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Modeling Naloxone Response in Simulated Opioid-Xylazine Overdose Scenarios: A Public Health Simulation Study

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ABSTRACT

In the United States, the overdose crisis has become a critical issue involving polysubstance combinations, especially with fentanyl mixed with xylazine, a non-opioid veterinary sedative not directly reversed by naloxone. This study addressed how xylazine involvement may affect simulated naloxone response in opioid-xylazine overdose scenarios. Using publicly available CDC/NCHS provisional drug overdose death counts from January 2019 to December 2024, national trends in overdose deaths involved with xylazine, fentanyl, and heroin were analyzed. Monthly changes in overdose deaths were estimated using a simple linear trend model, while theoretical recovery probability was estimated under different naloxone timing and xylazine-involvement conditions through an illustrative simulation model. There was an increase in xylazine-involved overdose deaths from 123 deaths in January 2019 to 6,079 deaths in December 2024. There was also an increase in fentanyl-involved deaths from 30,367 to 47,155 in the same time period. However, there was a decrease in heroin-involved deaths from 15,475 to 2,809 in the same study period. A strong upward trend was reported for xylazine deaths in the regression results, with an estimated increase of 104.6 deaths per month and $R^2 = 0.981$. In the simulation, modeled opioid-only recovery probability increased to 1.00 with immediate naloxone administration. However, immediate-response recovery probability decreased to 0.80 with full xylazine involvement. In the same condition, delayed response recovery probability decreased to 0.56. These simulated findings suggest that naloxone remains important for suspected opioid overdose response. However, xylazine involvement may reduce theoretical recovery probability under the assumptions of the model.

Keywords: Xylazine; naloxone; opioid overdose; fentanyl; public health simulation; overdose mortality

INTRODUCTION

In the United States, the overdose crisis has shifted from a main opioid-related emergency to a more complex polysubstance crisis that involved fentanyl, xylazine, stimulants, and other emerging substances. For instance, synthetic opioids, especially illicitly manufactured fentanyl, has become a primary driver of overdose mortality. However, according to recent public-health reports, xylazine has become an increasingly significant factor that complicated overdose events (Center for Disease Control and Prevention, 2024). Known as “tranq,” xylazine is a veterinary sedative that is not approved for human use. Particularly, it is known to cause central nervous system depression, slowed breathing, reduced heart rate, and low blood pressure (National Institute on Drug Abuse, 2024). Xylazine is especially dangerous when it appears with fentanyl due to the nature of fentanyl in increasing opioid-related respiratory depression, along with non-opioid sedation possibly added by xylazine that may not directly respond to standard opioid reversal medication (Food and Drug Administration, 2022).

Naloxone is known to be a life-saving medication for opioid overdose due to its nature of reversing opioid receptor activity, while restoring breathing when administered quickly (Giglio, 2015). Therefore, community naloxone distribution, bystander training, and emergency medical response have become primary parts of overdose prevention policy (Keane, 2018). However, a difficult public-health problem has been created by the emergence of xylazine: the opioid component of a fentanyl-involved overdose may be reversed by naloxone, but xylazine is not directly reversed since xylazine is not an opioid (Drug Enforcement Administration, 2023). This does not mean that naloxone should be withheld. Public-health agencies should still recommend giving naloxone whenever opioid overdose is suspected due to a possibility of presence of fentanyl or other opioids (Centers for Disease Control and Prevention, 2024). Instead, the problem is that overdose recovery may depend on time delay, polysubstance involvement, and how much xylazine contributes to respiratory or sedative effects as well as on naloxone availability.

Prior literature has documented the growing presence of xylazine in overdose deaths and drug supplies. Increasing xylazine detection has been reported in heroin and/or fentanyl-involved deaths in Philadelphia (Johnson, 2021). In addition, xylazine’s geographic spread across the United States has been described along with its relation to the synthetic-drug overdose crisis (Friedman, 2022). Furthermore, xylazine-related deaths in Cook County, Illinois, have been reported to be associated with fentanyl or fentanyl analogs (Chhabra, 2022), and xylazine-positive overdose deaths in Connecticut increased from 2019 to 2020 (Thangada, 2021). Rapid growth in xylazine-involved overdose mortality has been reported by more recent national analyses. Particularly, xylazine-involved overdose deaths were reported to have increased sharply from 2018 to 2021, with overwhelmingly fentanyl co-involved cases (Cano, 2024). Similarly, xylazine has been increasingly detected in illicitly manufactured fentanyl-involved overdose deaths across jurisdictions in the United States (Kariisa, 2023).

Despite this growing literature, there is an important gap. Many prior studies focused on xylazine trends, overdose deaths, or toxicology patterns, while naloxone studies often examined an opioid overdose response without quantitatively modeling how xylazine involvement may change expected recovery outcomes (Abdelal, 2022). The need for practical harm-reduction tools and better understanding of xylazine exposure has been emphasized among people who use drugs (Reed, 2022). However, there are only a few studies conducted to combine public overdose trend data with a transparent quantitative framework for the simulation of naloxone response under different xylazine-involvement scenarios. This gap is important as possible outcome patterns may be estimated by simulation modeling without using patient-level data.

In this study, CDC/NCHS provisional drug overdose death data are used along with a simplified simulation quantitative model to identify naloxone response in opioid-xylazine overdose scenarios. This study particularly seeks to answer the research question about how increasing xylazine involvement affects simulated overdose recovery probability when administering naloxone in different time delays. This study hypothesizes that naloxone administration will improve probability of simulated recovery in opioid-involved scenarios, but modeled recovery will be reduced by higher xylazine involvement and longer administration delays as naloxone does not directly reverse xylazine-related sedation. This study does not claim to measure real clinical efficacy of naloxone. Instead, it provides a public-health simulation in connection of national overdose trends with modeled emergency-response outcomes (Substance Abuse and Mental Health Services Administration, 2023).

METHODS AND MATERIALS

In this study, a quantitative, simulation-based design was used to examine how xylazine involvement may affect modeled naloxone response in opioid-xylazine overdose scenarios. Since only publicly available aggregate data and simulated outcomes were used in this study, no human participant, patient personal records, surveys, or identifiable information were used.

CDC/NCHS Provisional Drug Overdose Death Counts for Specific Drugs dataset was the main dataset used in this study. In the uploaded CSV file, monthly 12-month-ending overdose death counts from January 2019 to December 2024 were contained. The main variables included death_year, death_month, jurisdiction_occurrence, drug_involved, month_ending_date, and drug_overdose_deaths. Xylazine, fentanyl, and heroin were the drugs of interest. Fentanyl was used as the main opioid comparison group, and xylazine was used as the non-opioid sedative exposure of interest. Heroin was included as a historical opioid comparison group since it represents an earlier major driver of overdose crisis in the U.S. This allowed the study to contrast declining heroin-involved deaths with increasing fentanyl- and xylazine-involved deaths. In the dataset, national values for the United States as well as values by U.S. region were included, making it feasible to compare both national and regional trends.

Data cleaning process was conducted by first filtering for rows with drug_involved being equal to xylazine, fentanyl, or heroin. Death counts were converted to numeric values if necessary, and chronological order was applied to month-ending dates. For national trend analysis, only rows that had jurisdiction_occurrence equal to the United States were used. For regional trend analysis, rows with individual regions in the United States were retained and compared by final-year death counts and percentage change over time. For each drug category including beginning count, ending count, absolute change, and percentage change from 2019 to 2024, descriptive statistics were calculated.

To estimate whether overdose death counts increased or decreased over time, a simple linear trend model was used. Beginning month was January 2019, and month number was coded as t = 1, 2, and 3, going forward. The following model was used for each drug category:

$$D_t = \beta_0 + \beta_1 t + \varepsilon_t$$

In this model, D_t shows the 12-month-ending overdose death count in month t. β_0 is the estimated starting death count. β_1 is the average monthly change in deaths, and ε_t represents unexpected variation. A positive value of β_1 indicates an increase of deaths over time, while a negative value of β_1 indicates a decrease of deaths over time.

A simple simulation model was developed to connect the overdose trend analysis to the naloxone-response. Recovery probability under different overdose scenarios was estimated by the simulation using three different scenarios. The first scenario was when naloxone improved recovery if opioids were involved. The second scenario was that longer response delays reduced recovery. The third scenario was that xylazine involvement reduced recovery as naloxone did not directly reverse xylazine. The modeled recovery probability was developed as follows:

$$R = 0.90 - 0.08T - 0.20X + 0.10N$$

Where R represents simulated recovery probability, T represents naloxone delay level from 0 to 3, X shows xylazine involvement level from 0 to 1, and N represents naloxone administration coded binary with 1 if naloxone was given and 0 if it was not.

The coefficients in this simulation equation were not derived from patient-level clinical trials or real overdose-response records. Instead, they were selected illustrative public-health modeling assumptions to compare relative recovery patterns across different overdose-response scenarios. The baseline recovery term was set high to show an opioid-involved overdose scenario that recovery was possible with rapid response. In addition, due to the nature of naloxone reversing the opioid component of overdose, the naloxone coefficient was positive. The time-delay coefficient was negative since the probability of recovery was expected to be reduced by delayed overdose response. The xylazine coefficient was also negative due to the nature of xylazine as a non-opioid sedative without being directly reversed by naloxone. Therefore, the model should be interpreted not as a clinically validated prediction model but as a transparent scenario-based simulation.

This model was not developed to predict real patient outcomes or clinical naloxone efficacy but to compare relative changes across simulated overdose-response scenarios under clearly states assumptions. Sensitivity analysis was performed to test whether the main pattern remained stable under different assumptions by changing the xylazine penalty and time-delay penalty. In the base model, a xylazine penalty of 0.20 and a time-delay penalty of 0.08 per delay level were used. Alternative models tested lower and higher xylazine penalties of 0.15 and 0.25, as well as lower and higher time-delay penalties of 0.006 and 0.10.

RESULTS

A strong national increase in xylazine-involved overdose deaths between 2019 and 2024 was reported by the CDC/NCHS provisional overdose dataset. In the United States, the xylazine-involved overdose death counts were 123 in the 12-month period ending January 2019 that increased to 6,079 deaths in the 12-month period ending December 2024. This showed an absolute increase of 5,956 deaths, along with a percent increase of around 4,842.3% over the period of the study. This result indicates that xylazine changed from a rare contributor to mortality from overdose in 2019 into an emerging drug involved in overdose deaths by 2024.

Throughout the study period, deaths from fentanyl-involved overdose were reported to be much higher than the ones by xylazine. Death counts from fentanyl-involved overdose were reported to increase from 30,367 in January 2019 to 47,155 in December 2024. This was equivalent to an increase of 16,788 deaths, or around 55.3%. On the other hand, there was a decrease reported with death counts from heroin-involved overdose from 15,475 in January 2019 to 2,809 in December 2024. This represents a decrease of 12,666 deaths, or approximately 81.8%. These opposite trends suggest that there was a shift in overdose crisis away from heroin and toward synthetic and polysubstance patterns involving fentanyl and xylazine (Figure 1).

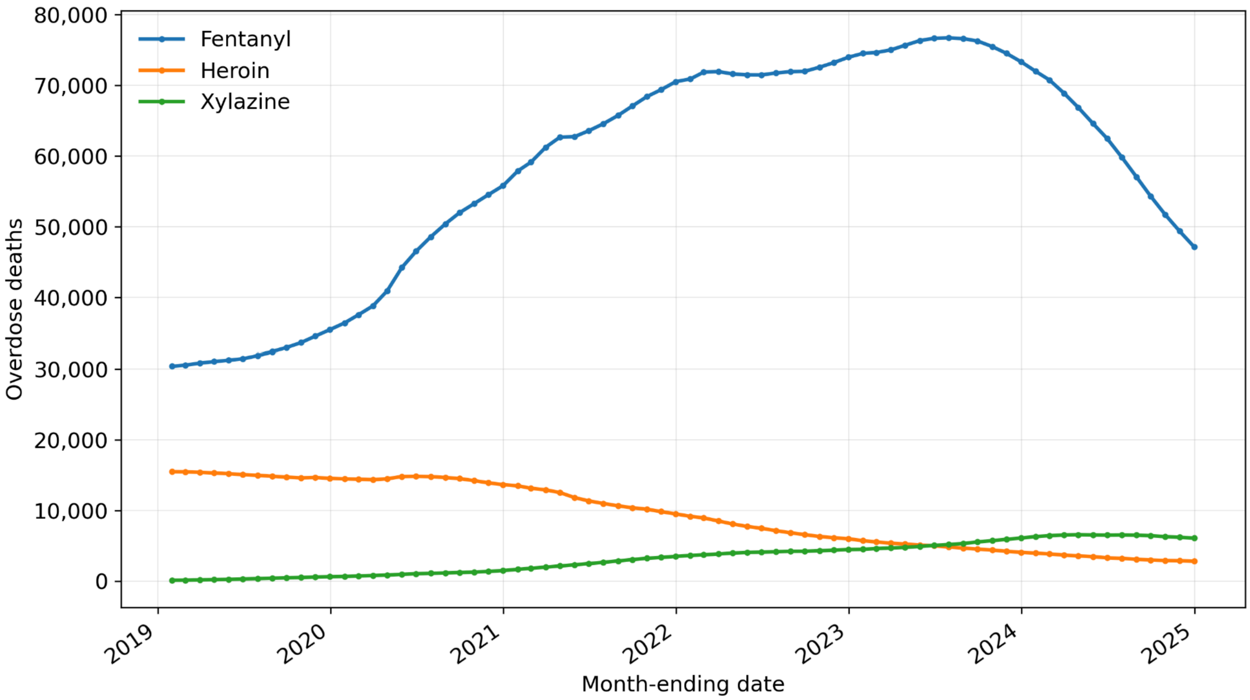

Figure 1. National 12-month-ending overdose death counts by drug, 2019-2024. Fentanyl-involved deaths remained the highest overall. However, there was a sharp increase of xylazine-involved deaths from a low baseline, while heroin-involved deaths steadily declined. This pattern indicates a shift from traditional heroin-related overdose mortality toward synthetic and polysubstance overdose patterns.

These patterns were also supported by the simple linear trend model. For xylazine, an average increase of approximately 104.6 xylazine-involved overdose deaths per month was estimated by the regression model over the 72-month study period. The model fit was reported to be very strong, and an estimated R^2 was 0.981. This means that around 98.1% of the variation in national xylazine-involved overdose deaths was explained by month number. For fentanyl, an average increase of approximately 550.9 deaths per month was reported. However, the model fit was weaker than the one for xylazine, with $R^2 = 0.534$. This suggests that fentanyl death counts increased overall but with more fluctuation over time than xylazine. For heroin, an average decrease of approximately 215.8 deaths per month was reported, along with negative estimated trend and a strong model fit of $R^2 = 0.962$ (Table 1).

Drug Involved	Jan, 2019 Deaths	Dec. 2024 Deaths	Absolute Change	Percentage Change	Monthly Trend Slope	R^2
Xylazine	123	6,079	5,956	4,842.3%	104.6	0.981
Fentanyl	30,367	47,155	16,788	55.3%	550.9	0.534
Heroin	15,475	2,809	-12,666	-81.8%	-215.8	0.962

Table 1. National overdose death trend summary from January 2019 to December 2024. The table compares beginning count, absolute change, percentage change, monthly trend slope, and R^2 for xylazine, fentanyl, and heroin.

Regional analysis reported that an uneven distribution of xylazine-involved overdose deaths was shown across the United States. The highest regional xylazine death count was observed in Region 3, with 1,481 deaths in December 2024, followed by Region 4 with 1,355 deaths, Region 5 with 969 deaths, Region 2 with 856 deaths, and Region 1 with 850 deaths. In Region 7, lower counts were observed as 229 deaths, followed by Region 9 with 179 deaths, Region 6 with 91 deaths, Region 10 with 45 deaths, and Region 8 with 24 deaths. These findings suggest that xylazine involvement was concentrated the most in eastern and Midwestern regions in the U.S. Several western and central regions had much lower xylazine-involved deaths by the end of the study period (Figure 2).

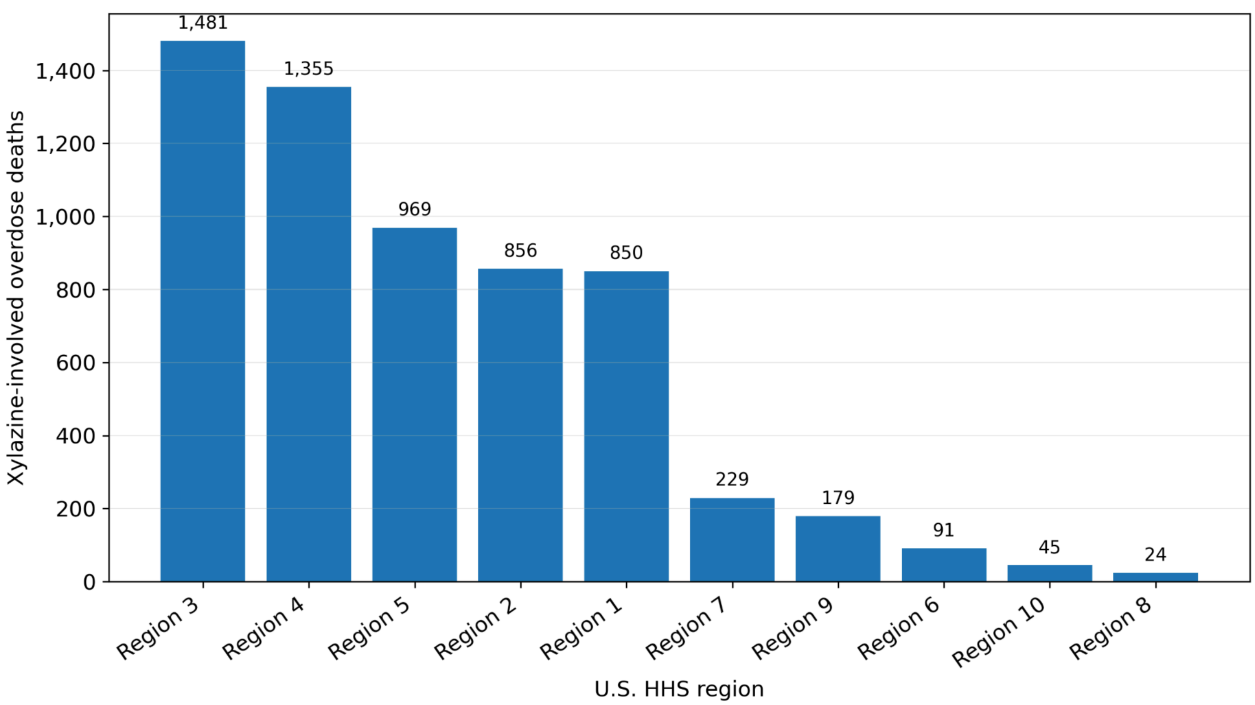

Figure 2. Regional xylazine-involved overdose death counts in December 2024. Region 3 showed the highest xylazine-involved death count, followed by Region 4 and 5. This suggests that xylazine involvement was concentrated more heavily in eastern and Midwestern regions than in several western and central regions.

There was a decrease in recovery probability as response delay and xylazine involvement increased as shown from the naloxone-response simulation. In the baseline opioid-only scenario without any delay or naloxone, the modeled recovery probability was estimated to be 0.90. When immediately administering naloxone in the same opioid-only scenario, there was an increase in recovery probability to the maximum value of 1.00. However, when xylazine involvement was added in full, a modeled recovery probability of 0.80 was produced by the immediate naloxone administration. This means that, under the assumptions of the simulation model, recovery probability decreased with xylazine involvement even when naloxone was administered.

The effect of delay was also clear. When there was xylazine involvement in full without naloxone delay, simulated recovery probability was estimated to be 0.80 when naloxone was administered. At delay level 1, it decreased to 0.72. At delay level 2, it decreased to 0.64. At delay level 3, it decreased to 0.56. Therefore, the lowest recovery probabilities occurred when there was high xylazine involvement, along with delayed naloxone administration across the simulated conditions.

Sensitivity analysis showed that the main simulation pattern remained stable under alternative parameter assumptions. In the base model, a modeled recovery probability of 0.80 was produced by immediate naloxone with full xylazine involvement. A modeled recovery probability of 0.56 was produced by delayed naloxone at delay level 3. When the xylazine penalty was reduced to 0.15, these values changed to 0.85 and 0.61. When the xylazine penalty was increased to 0.25, they changed to 0.75 and 0.51. When the time-delay penalty was reduced to 0.06, the delayed recovery probability increased to 0.62. When the time-delay penalty was increased to 0.10, it decreased to 0.50. Across all assumptions, higher xylazine involvement and longer delay consistently reduced simulated recovery probability (Table 2).

Sensitivity Condition	Immediate Naloxone + Full Xylazine	Delay Level 3 + Full Xylazine
Base model	0.80	0.56
Lower xylazine penalty	0.85	0.61
Higher xylazine penalty	0.75	0.51
Lower delay penalty	0.80	0.62
Higher delay penalty	0.80	0.50

Table 2. Sensitivity analysis of simulated recovery probability. The main pattern remained stable across alternative assumptions. Modeled recovery probability was reduced by higher xylazine involvement and longer response delay.

Overall, the results supported the hypothesis established in this study. Modeled recovery probability was improved by naloxone in opioid-involved overdose scenarios. However, the simulated benefit was reduced with xylazine as xylazine was treated as a non-opioid sedative component not directly reversed by naloxone. According to the empirical dataset, there was a sharp increase in xylazine-involved overdose deaths from 2019 to 2024. The simulation suggested that higher xylazine involvement was associated with lower theoretical recovery probability, especially when naloxone administration was delayed.

DISCUSSION

The findings in the analysis suggest that xylazine has become a significant emerging factor in overdose crisis in the U.S., representing a potential in complicating standard naloxone-based overdose response. There was a sharp increase in xylazine-involved overdose deaths from 2019 to 2024 as shown from the CDC/NCHS data. However, there was a decrease in heroin-involved deaths, while fentanyl-involved deaths remained high. This pattern suggests that the overdose crisis is no longer driven only by traditional opioids, such as heroin, but also by synthetic and polysubstance combinations. This is important in the area of public health as xylazine is not an opioid, and, hence, is not directly reversed by naloxone.

One limitation of the statistical analysis is that non-linear overdose trends may not be fully captured by simple linear regression. This is especially important for fentanyl-involved deaths that increased sharply during part of the study period but later slowed more fluctuation. Therefore, the monthly trend slope should be interpreted as an average direction of change across the full 2019-2024 period rather than an accurate forecast or causal estimate. It is highly recommended for future studies to use segmented regression, polynomial regression, or time-series models to better capture changes in trend direction over time.

These simulation results supported the hypothesis in this study. Modeled recovery probability in opioid-involved overdose scenarios was improved by naloxone. However, when xylazine involvement and response delay increased, recovery probability decreased. This means that the model supports the public-health importance of naloxone for reversing the opioid component of a suspected overdose. However, it does not measure actual clinical naloxone effectiveness. Since no patient-level overdose-response records were analyzed, the recovery probabilities in this study should be interpreted only as theoretical simulation outputs. Additional emergency support may include calling emergency medical services, rescue breathing, oxygen support, and continued monitoring after naloxone administration.

However, there are several limitations in this study. First, aggregate death counts were used in the CDC/NCHS dataset, not actual patient-level clinical records. Therefore, individual overdose outcomes or actual naloxone effectiveness cannot be determined by this dataset. Second, parameters used in the simulation were assumption-based rather than directly estimated from clinical trials. Third, real overdose events may vary by dose, route, drug mixture, health status, and emergency response quality, but xylazine involvement in this study was simplified into a single level. It is recommended that future research should use toxicology-confirmed clinical or emergency-response data to see whether the simulated patterns shown in this study correspond to real-world outcomes.

CONCLUSION

In this study, xylazine-involved overdose deaths were found to increase sharply in the United States from 2019 to 2024. Fentanyl-involved deaths remained high, while heroin-involved deaths declined. These trends suggest that there was a shift in the overdose crisis toward synthetic and polysubstance patterns, especially when combinations of fentanyl and xylazine were involved. In the theoretical simulation model, recovery probability improved in opioid-involved overdose scenarios when naloxone was administered. However, simulated recovery was reduced by higher xylazine involvement and longer response delays. Therefore, the results in this study support the hypothesis that naloxone is important for opioid overdose response, but xylazine may restrict the overall recovery effect due to its nature of not being directly reversed by naloxone. In this study, real clinical outcomes were not measured. Instead, it provided a transparent public-health simulation based on national overdose trends. Overall, the simulated findings emphasize the continued importance of rapid naloxone use, emergency medical support, and greater attention to xylazine in overdose-prevention strategies.

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