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Tranq Dope: Characterization of an ED cohort treated with a novel opioid withdrawal protocol in the era of fentanyl/xylazine

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ABSTRACT

Background: Treating opioid use disorder has reached a new level of challenge. Synthetic opioids and xylazine have joined the non-medical opioid supply, multiplying the complexities of caring for individuals in emergency departments (ED). This combination, known as 'tranq dope,' is poorly described in literature. Inadequate withdrawal treatment results in a disproportionately high rate of patient-directed discharges (also known as against medical advice dispositions, or AMA). This study aimed to describe a cohort of individuals who received a novel order set for suspected fentanyl and xylazine withdrawal in the ED.

Methods: This is a descriptive study evaluating a cohort of ED patients who received withdrawal medications from a novel protocol and electronic health record order set. Individuals being assessed in the ED while suffering from withdrawal were eligible. Individuals under age 18, on stable outpatient MOUD or who were pregnant were excluded. Treatment strategies included micro-induction buprenorphine, short acting opioids, non-opioid analgesics, and other adjunctive medications. Data collected included: demographics including zip code, urine toxicology screening, order set utilization and disposition data. Clinical Opiate Withdrawal Scale (COWS) scores were recorded, where available, before and following exposure to the medications.

Results: There were 270 patient encounters that occurred between September 14, 2022, and March 9, 2023 included in the total study cohort. Of those, 66 % were male, mean age 37 with 71 % residing within Philadelphia zip codes. 100 % of urine toxicology screenings were positive for fentanyl. Of the 177 patients with both pre- and post-exposure COWS scores documented, constituting the final cohort, patients receiving medications had their COWS score decrease from a median of 12 to a median of 4 ($p < 0.001$). The AMA rate for this cohort was 3.9 %, whereas the baseline for the population with OUD was 10.7 %. Recorded adverse effects were few and resolved without complication.

Conclusions: Fentanyl and xylazine withdrawal are challenging for patients and providers. A novel tranq dope withdrawal order set may reduce both COWS scores and rate of patient-directed discharge in this cohort of patients, though further investigation is needed to confirm findings.

1. Introduction

Opioid Use Disorder (OUD) remains a critical public health problem that impacts individuals and their communities in profound ways. More than 100,000 people in the United States died in 2021 from the overdose crisis, more than double the rate of victims of gun violence [1]. Patients with opioid use disorder frequent emergency departments (ED) due to the medical and social sequelae of addiction, approximately one in 80 visits nationwide [2]. The ED has therefore become an important venue for identification and treatment of those with OUD and their often serious medical and surgical emergencies [3,4].

Heroin has been abruptly replaced by fentanyl and its analogues in many locations across the United States, Canada and Europe [5-7]. The beginning of the fentanyl epidemic also coincided with the first documented cases of recreational human xylazine use in Puerto Rico [8-10]. Xylazine is an alpha-two agonist sedative approved solely for veterinary use by the U.S. Food and Drug Administration (FDA). The withdrawal syndromes faced by patients using fentanyl and xylazine are unprecedented, resulting in a high baseline rate of patients directing

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their own discharge (also known as against medical advice, AMA) [11,12]. Given the inadequacy of the term heroin and its colloquialisms to describe this novel combination, it has since been popularized as 'tranq dope.' To date, there are no standardized treatment plans to address this problem.

The purpose of this study was to characterize a cohort of patients who were treated for suspected fentanyl and xylazine withdrawal in the ED, with a novel electronic health record order set.

2. Methods

2.1. Study design and setting

This is a retrospective observational study based on real world experience after implementation of a novel order set to address acute fentanyl and xylazine withdrawal in the ED. This study occurred at two urban hospitals in Philadelphia, PA: one academic, one community. The academic hospital, which sees approximately 76,000 visits annually, is a level 1 academic tertiary care and trauma center. The community hospital, which sees approximately 34,000 visits annually, is a non-trauma center 2.5 miles from the main hospital.

2.2. Participant selection

The study took place from September 1, 2022, through May 5, 2023. Inclusion criteria included emergency department patients who self-reported non-medical opioid use disorder, and whose physicians deemed in need of withdrawal treatment, secondary to a medical or surgical condition. The final cohort for analysis consisted of all patients that presented with OUD, received at least one medication from one of four order pathways during the study period, and had both a pre- and post-exposure COWS score documented. Exclusion criteria included pregnancy, children under eighteen years of age, or patients taking stable doses of outpatient medication for opioid use disorder (MOUD).

Notably, it is currently difficult to ascertain toxicology data in assessing xylazine use. The time relevant Philadelphia Department of Public Health data showed 98 % of all non-medical opioid samples tested contained both fentanyl and xylazine [13]. Other studies confirm high levels of correlation between fentanyl and xylazine in the Philadelphia community [14]. Xylazine use was therefore assessed by clinical suspicion and patient report of non-medical opioid use.

2.3. Measurements

The authors created a codebook to evaluate and confirm accuracy and organize the data for patients. The variables recorded in the codebook included: patient demographic data, vital signs, medications ordered, and doses received, urine toxicology panels, pre- and post-treatment COWS scores, adverse events, and patient disposition data. Demographics, medication provision, COWS scores and disposition data were collected by an automated database report. Vital signs, urine toxicology results and adverse events were manually abstracted in the patient charts by the authors, where available. Adverse events were also tracked using the hospital event reporting system as well as the pharmacy event reporting system. Follow up was performed entirely by chart review. This study was evaluated and approved by the institutional review board with a waiver for informed consent, given the retrospective nature and de-identified dataset. A focused, methodological review was conducted utilizing Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines prior to data acquisition.

Interrater reliability for manually extracted data was addressed by having each author overlap charts with two other authors, with the lead author personally adjudicating discrepant or questionable data and calculating a kappa statistic.

2.4. Study development and protocol

The need to develop a novel withdrawal treatment protocol was driven by clinical experience showing existing treatment pathways (conventional buprenorphine and methadone induction) were insufficient to treat the symptomatology associated with withdrawal from fentanyl and xylazine. An internal group of experts (emergency and addiction medicine physicians) were convened, and a limited, modified Delphi analysis was undertaken to evaluate which medications, as well as what diagnostic testing and monitoring should be recommended for those individuals requiring treatment. After a literature review and expert survey, four specific order pathways were developed into a wider set of guidelines that reflected consensus on treatment and evaluation. The medications utilized included micro-induction buprenorphine, full mu-opioid agonists (oxycodone, hydromorphone) and adjunctive treatments. These adjunctive medications included ketamine, neuroleptics (droperidol, olanzapine), alpha-two-agonists (tizanidine, guanfacine), anticholinergics (diphenhydramine) and Ringer's lactate intravenous fluid solution.

Pathways were delineated by severity of withdrawal (mild vs. severe; COWS ≥12), availability or need for IV access, and known or concern for prolongation of the patient's electrocardiogram corrected QT interval (≥ 450 ms). The choice of 450 ms was made from an abundance of caution, given the use of multiple medications that have been associated with prolongation of the QT interval, in a patient population that are often at risk for this complication. Furthermore, given patients may or may not require IV access, the mild symptom pathways, which utilize oral medications only, were available regardless of severity.

The order set was built into the electronic health record (EPIC Systems, Madison, WI) to support the guidelines, automatically ordering screening diagnostic studies (including urine immunoassay toxicological screening) and monitoring (including ECGs to monitor potential cardiotoxicity and COWS testing). The four pathways are shown in Appendix A.

COWS scores were organized into categories denoting pre- and post-treatment COWS (1–4 h from first medication administration). Urine immunoassay toxicology screening included: amphetamines, benzodiazepines, opiates (non-fentanyl), barbiturates, cocaine, cannabinoids, methadone, and fentanyl. There was no toxicology screen available for xylazine during the study period at either hospital, and no patients received gas chromatography as part of their initial assessment.

2.5. Outcomes

Key outcome measures included pre- and post-exposure COWS scores, disposition data and any adverse events. Other recorded measures included patient demographics, order pathway utilized, which specific medications were given and urine toxicology screening. COWS scores were recorded numerically and were obtained by the database report based on the value most proximate to medication provision, for both pre- and post-exposure scores, with an hour offset for post-exposure scores to allow for impact of pharmacodynamic effects and within 4 h to prevent washout or the impact of subsequent treatment. Disposition data included whether patient remained in the hospital following evaluation (admission or observation), left the hospital (discharge or AMA) or transferred elsewhere (in this cohort, to a rehabilitation/recovery center).

Adverse events related to the use of medications from the order set were defined as follows. Events occurred within 12 h of receiving medications. Respiratory depression (RR < 10, need for supplemental O2, positive airway pressure support or intubation), opioid overdose (naloxone provided in the ED), cardiovascular events (SBP <90, HR <50 or >140, arrhythmia), allergic/dystonic reaction, seizure, or precipitated withdrawal (defined as increasing COWS score/symptom progression within 1 h of medication provision). Adverse events were either extracted directly from the chart or imported from the hospital reporting

systems. The hospitals utilize event reporting systems that derive reports from providers, nurses, and pharmacists. All reports were queried for the duration of the study and relevant results included in the analysis. Adverse effects were then evaluated using the Adverse Drug Reaction Probability Scale to determine likelihood of causal relationship [15].

2.6. Analysis

Statistical analysis was performed using R statistical software (R Core Team, 2023). Descriptive statistics were calculated utilizing demographic information documented in the codebook including interquartile ranges for non-parametric data. Statistical significance for non-parametric data was determined utilizing Wilcoxon rank sum.

From the total encounters included in the codebook, we identified those individuals that had both a pre- and post-treatment COWS documented. To further evaluate the four order sets, due to the smaller numbers who received each pathway, outcomes were described both by individual pathway as well as grouped into two subcategories: those individuals receiving order sets 1 or 2 were combined as a mild symptom cohort, while order sets 3 or 4 were combined into a severe symptom cohort. *t*-test was utilized to compare parametric data. A delta-COWS was calculated to determine the difference between pre- and post-treatment COWS score for each cohort and a linear regression model was developed to compare order set cohort to the measured delta-cows.

3. Results

3.1. Study cohort description

The study took place between September 14, 2022, and March 9, 2023. During the study period, there were a total of 37,101 encounters in the two ED, with a 24.3 % admission rate and a 1.1 % rate of AMA. There were 1284 patients during this time who screened positive for OUD in triage based on standardized questioning, with a 24.2 % admission rate and a 10.7 % rate of AMA disposition.

There were 270 encounters during the interval where patients received treatment from one of the order sets, with a median frequency of 34 (IQR 24.5–40.25) encounters per full month within the study period; this represents the total cohort evaluated in this study. The median age of the total cohort was 37 years old (IQR 33 to 46.75 years). 179 individuals were male (66.05 %, 95 % CI 60.03–71.6 %) with a median age of 38 years (IQR 33.5–49.0). The median age for females was 35 (IQR 32–39), (Table 1). There were 191 patients with a Philadelphia zip code (70.48 %, 95 % CI 64.60–75.77 %).

Urine toxicology screening was sent in 214 of the total encounters. 214 tests were positive for fentanyl (100 %), and many showed evidence of significant polysubstance use, with cocaine, amphetamines, and benzodiazepines as the most common concomitant drugs (Table 2).

Table 2
Urine toxicology screening results.

	Positive	%
Fentanyl	214	100
Cocaine	150	70.09
Amphetamines	74	34.58
Cannabinoid	72	33.64
Opiates	65	30.37
Benzodiazepines	57	26.64
Methadone	38	17.76
Barbiturates	5	2.34

Withdrawal severity was recorded variably. Of all 270 encounters in the total cohort, 197 (72.69 %, 95 % CI 66.91–77.82 %) had a pretreatment COWS score documented. Of all encounters, 185 (68.27 %, 95 % CI 62.31–73.69 %) of encounters had post-exposure COWS documented at 1–4 h post first medication administration. Overall, 177 (65 %, 95 %CI 59.28–70.91 %) encounters had a COWS score performed both before medications were given and within 4 h after. See Fig. 1 for details. The total cohort had a 69.6 % admission/observation rate and an AMA rate 4.4 %.

Of the 177 patients who met criteria for final analysis, 122 (68.93 %, 95 % CI 61.47–75.54) were male. The median age was 37 (IQR 33–47) with a slightly older male vs female population (38 [IQR 32–39] vs 34 [IQR 33.25–49.75], $p = 0.006$). Proportions of race and ethnicity were similar to the full cohort, 74.58 % White (95 % CI 67.39–80.68) and 84.75 % (95 % CI 78.40–89.54 %) being not Hispanic or Latino. 150 (84.75 %, 95 % CI 78.40–89.54 %) had urine toxicology screen performed, all were positive for fentanyl. 132 (74.58 %, 95 % CI 67.39–80.68 %) were from a Philadelphia zip code. In 60 (33.89 %, 95 % CI 27.07–41.44 %) encounters, patients received medications from the mild symptom pathways, while 117 patients (66.1 %, 95 % CI 58.56–72.93 %) received the severe symptom pathways (Fig. 1).

3.2. Main results

For the assessment of intra-rater reliability, 120 records were included. Intra-rater reliability was near perfect (Cohen's kappa = 0.99) with high agreement.

Medication ordering and patient acceptance of medications was variable. Frequency of medication inclusion per pathway is shown in Fig. 2. Most patients received all medications in the delivered pathway, with the outlier being buprenorphine, which was provided in around half of cases.

Overall, the median pretreatment COWS score was 12 (IQR = 8:18). The median post-treatment COWS score was 4 (IQR =2:7), which was both a statistically significant reduction ($p < 0.001$) and represents a reduction from moderate to mild on the COWS scale, see Figs. 3 and 4. There was also a statistically significant difference in median delta

Table 1
Demographic Data for study population.

Total Cohort with excluded patients				Final Study Cohort			
Sex		x	%	Sex		x	%
	Male	179	66.05		Male	122	68.93 %
	Female	91	33.70		Female	55	31.07
Race				Race			
	White	208	77.04		White	132	74.58
	Black	35	12.96		Black	27	15.25
	Other	23	8.52		Other	16	9.04
	Asian	2	0.74		Asian	0	
	American Indian or Alaskan Native	2	0.74		American Indian or Alaskan Native	2	1.13
Ethnicity				Ethnicity			
	Non-Hispanic/Latino	234	86.67		Non-Hispanic/Latino	150	84.75
	Hispanic/Latino	33	12.22		Hispanic/Latino	26	14.69
	N/A	3	1.11		N/A	1	00.56

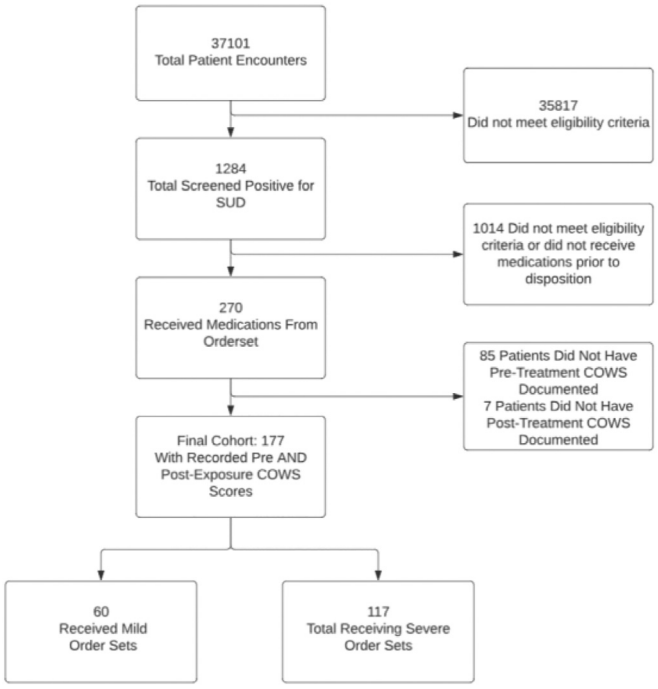

Fig. 1. Study Cohort.

COWs (the difference between pre- and post-treatment) when comparing mild symptom to severe symptom pathways (4 (IQR 1–6) vs. 9 (IQR 7:13), $p < 0.001$) (Fig. 5).

The regression model was statistically significant ($R^2 = 0.2267$, $p < 0.001$). The severe treatment pathways 3 and 4 were highly predictive of change in COWS ($\beta = 5.679$, $p < 0.001$, $\beta = 7.0998$, $P < 0.0001$).

Due to the variability of medications provided within the pathways, analysis was performed to evaluate the impact of individual medications on the pre- and post-exposure COWS scores (Fig. 6). There were no statistically significant differences in COWS scores based on receipt, or non-receipt, of any single medication, as compared to receiving all medications.

Of the 177 encounters, 108 (61.02 %, 95 % CI 53.39–68.16 %) resulted in admission, 24 (13.56 %, 95 % CI 9.05–19.70 %) were placed into observation, 35 (19.77 %, 95 % CI 14.33–26.56 %) were discharged, 4 (2.26 %, 95 % CI 0.7–6.06 %) went to a rehabilitation/recovery facility and 6 (3.9 %, 95 % CI 1.39–7.57 %) directed their own discharge (AMA).

3.3. Adverse events

Recorded adverse effects impacted eleven patients and all resolved without complication. These included two cases of overt dystonic reaction (dystonia in one, akathisia in a second), two cases of fluid responsive hypotension (both in patients with severe, acute illness), three case of asymptomatic bradycardia, one case of untreated, asymptomatic hypopnea, one case of mild hypoxia requiring 2 L of oxygen via nasal

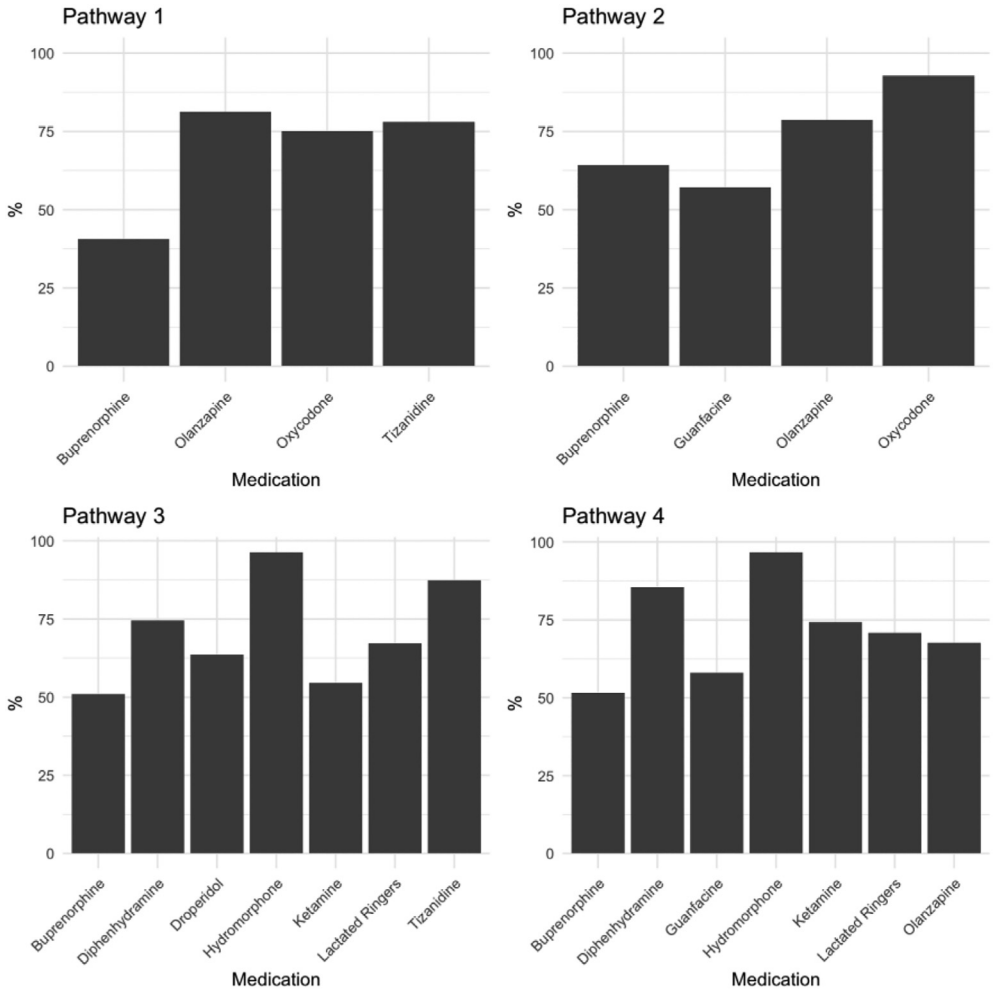

Fig. 2. Frequency of medications provided per treatment pathway.

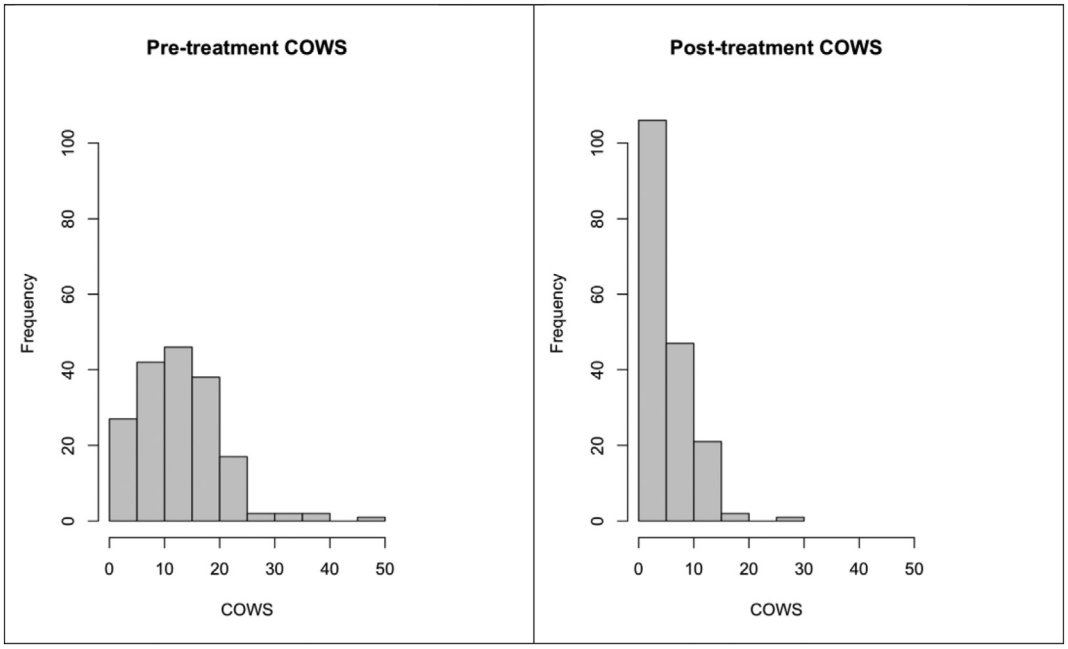

Fig. 3. Histogram of COWS pre and post treatment demonstrating reduction in score.

cannula, and one patient who required non-invasive positive pressure ventilation (PPV) 8 h after medication provision, in the setting of multifocal pneumonia. There was also one patient who suffered a single epileptic seizure, in the setting of concomitant benzodiazepine withdrawal. This seizure was treated with oral benzodiazepines and did not recur during their ED stay. There were no cases of ventricular dysrhythmias, intubation or need for reversal medications. There were also no recorded instances of precipitated withdrawal. All adverse effects were deemed, in their association to the treatment, as possible, or probable based on the Naranjo probability algorithm.

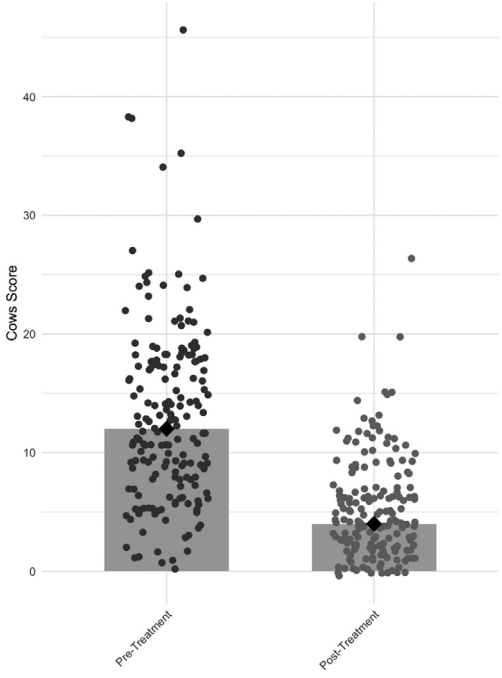

Fig. 4. Scatter plot of COWS pre and post treatment demonstrating reduction in median score.

4. Discussion

Overall, this study characterized a cohort of patients with OUD that received medications from a novel withdrawal guideline and order set. The patients were grouped into four pathways based on severity of withdrawal symptoms and QTc interval on EKG. We report a reduced COWS score in those patients who received medications. Fewer patients who received these medications directed their own discharge (AMA disposition) than the baseline for patients with OUD. There were few adverse events associated with the use of the order set.

This study represents the one of the first emergency department cohort studies of patients treated explicitly for opioid withdrawal in the era of 'tranq dope.' Xylazine withdrawal is a poorly understood and controversial condition, given that its use in humans has been so limited and so conjoined to synthetic opioids. Complicating treatment further, conventional toxicology screens do not include xylazine, limiting provider awareness to this condition. Severe cases have been described, and patients frequently demonstrate psychomotor agitation and anxiety, common in sedative withdrawal syndromes [16-18]. As there are no standardized tools or unique features to assist diagnosis or measure treatment response, it was felt utilization of the COWS (which contains heart rate, restlessness and anxiety as items) would reasonably guide treatment. Evaluation of xylazine withdrawal syndromes is a priority of the substance use research community [19].

Our patient cohort showed a high proportion of polysubstance toxicology screens, particularly with co-occurring fentanyl, cocaine, and amphetamine use. While this was not directly addressed during the development of the pathways, cocaine and amphetamine withdrawal produce agitation, irritability, and other vasomotor symptoms not dissimilar to those facing opioid and sedative withdrawal. Potential treatment strategies include alpha-two agonist therapy as well as GABAergic medications [20,21], and it is possible these treatment pathways could benefit those who use both opioids and sympathomimetics. Future studies should evaluate the cohort who explicitly use multiple substances to determine optimal treatment for this subset, as well as the potential impact of adding additional GABAergic medications to the current pathways.

The demographics of patients, largely young to middle aged white males, is similar to national and local data [22,23]. The large majority

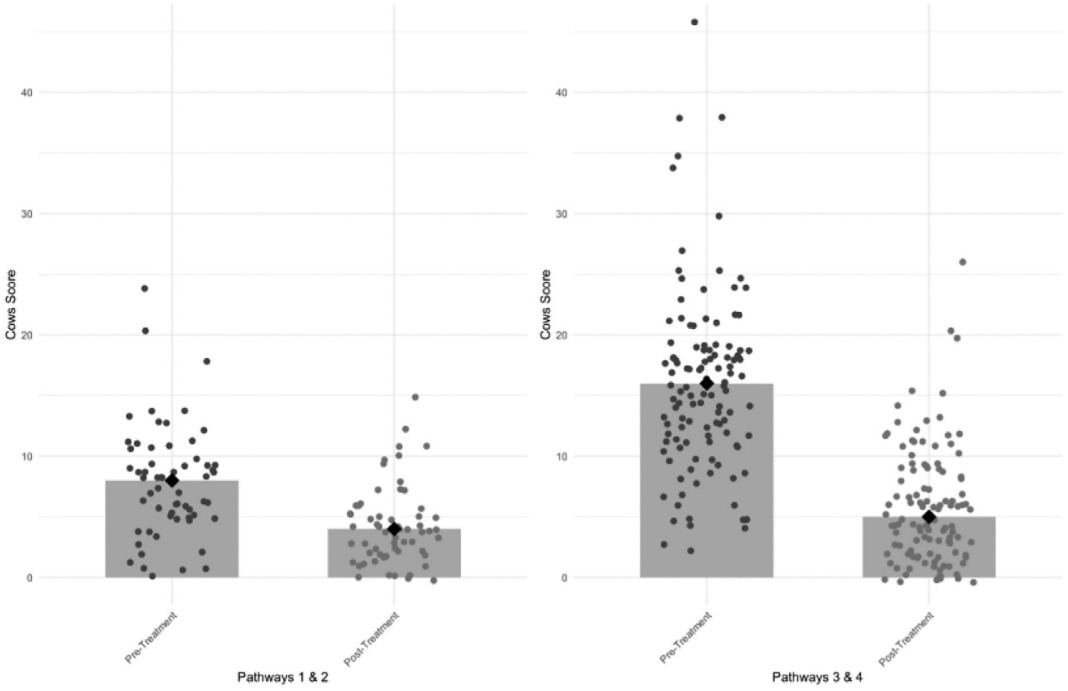

Fig. 5. Scatter plot of COWS pre- and post-treatment, separated by mild vs. severe symptom cohort, demonstrating reduction in median score.

had a Philadelphia zip code, the others often come from adjoining cities and states due to the ubiquity and availability of non-medical opioids in Philadelphia. All patients who received urine toxicology screening were positive for fentanyl. This speaks to the high accuracy of screening, patient history and provider gestalt in this cohort.

To date, the published data on fentanyl and xylazine withdrawal treatment are largely case reports and expert guidance [24-27]. Conventional buprenorphine strategies, the bedrock of ED management for the previous decade [28-30], have become beset by reports of unexpected precipitated withdrawal [31-34]. Questions as to the cause and impact of this phenomenon remain, but the stigma and distrust of buprenorphine in our community is significant [33]. A recent study demonstrated a low rate of precipitated withdrawal in a cohort of patients treated with conventional buprenorphine with fentanyl use disorder [35], but dramatic examples and patient reticence remain barriers. In this study, micro induction of buprenorphine, combined with a host of mu agonists and other adjunctive medications led to zero cases of precipitated withdrawal.

Conventional rapid methadone induction strategies became ineffectual when provided as monotherapy – owing to the vast doses of opioids being consumed and the need for careful up-titration of methadone for safety reasons [36]. This led to the choice of short acting opioids, whose titration and use are a common for emergency physicians, as a bedrock of these pathways. In this study, a short acting mu agonist, in combination with adjuncts, was associated in a lowering of COWS scores in this cohort. Future studies should examine how these treatments interact with methadone, for patients who are not currently interested in buprenorphine therapy.

Adjunctive treatments were deemed necessary given the large doses reported by patients, intentionally utilizing the concepts of synergism and potentiation to mitigate the smaller doses of short acting opioids, as well as to treat potential co-ingestions, such as xylazine. Ketamine, a widely used anesthetic drug, works by function of NMDA receptor antagonism, but also has effects on opioid receptors, monoaminergic receptors, muscarinic receptors, and others. It has long been shown, mostly in operative literature, to be an effective adjunct to opioids, both improving analgesia and reducing opioid induced hyperalgesia [37]. More recently, its use in the emergency department as an analgesic has increased drastically, to treat both acute and chronic pain [38]. Furthermore, ketamine has been shown to be increasingly useful as a tool to treat a host of substance use disorders and their associated sequelae [39].

Given the incidence of anxiety and agitation as primary symptoms of xylazine withdrawal, dopamine antagonist neuroleptic medications were included in the pathways. Consideration of benzodiazepines or other anxiolytics were deferred due to their own risk for tolerance, dependence and the risk of respiratory depression when provided with opioids. Droperidol, a widely used butyrophenone neuroleptic, is an effective analgesic for those with opioid tolerance and can act to decrease opioid requirements in those with acute pain stimuli [40]. Additionally, it is well known for its anxiolytic [41] and antiemetic effects [42]. Droperidol is labelled with an FDA black box warning for risk of QT prolongation and ventricular dysrhythmia, though the actual risk in this population is unknown, and other ED studies have shown a reasonable safety profile [43].

Given the unclear risk of droperidol induced prolongation of the QT interval in this patient population, olanzapine, a modern atypical antipsychotic, was chosen for the pathways where QT prolongation was a concern. Olanzapine has shown efficacy in treating opioid withdrawal and can potentially have its own opioid potentiating effects [44,45].

Given the alpha-two receptor agonism of xylazine, alpha agonist therapies were added to the pathways. The most commonly studied alpha-two agonists for opioid withdrawal have classically been clonidine and lofexidine [46]. The former was deferred due to the risk of prolonged hypotension when given with multiple other medications, and the latter due to cost. In their place, two other alpha agonists were utilized: tizanidine and guanfacine. The former is marketed as a muscle relaxant, an additional benefit given the myalgias many patients suffer, and has been demonstrated to be efficacious in opioid withdrawal [47]. Guanfacine is used to treat attention deficit hyperactivity disorder and benefits from a low risk of QT prolongation. It has also been studied as a potential treatment for opioid withdrawal [48].

Diphenhydramine is an effective antihistamine and anticholinergic medication that can treat the pruritus and the cholinergic symptoms of opioid withdrawal [49]. Ringer's lactate intravenous fluid solution was added due to the common risk of hypovolemia and electrolyte

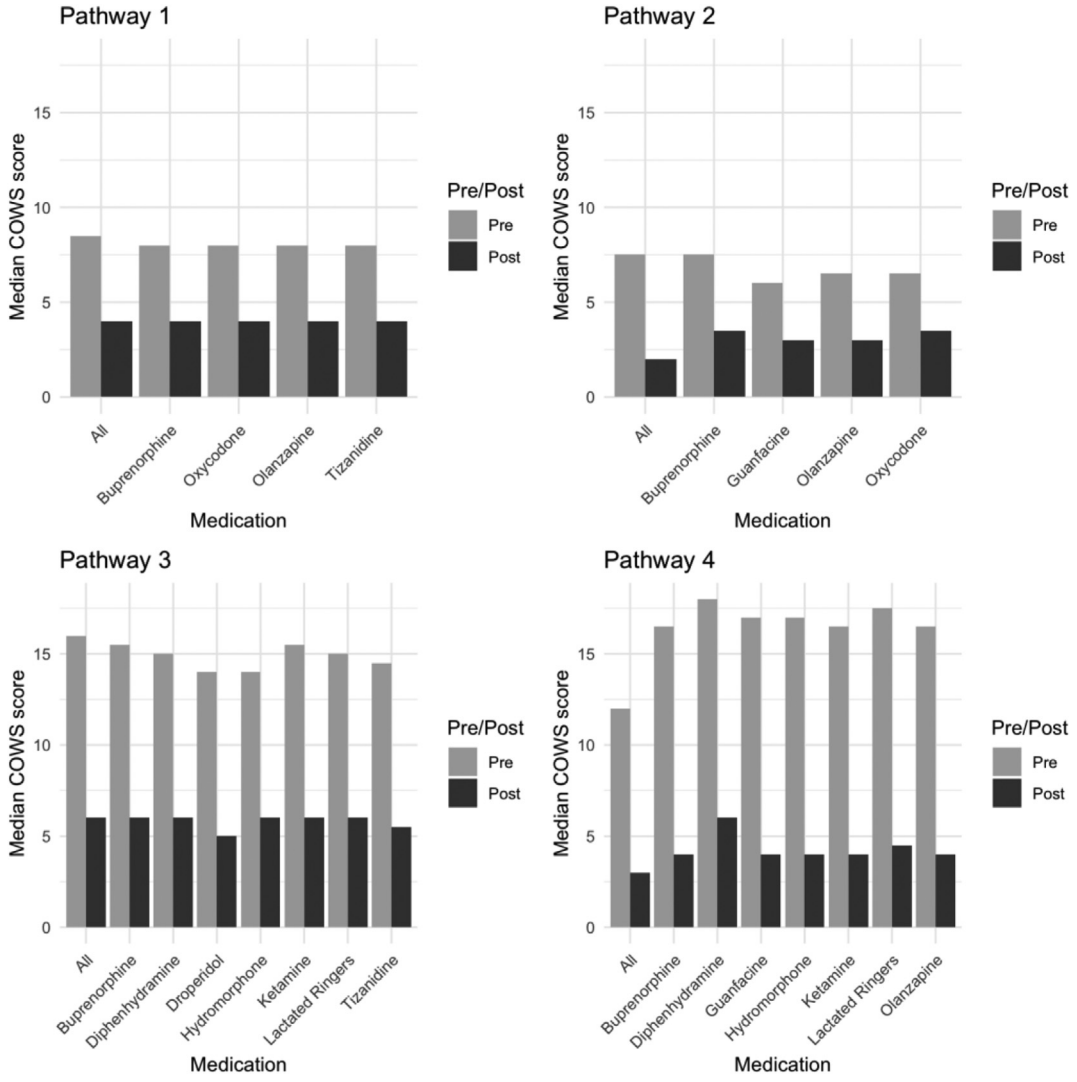

Fig. 6. Median pre and post treatment COWS scores delineated by all vs. individual medications received in each pathway.

derangement in patients suffering from severe withdrawal, both to prevent treatment related hypotension and mitigate risk of electrolyte mediated prolongation of the QT interval. In combination, these adjunctive interventions demonstrated significant impact.

This group of patients had on average a moderate withdrawal syndrome (COWS = 12), however a large IQR demonstrates the variety of withdrawal severities treated. It should be noted that many patients in the emergency department have not abstained long enough to be in overt withdrawal and may clinically worsen with or without intervention.

Most patients in the cohort received a severe treatment pathway. The treatment groups were notably different in terms of response, with a statistically significant delta COWS of 10.03 between the high dose group and 3.67 in the low dose group. Given a similar safety profile, it may be reasonable to utilize severe pathway medications when the likelihood of worsening withdrawal is high.

The main concern with using multiple adjunctive medications to synergize and potentiate opioid effects are the risks of oversedation and other adverse effects related to pre-existing patient polysubstance use. In this cohort, with an exceptionally large population of polysubstance users, there were surprisingly few adverse effects and only two adverse effects adjudicated as severe (seizure and need for PPV). In both of those cases, by Naranjo criteria, neither were adjudicated as higher than possibly associated. With no significant difference in the few adverse reactions between the groups, it indicates that withdrawal symptoms may be safely and appropriately managed using a combination of pharmacologic interventions.

In this cohort, over 70 % of patients with toxicology screening were positive for both fentanyl and cocaine, more than a third positive for amphetamines, and more than a quarter had benzodiazepine exposure as well. This speaks to a profound level of multi-substance use in this group. More than one in six patients also tested positive for methadone, speaking to the complex milieu of vulnerable substance use and recovery. Further studies should assess how concomitant sympathomimetic, and benzodiazepine use disorders impact treatment as well as the safety of these pathways in those already on MOUD.

While not a primary focus of this study, there were no occurrences of ventricular dysrhythmias in this cohort. Future studies should evaluate the impacts on the QT interval with these treatments, given the similar COWS outcomes between normal and prolonged QT pathway cohorts.

Only 21 % of patients who screened positive for OUD at triage received medication for withdrawal in this cohort. While some may not have been suffering overt withdrawal in the ED due to prehospital use or prompt disposition, it is likely many patients suffering from withdrawal went untreated or undertreated. Nearly half of patients received fewer than every medication in the pathway chosen, with the majority being refusing buprenorphine. Future research should evaluate

mechanisms of improving uptake and utilization of withdrawal treatment protocols.

Patients with OUD suffer from myriad serious illnesses as sequelae and collateral to their use, as demonstrated in this study. In the two centers involved in this study, the patients included in the total cohort were admitted or observed at a rate three times higher than the general population (74.6 % vs 24.3 %). Management of withdrawal in patients with opioid dependence can be critical to proper medical care. With most patients receiving the severe dosing pathway and most patients being admitted to the hospital, this represents a higher acuity cohort than both the general census of the emergency departments, or the subgroup with opioid use disorder. Additional research should evaluate withdrawal management in a larger ambulatory cohort to assure safety and appropriate use.

Remedying withdrawal allowed for a healing environment for patients, reducing the risk of patient-directed discharge (AMA disposition). The AMA rate in patients receiving medications, as compared to the entire cohort who visited the ED while screening positive for OUD was less than half (3.9 % vs 10.7 %). The rate of AMA, however, was still higher in the study cohort than the general census of the ED (1.1 % vs. 3.9 %) and further studies should investigate other interventions to reduce risk of this outcome in patients with substance use disorders.

Secondary benefits to withdrawal management could include providing a calmer and less emotionally charged care experience and increasing acceptance of necessary aspects of care. Future research should assess attitudes of patients, providers, and nurses on the use of these treatment pathways. Reduction in patient and staff stigma as it relates to OUD should be a primary aspect of overall treatment planning and research foci.

Given that patients may display similar COWS scores despite significantly different usage patterns, additional research should be performed to evaluate if a dose-conversion strategy (IE: medications and doses based on patient quantification of drug intake) is more optimal than one based on solely on withdrawal severity. Additional opportunities include investigating the treatment of severe withdrawal in individuals who do not have access to an IV or who require treatment before an IV is placed. Long term recovery outcomes and short-term medical outcomes should also be investigated.

Lastly, there appears to be no end to the number of contaminants to the non-medical opioid supply. Recently, an increase in even more powerful opioids than fentanyl, nitazene analogs, has been found infiltrating our communities [50]. Other non-medical sedatives have also been found in increasing numbers, including other veterinary alpha agonists, such as medetomidine and novel benzodiazepines, such as bromazolam [51,52]. The impacts of these constituents on withdrawal syndromes and treatment is also an important topic of future research and are currently unknown.

5. Limitations

There are numerous limitations to this study. First, it is based on retrospective chart data, limiting data standardization and causal association. This means many in the total cohort (35 %) did not receive pre- and post-exposure COWS assessment, limiting the size of the final cohort. Furthermore, the timing of the COWS assessments was not standardized, due to the difficulty of obtaining data in a chaotic ED setting and the limitations of a retrospective study.

Additionally, not every patient received every medication in the pathways. It is notable, however, that the reductions in COWS scores were equal or greater in individuals who received all medications as opposed to the a la carte ordering. Future prospective research should assess the findings of this study in a standardized, consistent fashion.

Furthermore, patients were treated with the same medications and doses despite sometimes vastly different usage patterns and co-ingestions. Notably, alcohol levels were not obtained in this cohort. Given the large population that was benzodiazepine toxicology positive, and a single patient who suffered an epileptic seizure during treatment, it would be beneficial for future studies to evaluate co-occurring alcohol/sedative use disorders and their impact on the treatment outcomes. Impact of co-existing stimulant use disorders on patient outcomes should also be studied.

Despite these pathways being designed to treat xylazine withdrawal, no direct xylazine toxicologic data exists for this cohort. A separate, unpublished internal analysis of seven patients receiving gas chromatography mass spectroscopy testing after a positive urine fentanyl screen demonstrated all positive for xylazine. Future investigations should attempt to perform comprehensive toxicology screening, including for xylazine. Regardless, given our experience, as well as the accumulating evidence [13,14] of the ubiquity of xylazine in the non-medical opioid supply, it may be reasonable to infer that in Philadelphia, until xylazine screening assays are made routinely available, fentanyl screening can be considered equivalent to xylazine testing in the cohort of patients who use non-medical opioids.

Lastly, some data were manually abstracted where not available in the database report. It is possible human error resulted in inaccurate results, but the kappa statistic demonstrates that the overlapping assessments were highly consistent. Patients were only followed during their ED visit. It is possible additional adverse effects and higher rates of patient-directed discharge (AMA) would be seen if patients were followed post ED disposition.

6. Conclusion

A novel set of withdrawal treatment pathways in an electronic health record can be used in the treatment of fentanyl withdrawal with presumed xylazine exposure and may reduce COWS scores and the rate of patient-directed discharge (AMA). Adverse events were few, mild and self-resolving or complicated by severe acute medical pathology or concomitant polysubstance withdrawal.

Presentations

Poster presentation at SAEM 2024.

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CRediT authorship contribution statement

Kory London: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yutong Li:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Jennifer L. Kahoud:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis. **Davis Cho:** Writing – review & editing, Formal analysis, Data curation. **Jamus Mulholland:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Sebastian Roque:** Investigation. **Logan Stugart:** Investigation. **Jeffrey Gillingham:** Supervision, Software, Resources, Project administration, Data curation, Conceptualization. **Elias Borne:** Investigation, Formal analysis, Conceptualization. **Benjamin Slovis:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology.

Declaration of competing interest

KL has no conflicts to report.
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Appendix A. Four Withdrawal Order Set Pathways

Pathway 1: Mild (or no IV) AND Normal QTc
- Buprenorphine 150 mcg Buccal
- Oxycodone 10 mg PO Liquid
- Olanzapine 5mg PO ODT
- Tizanidine 4 mg PO

Pathway 2: Mild (or no IV) AND Prolonged/Unknown QTc
- Buprenorphine 150mcg Buccal
- Oxycodone 10 mg PO Liquid
- Olanzapine 5mg PO ODT
- Guanfacine 2 mg PO

Pathway 3: Severe AND Normal QTc
- Buprenorphine 150 mcg Buccal
- Hydromorphone 2 mg IVP
- Ketamine 0.15 mg/kg up to 15 mg (rounded to nearest 5mg) via IVP over 2 minutes
- Droperidol 2.5 mg IVP
- Diphenhydramine 25 mg IVP
- Tizanidine 4 mg PO
- Lactated Ringers 1L Bolus

Pathway 4: Severe AND Prolonged/Unknown QTc
- Buprenorphine 150 mcg Buccal
- Hydromorphone 2 mg IVP
- Ketamine 0.15 mg/kg up to 15 mg (rounded to nearest 5mg) via IVP over 2 minutes
- Olanzapine 10 mg PO ODT
- Diphenhydramine 25 mg IVP
- Guanfacine 4 mg PO
- Lactated Ringers 1L Bolus

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