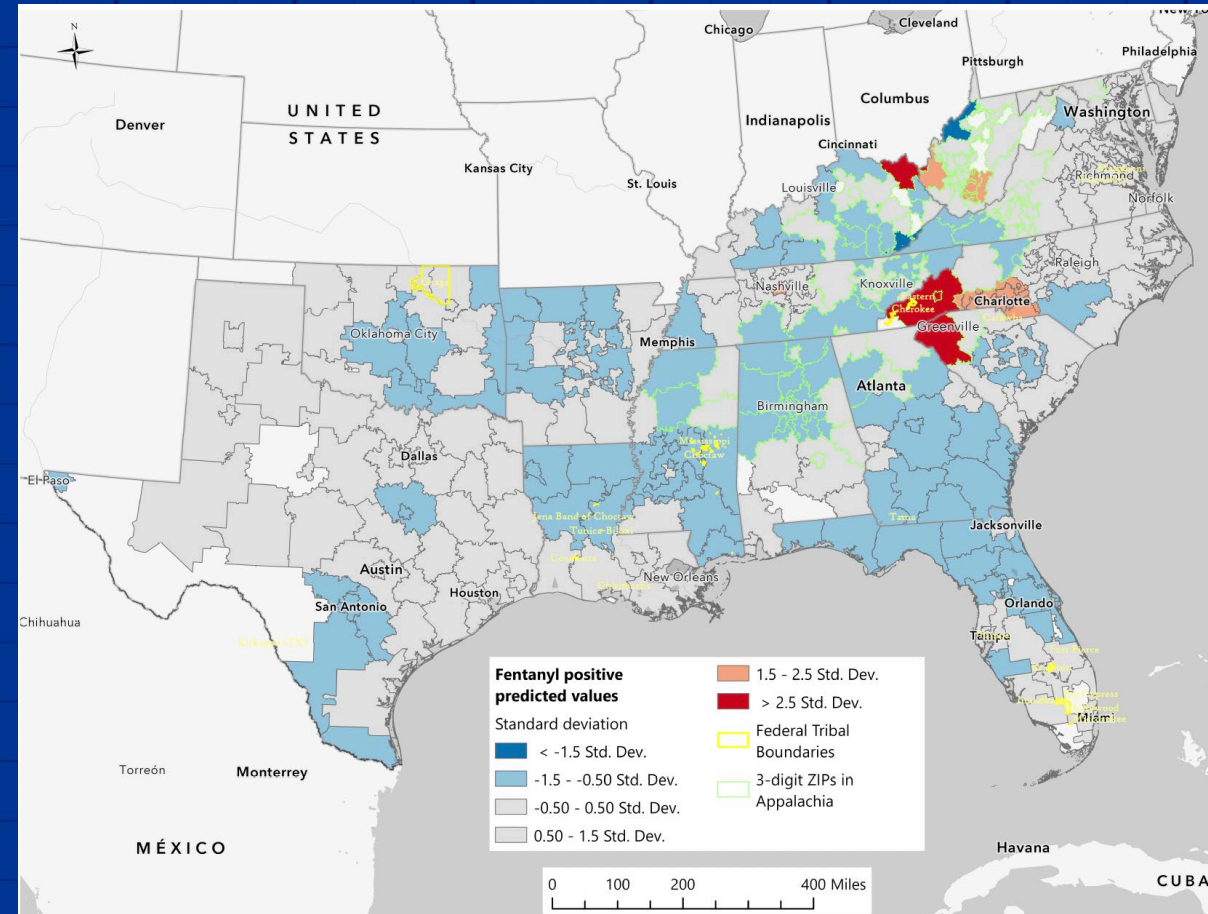
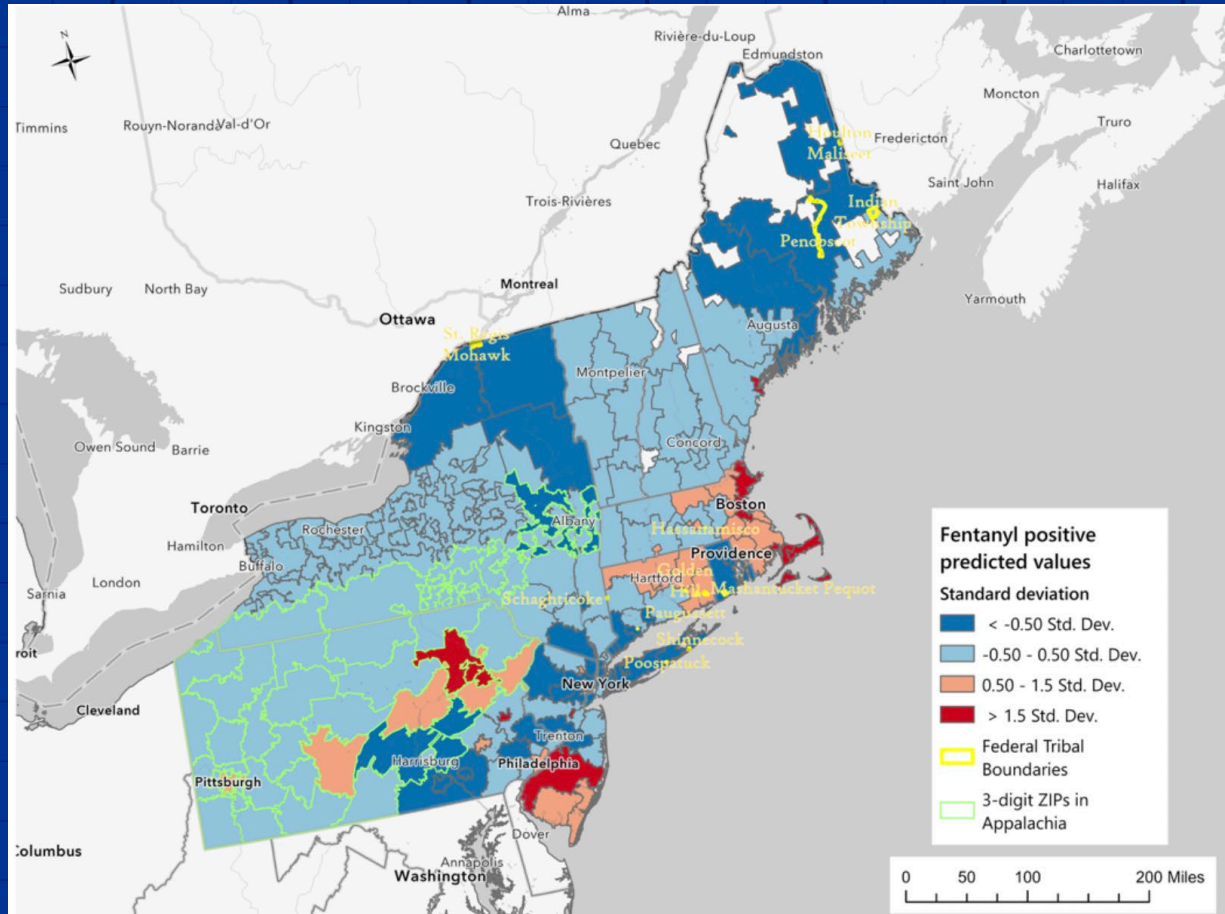
- De-identified data was obtained from Quest Diagnostics (n=1,168,829)
- The unit of analysis was urine samples tested for fentanyl in the 2021 calendar year
 - Quest excluded samples testing outside the U.S., pre-employment drug screenings, and other undisclosed customers/partners
 - UDS tested using standard immunoassays; positive results confirmed via mass-spectrometry or direct mass-spectrometry testing
 - Fentanyl positive tests based on detection of fentanyl or norfentanyl metabolite
- Quest aggregated the data at the 3-digit zip code and zip codes with low counts were suppressed to the 2-digit zip code level
 - Data was available for 64% of the 884 3-digit zip codes

Aim 1 Methods

- Primary Outcome: standardized proportion of Quest UDS positive for fentanyl
- Covariates:
 - Area Deprivation Index (ADI) where 1 is the lowest disadvantage & 100 is the highest disadvantage
 - Count of substance use providers was obtained from the National Provider Identifier registry
 - Population density was calculated using the 2018-2022 American Community Survey & the 2022 TIGER/Line shapefile data
 - Number of patients tested
- Moran's I was used to determine if the rates were spatially autocorrelated
- Multiscale geographically weighted regression, using a Gaussian distribution, was used
- Given the high rate of missing data, various sensitivity analyses were performed using imputation, Getis-Ord G_i^*

Fentanyl Hotspot

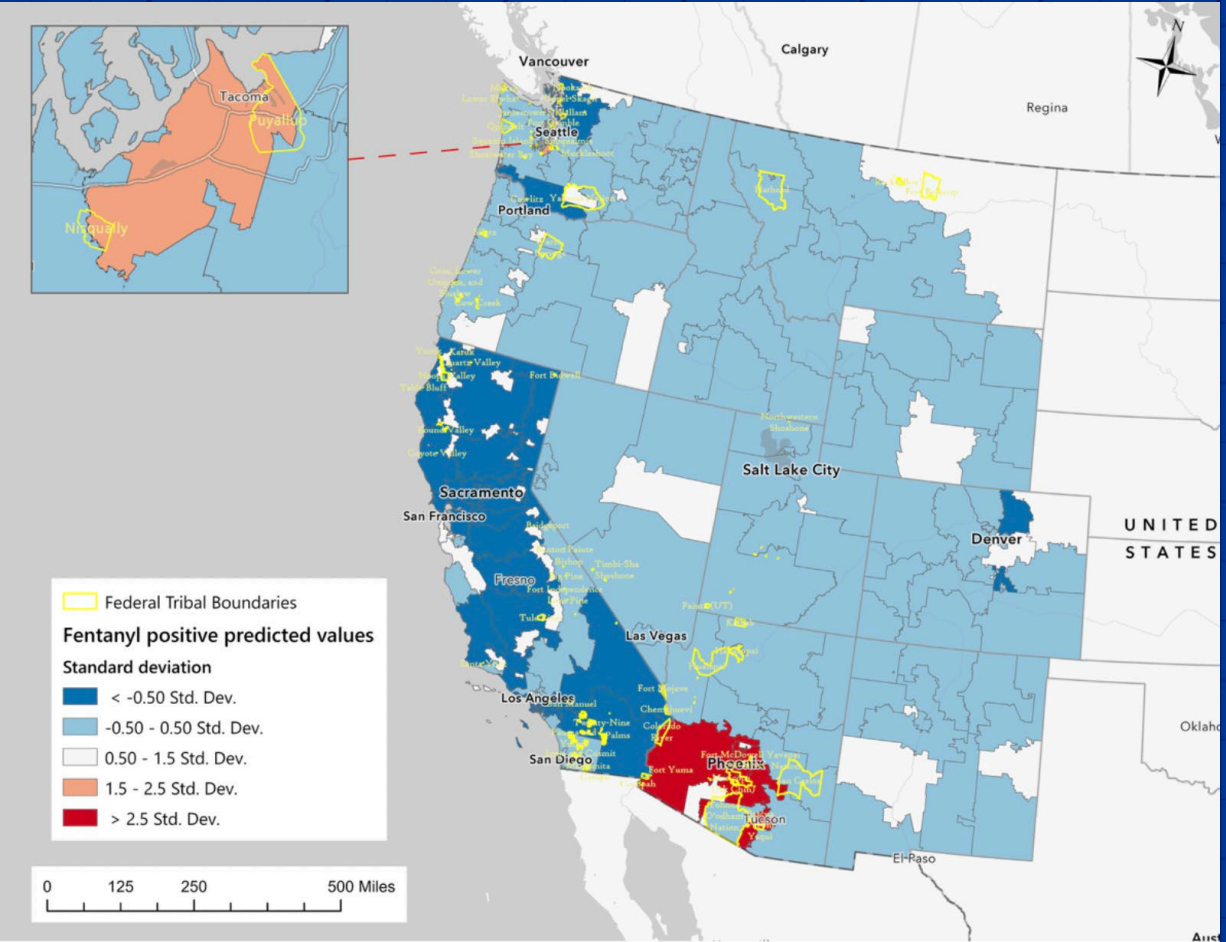
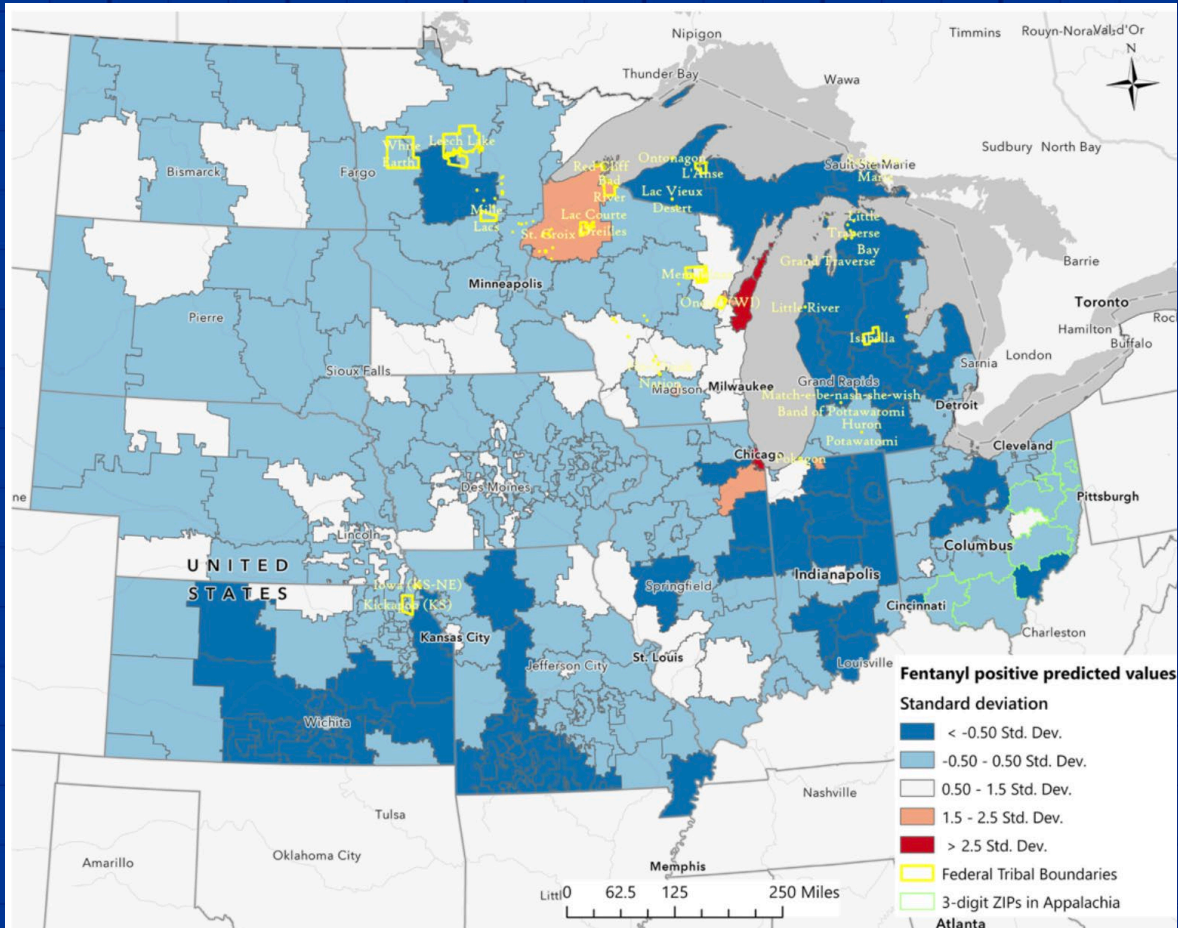
Overall, 14% of UDS tested positive for fentanyl in 2021



99% of geographic regions had at least 1 fentanyl+ UDS



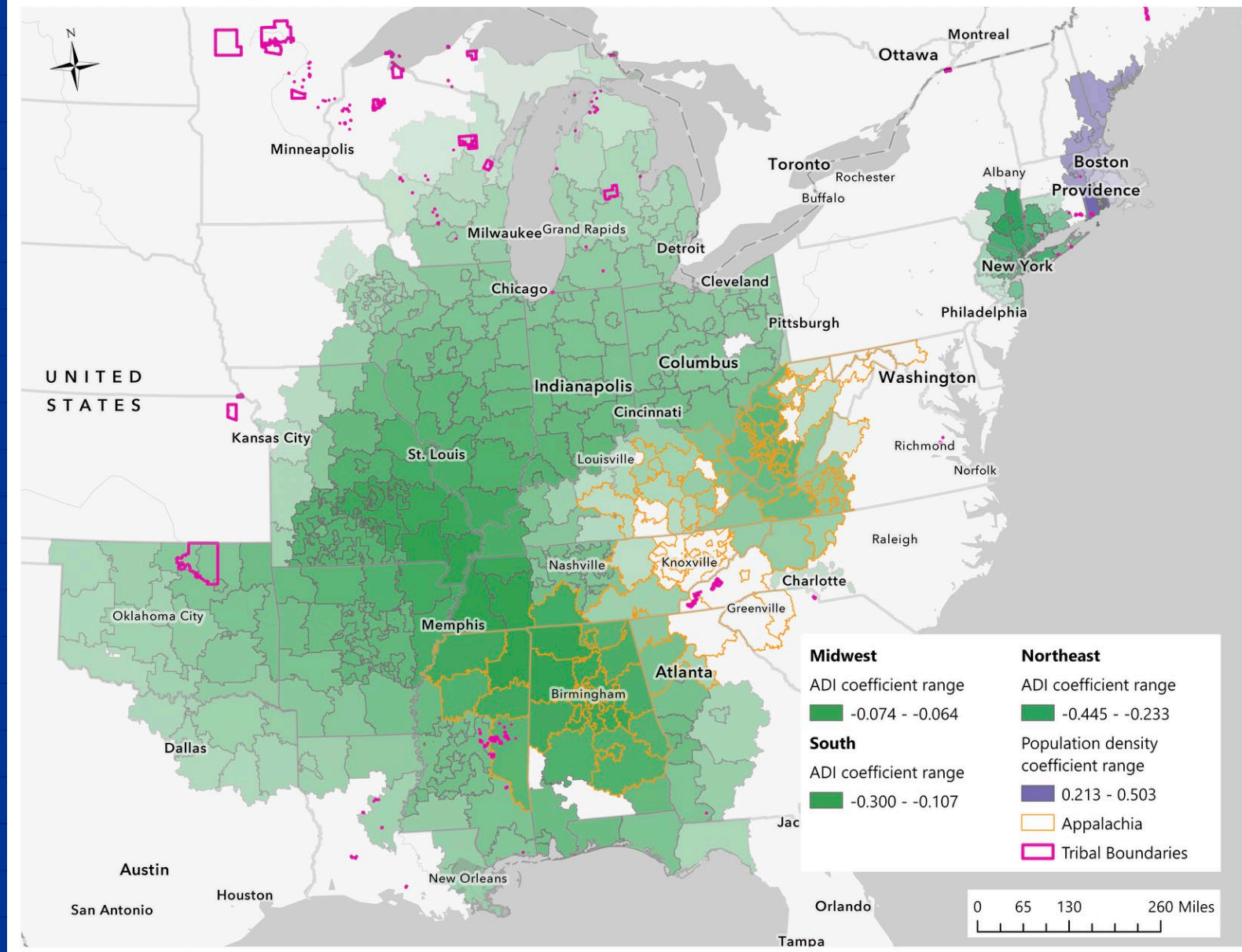
Fentanyl Hotspots



Aim 1 Results

- Area Deprivation Index (ADI) was negatively associated with fentanyl positivity in the Midwest, although fentanyl positive rates were low overall in this region
- In the northeast, population density was positively associated with fentanyl positivity

Figure 2. Significant local associations between Area Deprivation Index (ADI) and population density (independent variables) and fentanyl positivity



Aim 1 Discussion

- Fentanyl use appears to be ubiquitous in that 99% of geographic units had at least 1 fentanyl+ UDS; however, the percent of UDS fentanyl+ was low (14%) and varied by geographic regions
 - For example, 0.20% south central KY & 82% on south side of Chicago
- Spatial clusters of fentanyl+ UDS were found in urban and rural areas
 - Contrary to our hypothesis, there were not more hotspots east of the Mississippi
 - No clear pattern that would explain the geographic regions with hotspots
- In previous studies, ADI has been associated with geographic variability in overdose deaths

CTN-0135 Aim 2

Background – Why is Fentanyl Problematic

- Pharmacology of fentanyl is based on pharmaceutical-grade fentanyl, less is known about illicitly manufactured fentanyl and fentanyl analogs
- Fentanyl is highly lipophilic and has a variable clearance rate (Suzuki & El-Haddad 2017; Huhn et al. 2020)
- Fentanyl has a secondary peaking phenomenon (“fentanyl rebound”)
- There is evidence that fentanyl-exposed individuals have more severe opioid withdrawal compared to those non-fentanyl/opioid exposed
 - Non-fentanyl/opioid exposed had linear decline in opioid withdrawal
 - Fentanyl-exposed had a decline on day 1, with rebound days 2-3 (Sharma et al 2024)

Background – Opioid Withdrawal

- There are anecdotal reports of problems initiating buprenorphine treatment among patients using fentanyl from across the US (Volkow 2021)
 - Spontaneous opioid withdrawal – onset within 4-6 hours of stopping opioids
 - Precipitated opioid withdrawal (POW) – occurs after opioid antagonist administration preceded by a period of opioid abstinence
 - Potential POW-specific symptoms: runny eyes, yawning, runny nose, sweating, hot flashes & pupil size (Dunn et al 2023)

Background – PW & Other Problems

- Problems initiating buprenorphine treatment among patients using fentanyl has been largely described as PW
- However, studies in emergency departments have reported extremely low (0.76%) prevalence of POW (D’Onofrio et al 2023; D’Onofrio et al. 2026)
- Other problems:
 - Patient preference for methadone
 - Patients reporting that buprenorphine does not work for them or that they are “allergic”
 - Higher rates of missed visits or early discontinuation

Background – Micro/Macro Induction

- Despite this low prevalence of POW, there are several case reports and series on how to modify standard buprenorphine induction protocols in patients using fentanyl (Edinoff et al. 2023; Snyder et al. 2023)
- There are qualitative reports of patient experiences (Simpson et al. 2024)

“Yeah [using fentanyl vs heroin] made [withdrawal] like way worse. Like way worse. Like, it’s more intense. It’s stronger. It comes on quicker. It seems like it takes more to get well...it just really sucks. Actually heroin --I miss heroin withdrawal. Heroin withdrawal was easy.”

TABLE 2. Clinical Decision Support for Buprenorphine Initiation Techniques Based on the Clinical Setting

Initiation Strategy*	Fastest Slowest		
	HDB†	Standard‡	LDB-OC§
Possible advantages	-Quick stabilization -Bridge access barriers to ongoing buprenorphine	-Most common and well-described technique	-Opioid abstinence not initially required
Need for opioid withdrawal?	Yes	Yes	No
Premedicate with adjuvant medications?	Consider	Yes	Yes
Initial starting dose¶ (buprenorphine SL formulation)	8–16+ mg	2–8 mg	0.25 mg–1 mg
Duration of initiation until stabilization	≤2 h	1–3 days	3–10 d (may be longer in certain situations)
Need for opioid continuation	No	No	Yes
Full agonist opioid continuation dose	None	None	Examples: Methadone 30 mg PO daily or Hydromorphone 4 mg PO every 4 hr or Self-directed illicit/nonprescribed opioid use
Care coordination required	Moderate	Moderate	High

*See Appendix C (<http://links.lww.com/JAM/A431>) for example protocols of these strategies.

†HDB = high-dose buprenorphine; this is sometimes referred to as “macro dosing.”

‡Standard buprenorphine initiation is based on the ASAM NPG and typically occurs with medically managed instructions for home buprenorphine initiation.³

§LDB-OC = low-dose buprenorphine with opioid continuation; this is sometimes referred to as “micro dosing” or “microinduction” but the most clinically accurate term is used here.

||Adjuvant medications include clonidine, hydroxyzine, acetaminophen, and NSAIDs (Appendix D, <http://links.lww.com/JAM/A431>).

¶This refers to the initial dose only. The total daily dose on day 1 and subsequent days is likely more than this initial dose.

CTN-0135 Study Aims

- Estimate the national prevalence of clinician-reported problems initiating buprenorphine treatment in patients using fentanyl and summarize how these problems are changing clinical practices.

Hypothesis 1: We hypothesized that ~40% of clinician respondents will report problems initiating buprenorphine treatment.

Hypothesis 2: We hypothesized that the most common problem with initiating buprenorphine treatment is precipitated opioid withdrawal among patients chronically (≥ 3 weeks) using fentanyl.

Methods: Survey Development

- Survey draft was pilot-tested with 19 clinicians, from different clinical settings (e.g., emergency department, hospital, outpatient, methadone programs) across 10 regions in US, brief follow-up interviews were conducted with the clinicians to clarify their feedback
- Final survey took <15 minutes, included 96 questions across 6 domains:
 - Patient characteristics & fentanyl use
 - Standard buprenorphine induction practices & challenges
 - Strategies to address buprenorphine induction problems
 - Clinician characteristics
 - Practice characteristics



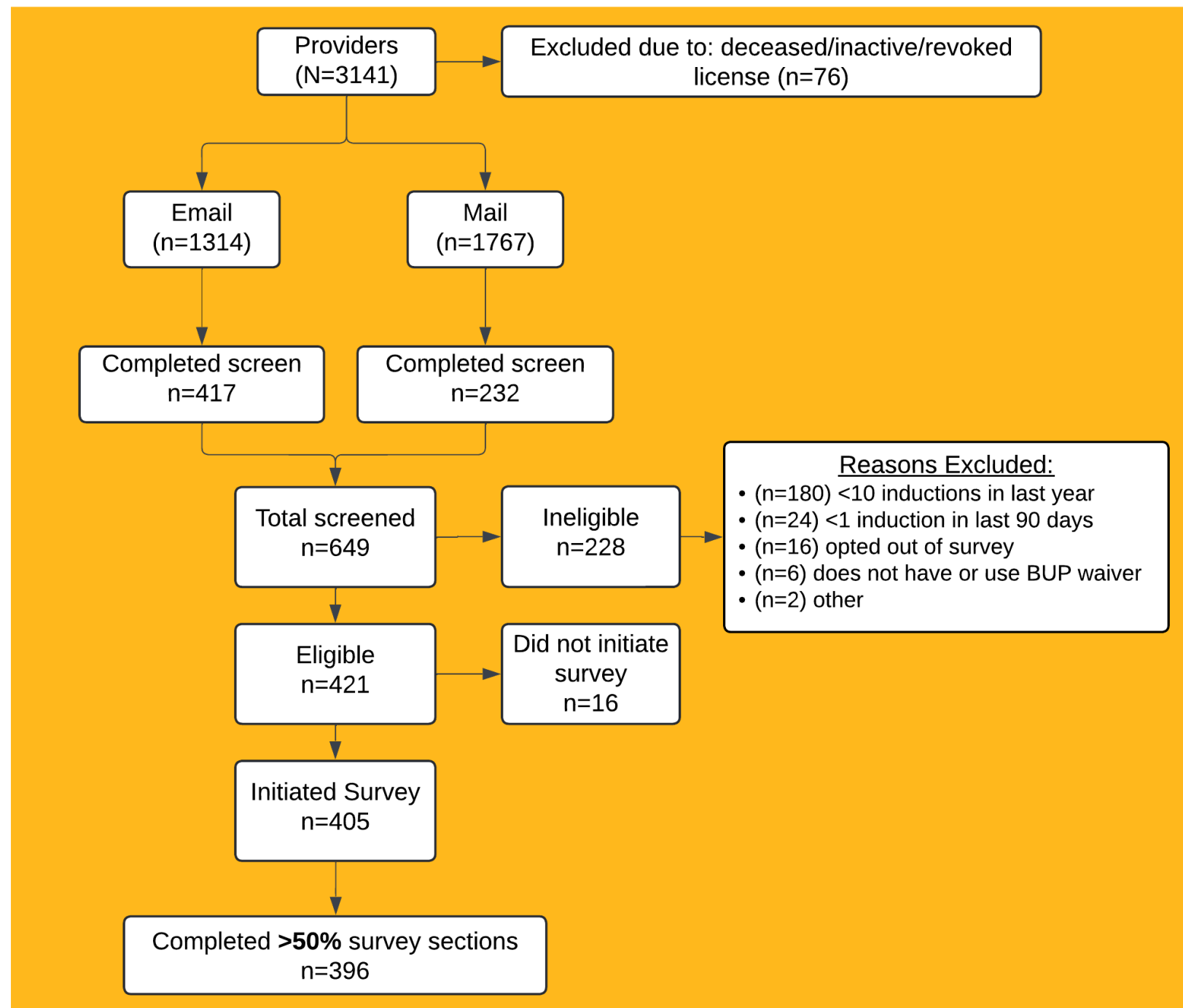
Methods: Provider Sampling and Distribution

- Stratified random sample was taken from DEA X Waiver registrant database
- Contact information verified through online searches and direct calls.
- Recruitment waves:
 - **Wave 1:** 922 clinicians
 - **Wave 2:** 2,219 clinicians
- Email was automatically sent via REDCap, the majority received a survey invitation via standard mail
- Pre- & post- notification post cards were also sent
- Survey was open June 2, 2023- March 18, 2024

Reminder Postcards

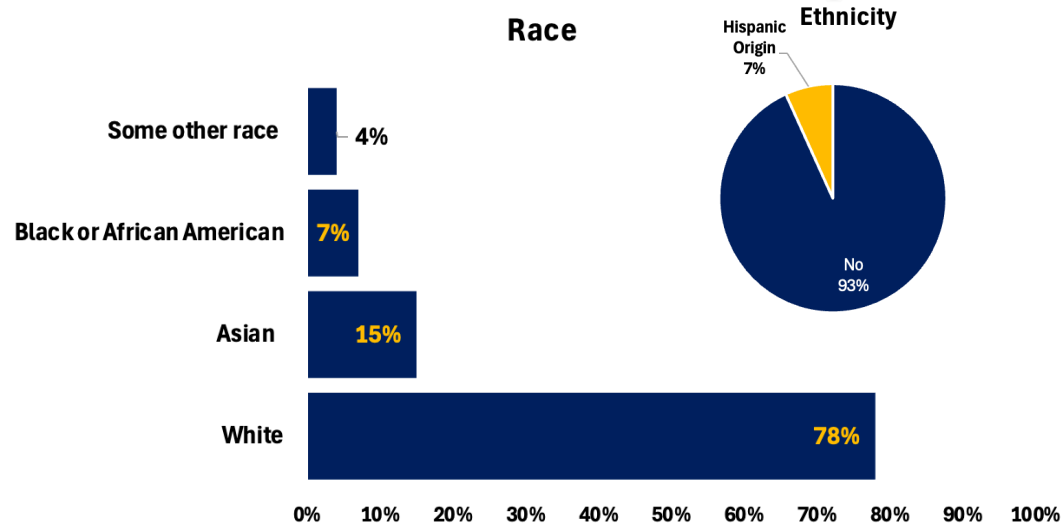
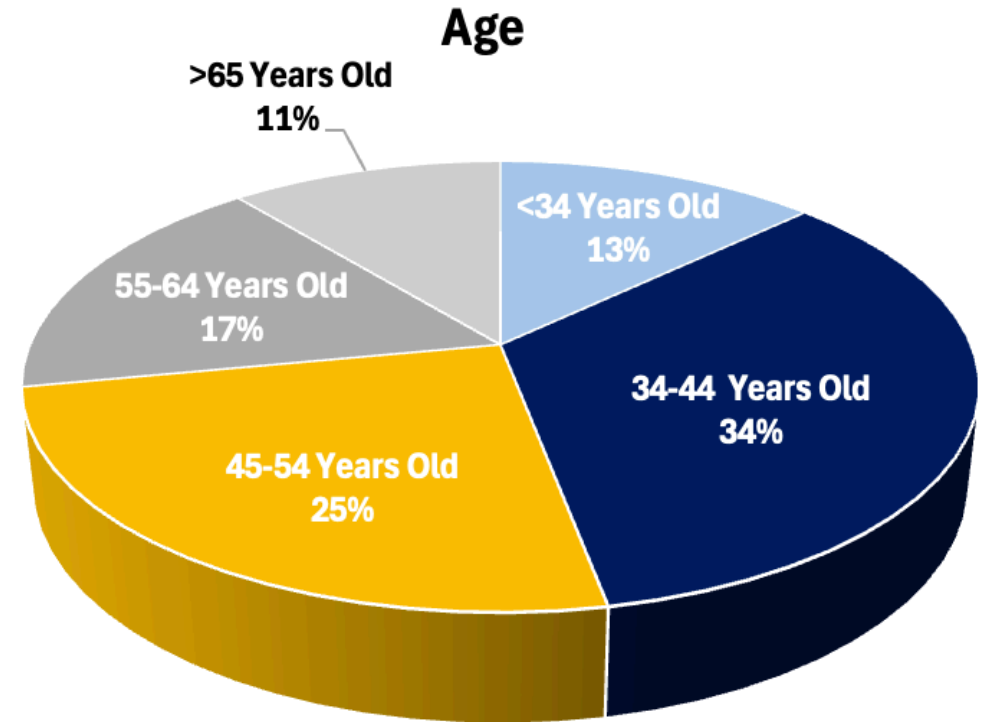


Results



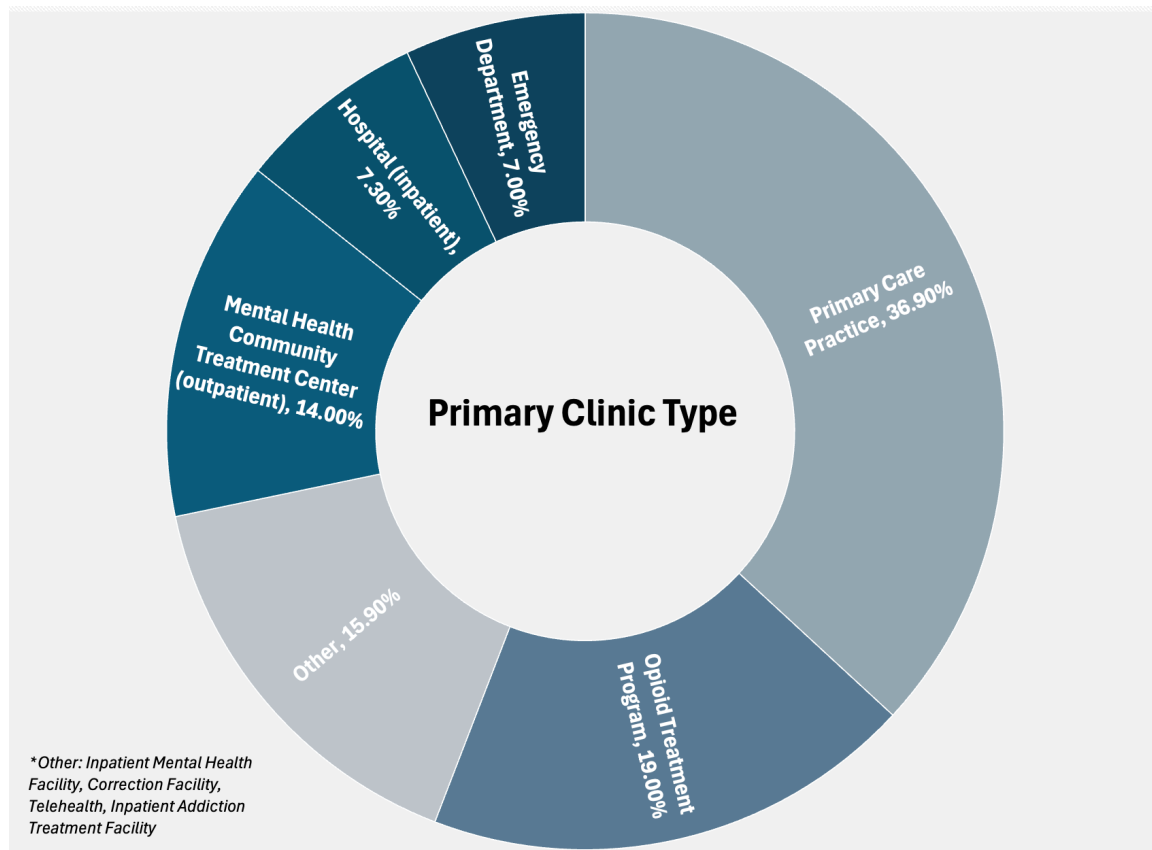
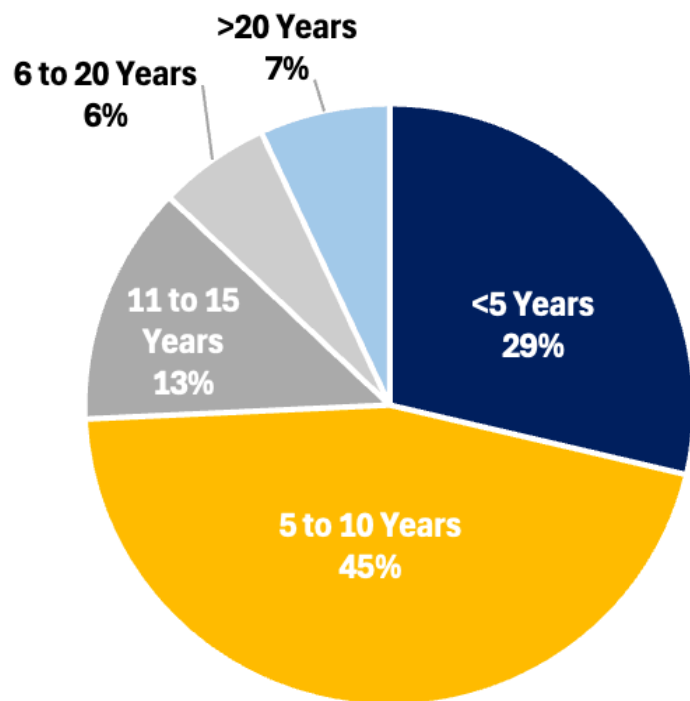
Participant Demographics

- 51% were female
- Mean age was 47.5 years
 - SD: 12.08
 - Range: 25-88



Participant Experience & Practice Setting

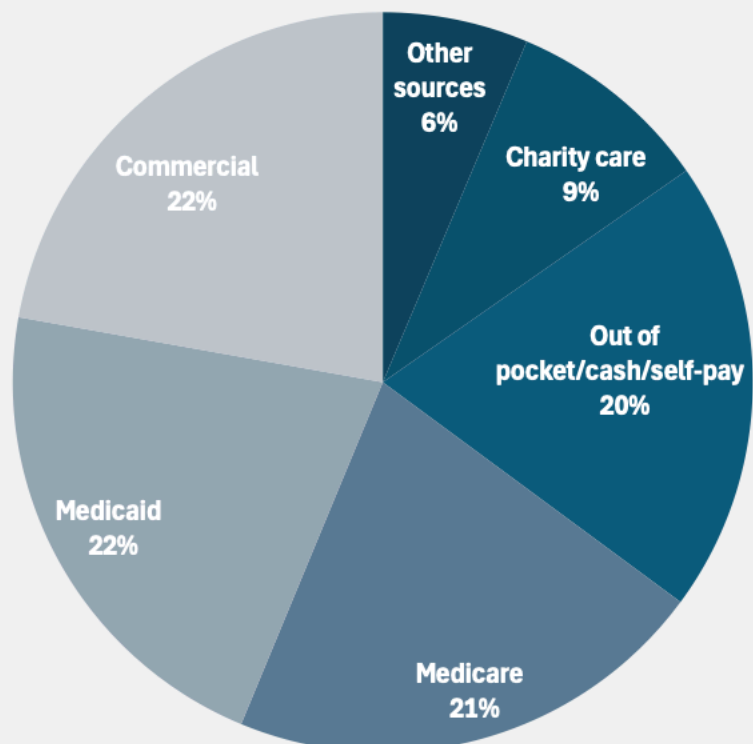
Years treating patients with OUD



40.5% worked in more than 1 setting

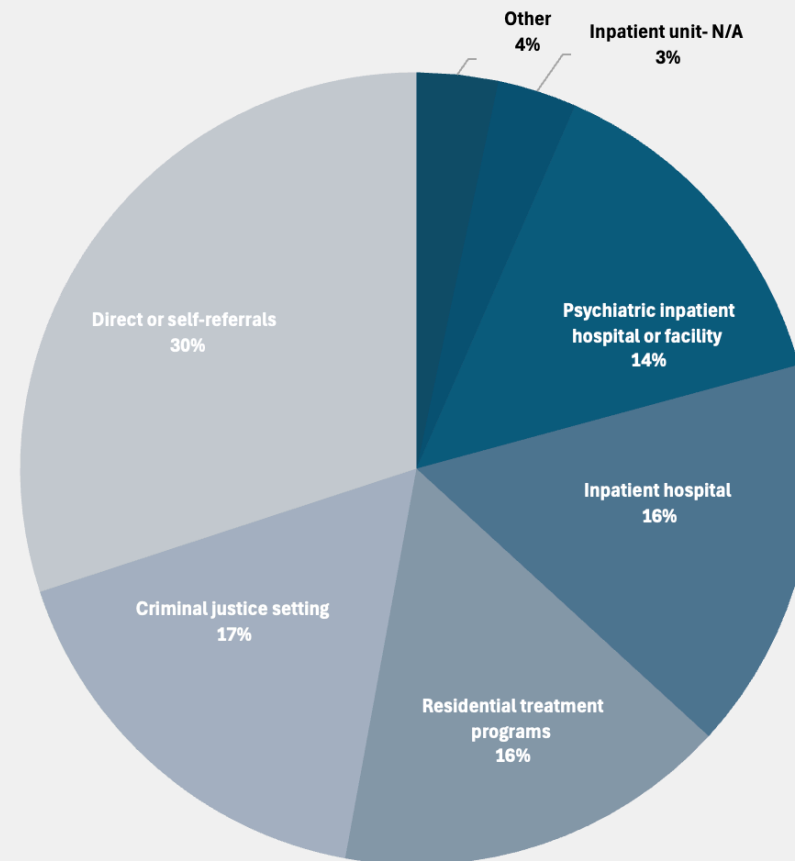
Participant Practice Setting

Payer Information



*Other: Block Grant Funding, VA, Grant Funding, etc.

Where Are Patients Referred From



Induction Settings

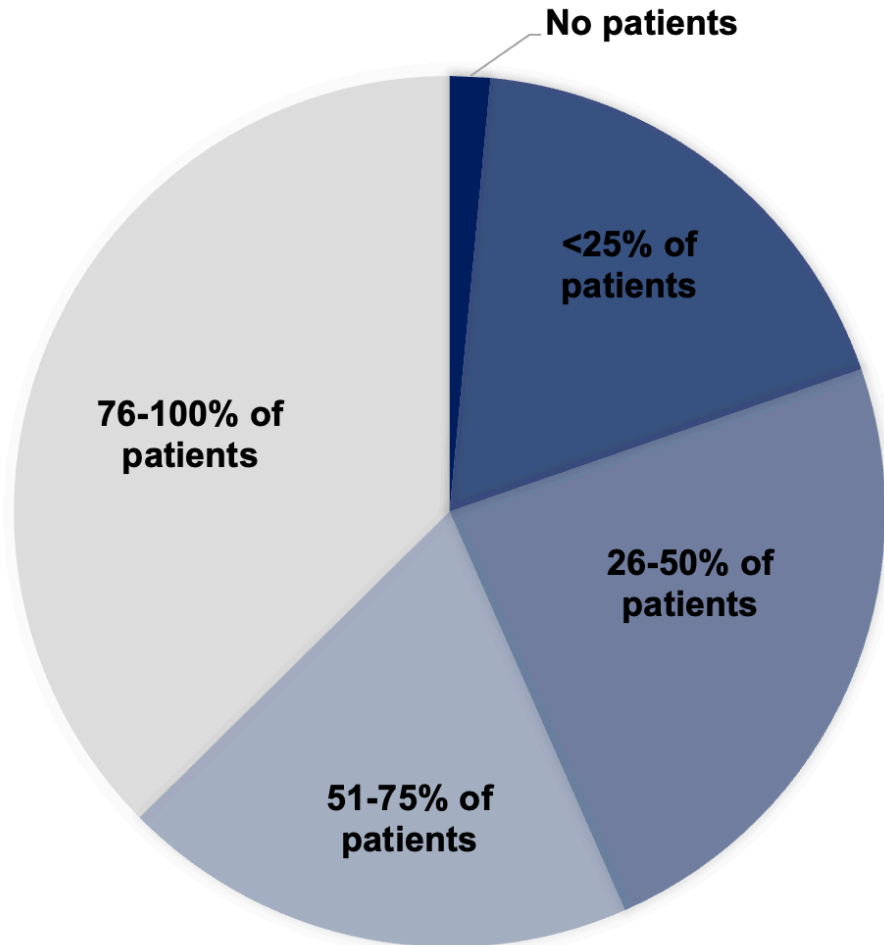
- 74.9% outpatient clinic
- 31.6% inpatient
- 29.3% at home
- 11.9% inducted elsewhere & then transferred to your setting/practice



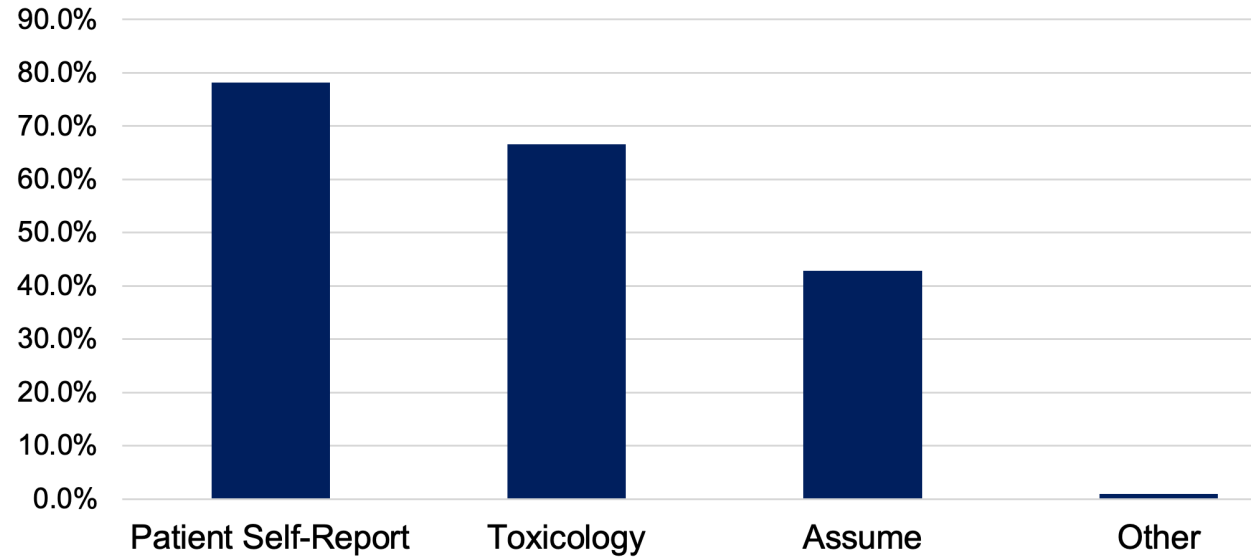
10.3% reported that patients are waiting >1 week, on average, to start buprenorphine treatment

Results

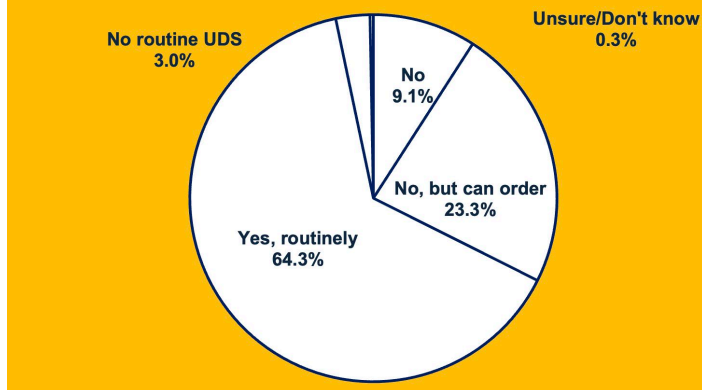
PROPORTION OF PATIENTS USING FENTANYL



How Clinicians Knew Patients Used Fentanyl

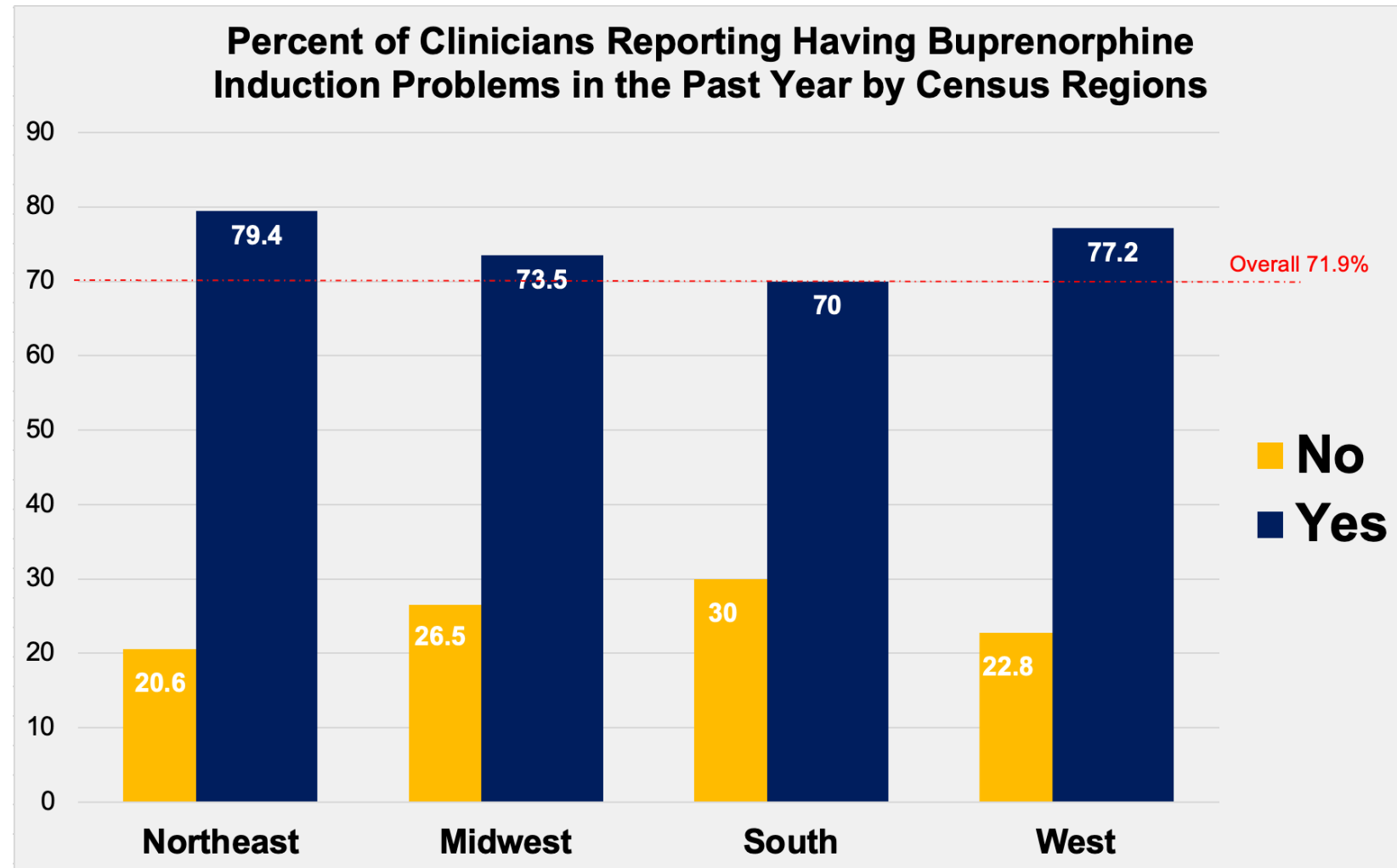


DOES YOUR USUAL DRUG SCREEN INCLUDE FENTANYL



37.6% had access to test for fentanyl analogs or other novel opioid

Results

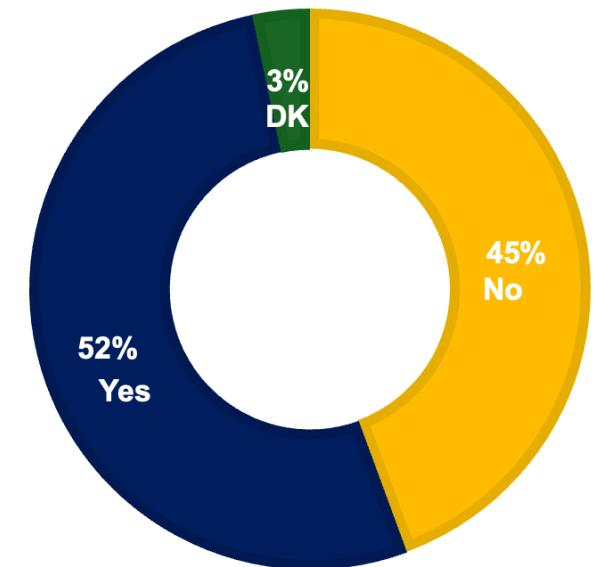


Results

Types of problems that clinicians encounter when trying to start patients using fentanyl onto buprenorphine (*check all that apply*):

- 69.5% (n=271) increased opioid withdrawal symptoms per patient report
- 48.5% (n=189) Patients more frequently dropping out after first appointment or increasing number of patients missing appointments
- 24.4% (n=95) More patients being “allergic” to buprenorphine
- 21.5% (n=84) More patients reporting a preference for methadone treatment
- **10.0% (n=39) I have not encountered problems**
- 9.5% (n=37) Other

HAVE ANY PATIENTS TOLD YOU THAT BUP DOES NOT WORK



Results

- 71.9% (n=285) clinicians reported having patients that experienced precipitated or prolonged withdrawal in the past year
 - 61.5% endorsed precipitated withdrawal & 52.8% endorsed prolonged withdrawal
 - 64.9% (n=255) reported that these problems were moderately or very important
- In the multivariable logistic regression model, clinicians that were waived to treat up to 275 patients & those reporting 75%+ of their patients were using fentanyl, were more likely to report treatment initiation problems

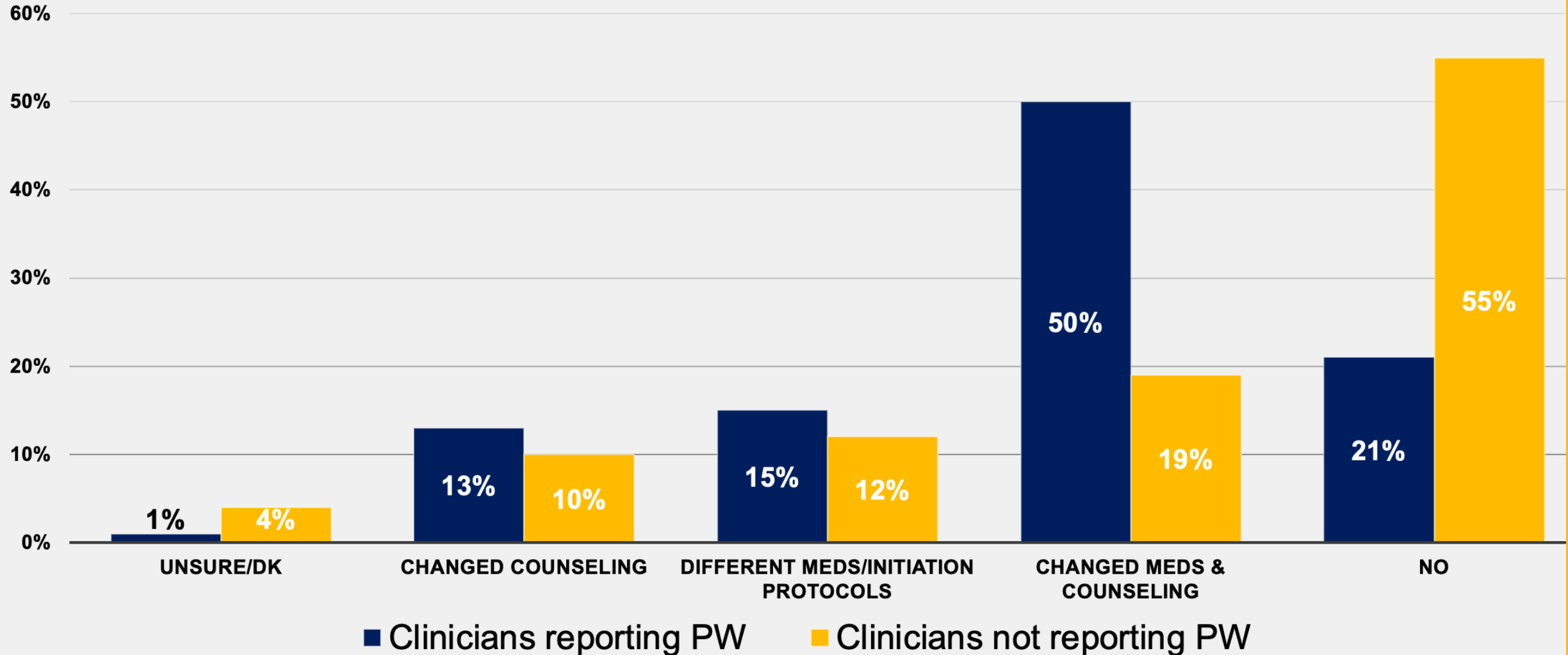
SAMPLE DISTRIBUTION

PW/Prolong WD	Odds ratio	p-value	Confidence Interval	
	Y/N			
Setting	<i>outpatient only (reference)</i>			
Inpatient only	1.28	0.685	0.39	4.20
ED only and other	3.00	0.132	0.72	15.53
Combo	0.79	0.563	0.35	1.78
Provider type	<i>NP/PA/MD 30 or 100 (reference)</i>			
NP/PA/MD 275	1.92	0.026	1.08	3.4
Census Region	<i>Northeast (reference)</i>			
Midwest	0.71	0.432	0.30	1.68
South	0.59	0.176	0.70	3.81
West	0.70	0.421	2.59	15.35
Patients who use fentanyl	<i>0-24% (reference)</i>			
25-50% of patients	1.31	0.482	0.62	2.77
51-75% of patients	1.64	0.253	0.70	3.81
76-100% of patients	6.31	0.000	2.59	15.35
Years treating patients with OUD				
Years in practice, estimated for every five years	0.88	0.132	0.74	1.04
Induction Setting	<i>outpatient only (reference)</i>			
Only Inpatient	2.07	0.157	0.76	5.69
Combo and other	2.79	0.004	1.39	5.61

Results

67.3% of clinicians reported having modified buprenorphine initiation among patients using fentanyl

Have You Modified the Way You Initiate Buprenorphine Treatment in Patients Using Fentanyl?



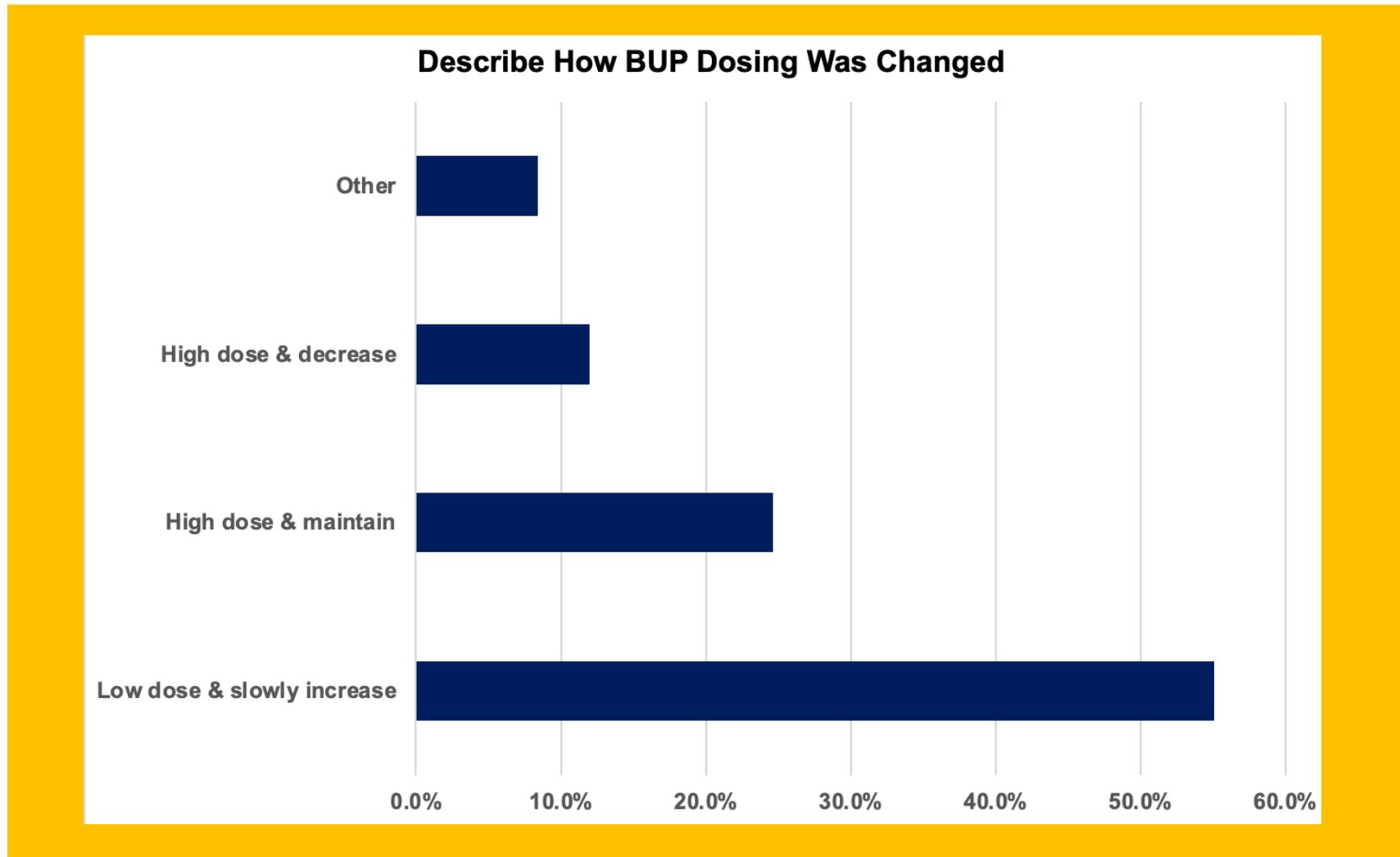
Results

How Clinicians Have Changed Practices:

- 76.6% (n=167) change in titration schedule for buprenorphine (low or high dose)
- 68.3% (n=149) Comfort medications prescribed
- 67.9% (n=148) Change in dosage of first dose of buprenorphine
- 53.2% (n=116) Longer lag time before first dose of buprenorphine

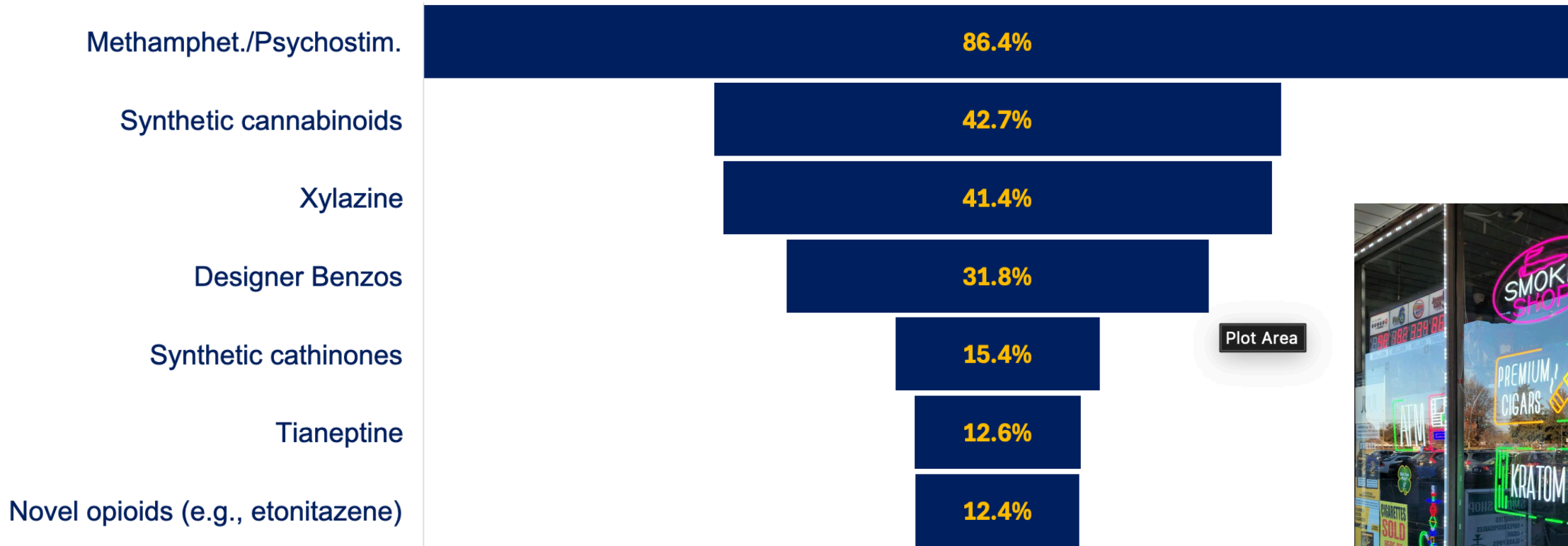
30.8% reported encountering pharmacy-related challenges that impacted their modified BUP induction procedures

Results



Additional Survey Results

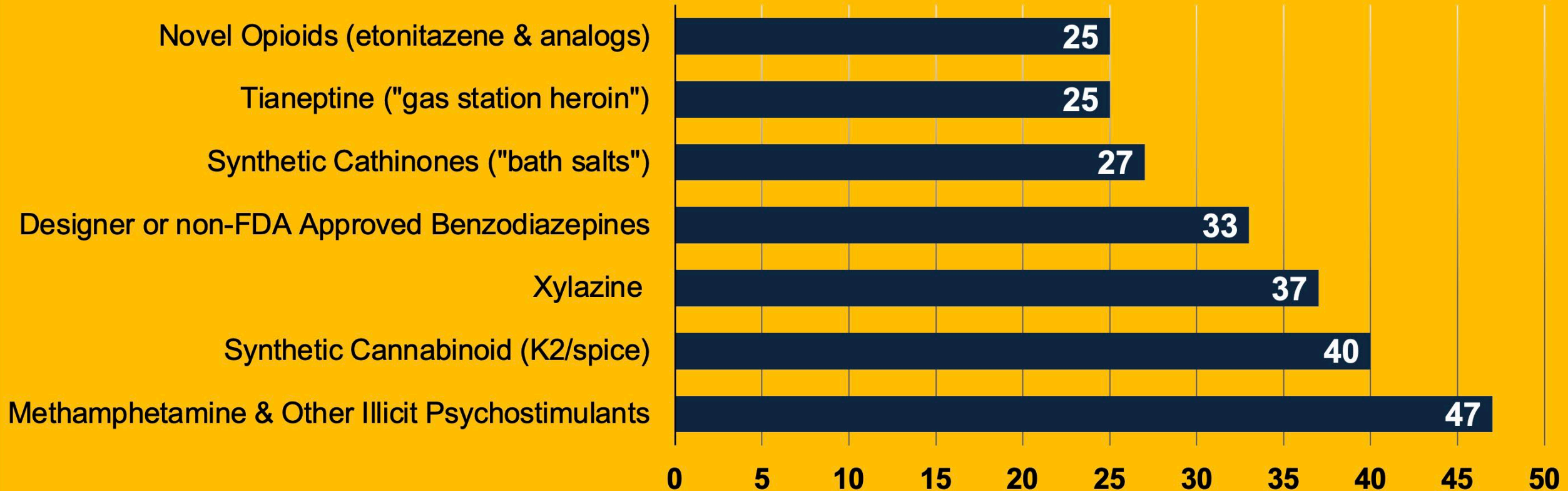
Other Drugs Complicating Treatment (Excluding fentanyl)



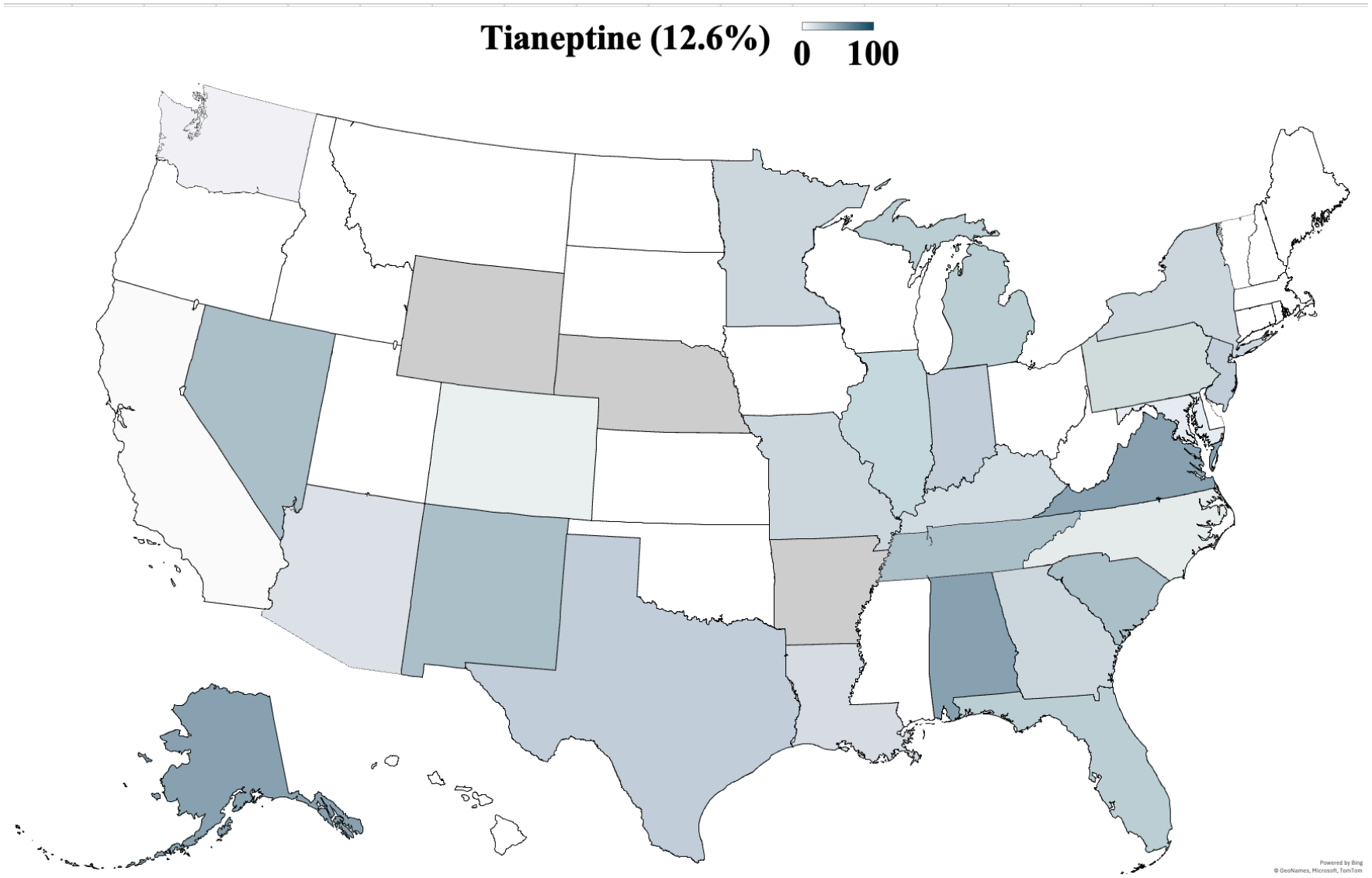
SOURCE: J of Studies on Alc & Drugs

Additional Survey Results

Number of States with Clinicians Reporting Drugs Complicating Treatment



Results – Other Drugs Causing Problems



Study Limitations

- Data reflects clinicians' subjective opinions and it is unclear the extent to which those are based on use of standardized clinical tools to assess opioid withdrawal
- Potential sources of bias:
 - Recall clinical problems experienced over the past year
 - Clinicians encountering challenges treating patients using fentanyl may have been more inclined to participate in the survey

Discussion

- 72% clinician respondents reported having patients that experienced precipitated and/or prolonged opioid withdrawal in the past year
- Other drugs, like xylazine & synthetic cannabinoids, are believed by US clinicians to be complicating buprenorphine treatment
- More than half of clinicians reported that these problems were important & had changed how they initiate buprenorphine in patients using fentanyl
- Treatment modifications included dose modification, changing the frequency of counseling & adding comfort medications
- Differential reports of precipitated withdrawal in patients using fentanyl across the US may reflect a) use of different measurement tools & b) may vary by practice setting



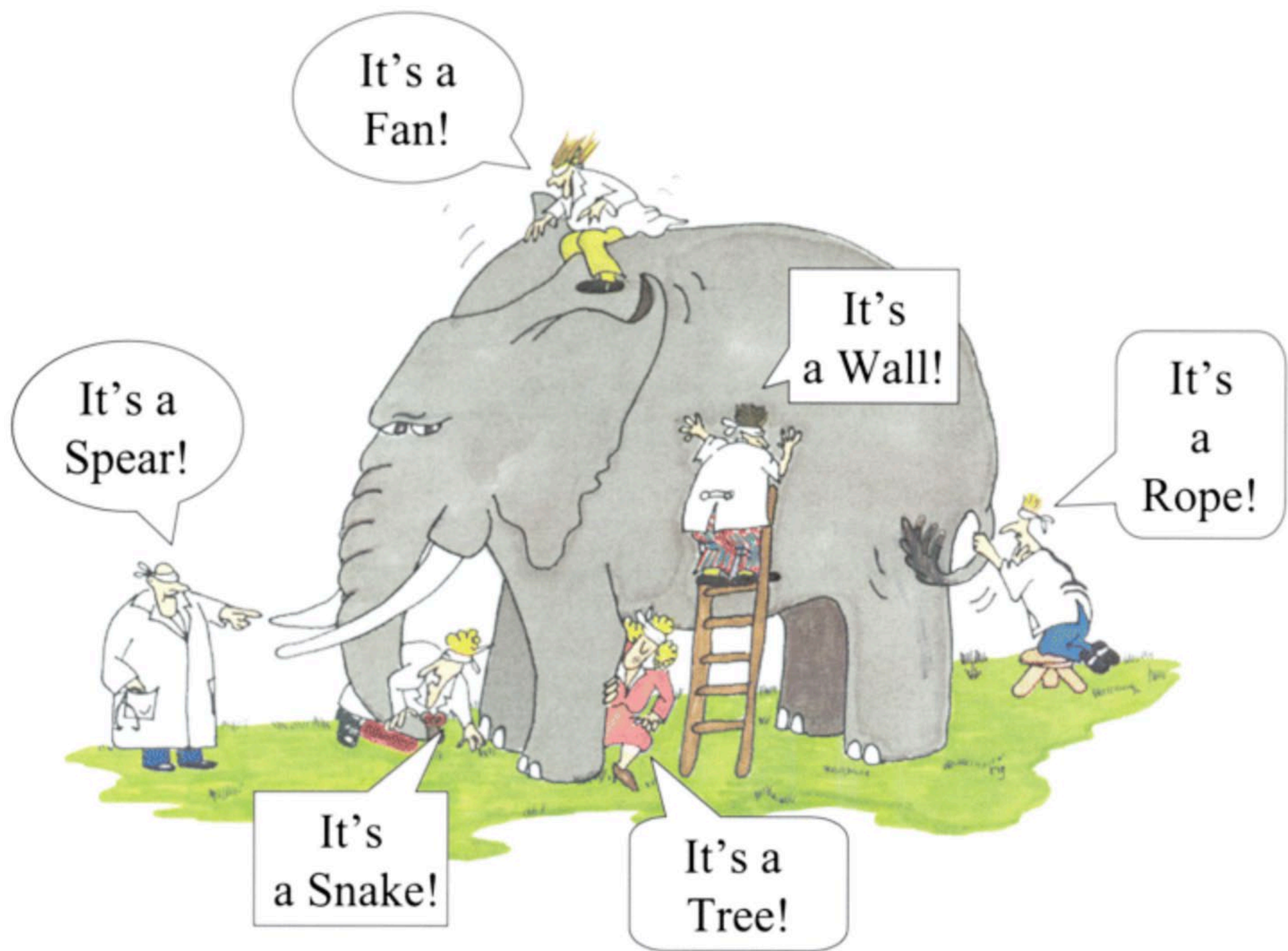
Original Investigation | Substance Use and Addiction

Barriers to Buprenorphine Initiation in Patients Using Fentanyl

Sarah S. Kawasaki, MD; Jane M. Liebschutz, MD, MPH; Cristina Murray-Krezan, PhD; Galen E. Switzer, PhD; Samantha Nash, BS; Kwonho Jeong, MS; Erin L. Winstanley, PhD

Conclusions

- Fentanyl use is ubiquitous; however, there are “hot” and “cold” spots of use that are not bonded by a geographic region
- Most clinicians are encountering challenges when initiating patients onto buprenorphine --> but it's not just precipitated opioid withdrawal among patients using fentanyl
- Availability of fentanyl, fentanyl analogs and other novel psychoactive substances vary at the local level
- We have limited knowledge of individual-level factors that explain differential clearance of fentanyl
- Surveillance of changing drug use patterns is often delayed & it's impact on treatment engagement & retention is often unknown



CTN-0135 – Next Steps

Next Steps

- Finalizing a qualitative analysis of the open-ended survey items
- Developing a data dashboard:
 - a) Piloting initial draft
 - b) Formal evaluation with initial survey participation that agreed to be re-contacted



Qualitative Analysis

Open-ended questions included:

- Is there anything else you'd like us to know about your patients who use fentanyl
- 'Other' buprenorphine induction problems you've encountered
- What else can clinicians/programs do to improve engagement/retention in treatment among patients using fentanyl
- Anything else you'd like to tell us about how you have modified your treatment procedures for patients using fentanyl
- Anything else our team should know

CTN-0135 Data Dashboard



Click on menu bar to move through sections

CTN-0135 Dashboard Welcome Patients' Use of Drugs More about the survey Meet the Study Team Contact Us

Welcome to the CTN-0135 study dashboard!

We developed this dashboard to share the results of a national survey of buprenorphine clinicians regarding problems they may have encountered when starting buprenorphine treatment for patients with opioid use disorder (OUD) and fentanyl.

Why Does Fentanyl Complicate Buprenorphine Treatment?

Fentanyl is a highly potent opioid compound, with a high affinity at the mu opioid receptor, and there is a lot of variability in how long it takes patients to clear fentanyl from their system ([days to weeks](#)). Some patients using fentanyl may experience opioid withdrawal symptoms when they start buprenorphine treatment, while others may not believe that buprenorphine 'works' or they may prefer other medications ([like methadone](#)) .

Survey Details:

An online survey was sent to a national random sample of clinicians and 396 clinicians completed it. The survey included 96 questions including: 1) characteristics of patients who used fentanyl, 2) standard clinical procedures to start buprenorphine treatment, 3) how clinical procedures have been modified for patients who used fentanyl and 4) clinician/practice setting characteristics.

Interpreting the Survey Results:

The survey results are from the clinician perspective and hence the data is not at the patient-level. While the survey data can be aggregated at the state-level, the number of survey respondents within a given state is limited and they may not represent all clinicians treating patients with buprenorphine within a specific state. Additionally, clinician perspectives on problems initiating buprenorphine treatment are reflective of the level of care in which they prescribe buprenorphine.



Data Dashboard – Pilot



Data Dashboard Evaluation AAA

We have created an interactive data dashboard to disseminate results from a national survey on buprenorphine initiation problems (CTN-0135) that clinicians have encountered in patients who use fentanyl in the United States. A data dashboard is an approach for sharing research findings through an interactive website, enhancing transparency and accessibility. It allows a wide range of users to efficiently explore results and engage with complex analytical methods with ease.

The purpose of this survey is to informally evaluate an online data dashboard as a tool to disseminate research findings to clinicians, key stakeholders, and community members prior to formally evaluating the dashboard.

As part of this informal evaluation, we will ask you to review the online data dashboard [insert link] and to take a brief survey about your opinions about the data dashboard. Your participation in this survey is voluntary and there are no consequences if you choose not to participate. Only individuals 18 years of age or older are able to participate. For any additional questions please contact the research coordinator, Samantha "Sam" Nash (SAN288@pitt.edu).

This informal dissemination evaluation is being conducted by Erin L. Winstanley, Ph.D. at the University of Pittsburgh. If you have any questions, you can contact Dr. Winstanley via phone (412-624-1607) or via email at elw194@pitt.edu.

Do you agree to participate in this research survey? Yes No reset



Acknowledgements & Funding

- This study was funded by the National Institute on Drug Abuse's (NIDA) Clinical Trials Network (CTN) & was conducted as part of the Appalachian Node (CTN-0135)



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