# Disparities in Opioid Distribution in Puerto Rico and the Continental United States (2018-2023)

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**Objective**: The objective of this study was to analyze and compare the distribution patterns of fentanyl, morphine, meperidine, and codeine in the continental US compared to Puerto Rico from 2018-2023. Attention was given to meperidine due to its extensive adverse effect profile and irreversible central nervous system toxicity.

**Methods**: Data was collected from Automation of Reports and Consolidated Orders Systems (ARCOS). The dataset included annual distribution data for meperidine, fentanyl, morphine, and codeine in the US and Puerto Rico. Population data was collected from US Census data and the American Community Survey. Data analyses were conducted using Microsoft Excel Version 2410. For each opioid, the mean distribution and standard deviation (SD) were calculated for the continental US. The mean distribution in Puerto Rico was compared to the US mean distribution with a 95% confidence interval. ANOVA tests were performed to assess differences in distribution of each opioid across years (2018, 2020, and 2022) within the continental US. All descriptive statistics and ANOVA calculations were conducted with statistical significance determined at p < 0.05.

**Results:** From 2018 to 2023, meperidine distribution declined in both regions but decreased more sharply in the continental US (82.6%) compared to Puerto Rico (43.5%). Distribution levels exceeded six standard deviations above the US mean in 2023. Fentanyl and morphine distributions were consistently lower in Puerto Rico than in the continental US.

**Conclusion**: There was a disproportionately high distribution of meperidine in Puerto Rico compared to the continental US across the years studied.

#### [P R Health Sci J 2025;44(2):84-88]

Key words: Meperidine, Morphine, Fentanyl, Codeine, Opiate

pioid medications play a large role in managing moderate to severe pain in both acute and chronic settings. However, their use carries risk of adverse effects, misuse, and physical dependency. Among the many opioids available, meperidine hydrochloride (Demerol) is a quick-acting synthetic opioid analgesic in the phenylpiperidine family historically used for acute pain management, postoperative pain (1), migraines (2), and labor pain (3). Its mechanism of action involves agonizing both the mu and kappa receptors and interacting with sodium channels. It also inhibits the dopamine transporter (DAT) and norepinephrine transporter (NET) which results in stimulant effects, in addition to its antimuscarinic properties and inotropic effects on the heart (4). The metabolism of meperidine produces the toxic metabolite normeperidine through N-demethylation by cytochrome liver enzymes, which can result in central nervous system toxicity due to increased synaptic serotonin properties. The accumulation of normeperidine can manifest as seizures, syncope, myoclonus and hallucinations, particularly in elderly patients and those with renal impairment. A potential consequence of meperidine use is serotonin syndrome, which manifests as tachycardia, agitation, hyperreflexia, and hypertension, and is drastically substantiated with concurrent use of other serotonergic drugs. In use for post-operative and labor pain, meperidine showed similar analgesic effects compared to other opioid drugs but with an increase in sedation

and respiratory depression (3). Meperidine also demonstrates a greater potential for dependency and abuse due to its short onset of action. Previously, meperidine was believed to have a lower risk of complications such as pancreatitis and biliary colic compared to alternative opioid therapies; however, this notion has now been widely rejected (5). Due to these risks, meperidine has largely fallen out of favor in clinical practice and was removed from the World Health Organization's (WHO) list of essential medications in 2003 (6).

In contrast, other opioids such as fentanyl, morphine, and codeine continue to maintain large clinical utility in pain management. Fentanyl, a potent synthetic opioid, is widely used for severe acute pain, anesthesia, and palliative care but carries misuse potential due to its high potency and fast onset of action. Morphine, a naturally derived opioid, has use in both acute and

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The authors have no conflict of interest to disclose. Brian J. Piper was (2019-2021) part of an osteoarthritis research team supported by Pfizer and Eli Lilly.

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chronic moderate to severe pain, especially in palliative care and cancer treatment (7). A less potent option than morphine, codeine plays a role as an antitussive and in management of mild to moderate pain (8). Each of these opioids has a slightly varied side effect profile and clinical indication, which are important to consider when analyzing their distribution trends.

Investigating the patterns in meperidine, fentanyl, morphine, and codeine distribution in the US and Puerto Rico over the span of six years provides insight into the potential risk to public health, especially considering the spectrum of dependency risk and adverse effects unique to each drug. Opioid distribution differences between Puerto Rico and the continental US should be analyzed while recognizing the differences in their healthcare infrastructure and socioeconomic factors which may influence opioid availability. This study examines the distribution patterns of meperidine, fentanyl, morphine, and codeine, in the continental US and Puerto Rico from 2018-2023 using data obtained from Automation of Reports and Consolidated Orders System (ARCOS). The goal of comparing trends in opioid distribution was to expand the understanding of implications for public health.

# Materials and Methods \_

### **Database and Participants**

Data was collected from the Automation of Reports and Consolidated Orders Systems (ARCOS). ARCOS is a comprehensive data collection system operated by the US Department of Justice and Drug Enforcement Agency (DEA). ARCOS tracks transactions of controlled substances from manufacturers and distributors (9). Data was collected from the ARCOS reports determining the distribution of opioids meperidine, fentanyl, codeine, and morphine from 2018 to 2023. A selection of opioids (meperidine, fentanyl, morphine and codeine) were chosen based on their clinical profiles. Meperidine was chosen due to its long-term adverse effects. Fentanyl was chosen due to its high potency. Codeine was chosen due to its weak opioid nature.

Population information was also collected from US census data from 2020 (10). Research methods were approved by Geisinger Commonwealth School of Medicine and confirmed that an IRB protocol was not needed (i.e., no personal data shared). The population was used to determine meperidine distribution per capita. There were no considerations of covariates as ARCOS does not collect variables such as age, gender or sex.

Calculation of the mean, standard deviation (SD), and standard error of mean (SEM) in addition to single-factor analysis of variance (ANOVA) tests were completed with Microsoft Excel Version 2410 Build 16.0.18129.20200. Post-hoc analysis was conducted using Tukey's Honestly Significant Difference (HSD) test to identify pairwise group differences. The Tukey HSD test was performed using the online statistical tool provided by Astatsa (http://astatsa.com/OneWay\_Anova\_wth\_TukeyHSD/). Line graphs were generated using GraphPad Prism Version 10.4.1. Analyses were conducted to determine if distribution for a territory was within a 95 percent confidence interval of the continental US.

#### **Results**

The analysis of opioid distribution from 2018 to 2023 revealed distinct trends across Puerto Rico and the continental US for meperidine, fentanyl, morphine, and codeine.

### Meperidine

In the continental US, meperidine distribution decreased by 82.6% from 2.01 mg/person in 2018 to 0.35 mg/person in 2023. In Puerto Rico, meperidine distribution also declined but at nearly half the rate, with a 43.5% reduction from 3.35 mg/person in 2018 to 1.89 in 2023. Despite its decline, there was a disproportionately higher meperidine distribution in Puerto Rico compared to the continental US, with levels more than six standard deviations above the US mean in 2023. For all other opioids studied aside from meperidine, distribution in the US was higher than in Puerto Rico. However, meperidine distribution was higher in Puerto Rico compared to the US for every year examined (Figure 1).

Within the continental US, ANOVA with post-hoc analysis revealed a significant difference in meperidine distribution from 2018 to 2020. However, no significant difference was found between 2020 and 2022, indicating that meperidine distribution plateaued after its initial decline. Notably, the distribution of all other opioids (morphine, codeine, and fentanyl) in the US declined significantly from 2020 to 2022 except for meperidine (Table 1).

#### Fentanyl

Fentanyl distribution in the continental US significantly declined between each of the three years studied (2018, 2020, and 2022), dropping from 0.87 in 2018 to 0.36 in 2023. Puerto

**Figure 1**. Meperidine distribution as reported to the Drug Enforcement Administration's Automated Reports and Consolidated Orders System in the US Territories compared to continental US from 2018 to 2023. Error bars for the US Continental represent + SEM. Meperidine distribution in Puerto Rico from 2019 to 2023 was greater than mean continental US meperidine distribution (95% CI).



Table 1. Mean opioid distribution (mg/person) in the continental US and US Territories as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders System. ARCOS drug data reported in g/100k converted to mg/person by dividing by a conversion factor of 100.

		Meperidine		Fentanyl		Morphine		Codeine	
		м	SD	М	SD	М	SD	М	SD
US Continental	2018 2020 2022	2.01ª 0.48 <sup>b</sup> 0.40 <sup>b</sup>	1.46 0.38 0.31	0.87ª 0.59 <sup>b</sup> 0.43 <sup>c</sup>	0.20 0.14 0.12	47.71ª 36.86 <sup>b</sup> 27.99°	14.58 10.38 7.79	37.90ª 29.81ª 22.68 <sup>b</sup>	22.83 18.68 14.14
Puerto Rico	2018 2020 2022	3.35 2.38 1.86	- -	0.13 0.17 0.18	- -	1.83 1.51 1.33	-	12.59 9.07 9.53	- -

Means with different superscripts differed significantly (paired t-test, p < 0.01).

Rico demonstrated consistently lower fentanyl distribution levels compared to the continental US across the years studied. In each year from 2018-2023, distribution of fentanyl in Puerto Rico was significantly lower than the mean US distribution (95% CI).

#### Morphine

Morphine distribution in the US decreased from 47.71 in 2018 to 27.99 in 2022, with a significant difference between each year studied in Table 1 (2018, 2020, and 2022). Similar to fentanyl, distribution of morphine in Puerto Rico was significantly lower than the mean US distribution in every year from 2018-2023 (95% CI).

### Codeine

There was no significant difference in codeine distribution in the US between 2018 and 2020. However, when comparing 2020 to 2022, there was a significant decline in codeine distribution from 29.81 to 22.68 (Table 1). In contrast to fentanyl and morphine, when comparing Puerto Rico to the continental US, distribution of codeine was within a 95% CI of the US mean distribution for each year studied.

#### **Discussion**

For all opioids except meperidine, the US consistently demonstrated higher (fentanyl, morphine) or similar (codeine) distribution rates across all years (2018-2023) when compared to Puerto Rico. Meperidine was the only opioid to exhibit a persistently higher distribution in Puerto Rico compared to the continental US from 2019-2023. Within the continental US, the rate of decline in meperidine distribution plateaued from 2020 to 2022, with no significant difference between these years. All other opioids studied demonstrate a decrease in distribution in the continental US over this time. Of importance, meperidine distribution in Puerto Rico in 2023 was greater than six standard deviations above the continental US mean.

The consistently higher distribution of meperidine in Puerto Rico raises several questions about prescribing patterns, healthcare infrastructure, and patient demographics that might contribute to this trend. These findings may suggest a need for targeted interventions in Puerto Rico to address the unique factors contributing to the disproportionately high distribution of this opioid (11). Possible contributing factors include differences in provider preferences and access to alternative analgesics but further studies are needed to address the etiology of such discrepancies (12). This highlights a concerning pattern given the well-known adverse effect profile of meperidine and preference for safer alternative opioids in clinical medicine.

To build on these findings, future studies should examine prescribing practices at the healthcare provider level to better understand the factors contributing to meperidine's disproportionately high distribution in Puerto Rico. Additionally, longitudinal studies assessing the relationship between opioid distribution

trends and patient outcomes, such as rates of dependency, overdose, and adverse events, would provide valuable insights. Efforts should also be directed toward understanding the role of socioeconomic determinants, healthcare infrastructure, and regulatory policies in shaping opioid availability and use in Puerto Rico. Finally, expanding the scope of research to include illicit opioid use data could provide a more comprehensive understanding of opioid-related public health challenges (13).

The implementation of opioid and non-opioid alternatives with a lower adverse effect profile should continue to reduce the clinical utility of meperidine for pain management. While this study

**Figure 2.** Morphine distribution as reported to the Drug Enforcement Administration's Automated Reports and Consolidated Orders System in the US Territories compared to continental US from 2018 to 2023. Error bars for the US Continental represent  $\pm$  SEM. Morphine distribution in Puerto Rico was lower than mean continental US distribution for each year from 2018-2023 (95% Cl).



Figure 3. Codeine distribution as reported to the Drug Enforcement Administration's Automated Reports and Consolidated Orders System in the US Territories compared to continental US from 2018 to 2023. Error bars for the US Continental represent  $\pm$  SEM. Codeine distribution in Puerto Rico from 2018 to 2023 was not significantly different from mean continental US distribution (95% CI).



underscores a promising overall decline in opioid distribution in both the continental US and Puerto Rico, the disproportionately high distribution of meperidine in Puerto Rico highlights a substantial public health concern. Addressing this disparity requires a multifaceted approach, including provider education, improved access to alternative treatments, and systemic interventions tailored to the unique healthcare landscape in Puerto Rico (14). By prioritizing these efforts, it is possible to reduce reliance on highrisk opioids like meperidine and promote safer, more effective pain management strategies. Additionally, research should be conducted on both the distribution and the average dose prescribed. Further research may also seek to understand the underlying etiologies of meperidine distribution compared to other opioids in Puerto Rico and its relationship to the COVID-19 pandemic.

#### Limitations

This study has several limitations inherent to the use of ARCOS data. First, while ARCOS provides detailed data on the distribution of opioids, it lacks information regarding drug use. Distribution data merely indicates the quantity of each drug supplied to the region rather than reflecting its consumption. Additionally, ARCOS lacks co-variables such as patient sex, age, race, and other socioeconomic and epidemiologic factors. The absence of these covariables limits the studies' ability to contextualize distribution trends within specific populations.

This study also excludes comparisons between each opioid using morphine milligram equivalents (MME). In particular, the inclusion of fentanyl in this study presents several challenges due to its high potency, multiple routes of administration, and consideration of the first-pass effect with regards to drug **Figure 4.** Fentanyl distribution as reported to the Drug Enforcement Administration's Automated Reports and Consolidated Orders System in the US Territories compared to continental US from 2018 to 2023. Error bars for the US Continental represent <u>+</u> SEM. Fentanyl distribution in Puerto Rico was lower than mean continental US distribution for each year from 2018-2023 (95% CI).



metabolism. These factors impact conversion of fentanyl to its morphine equivalent and therefore limits its comparison to the other opioids listed in the study.

Furthermore, ARCOS drug data does not account for illicit opioid distribution which serves as a major contributor to opioidrelated morbidity and mortality. This limitation may result in an underestimation of opioid distribution in particular regions. Lastly, the study does not account for differences in the size of populations and healthcare systems between the continental US and Puerto Rico, which likely influences opioid distribution.

In conclusion, this study determined that Puerto Rico had much greater meperidine distribution, but lower fentanyl and morphine, than the continental US. Further studies are needed to understand the origins of these disparities.

# **Resumen**

Objetivo: El objetivo de este estudio fue analizar y comparar los patrones de distribución de fentanilo, morfina, meperidina y codeína en los Estados Unidos continentales en comparación con Puerto Rico desde 2018 hasta 2023. Se prestó atención especial a la meperidina debido a su extenso perfil de efectos adversos y a la toxicidad irreversible en el sistema nervioso central. Métodos: Se recopilaron datos del Sistema de Automatización de Informes y Órdenes Consolidadas (ARCOS). El conjunto de datos incluyó información anual sobre la distribución de meperidina, fentanilo, morfina y codeína en los EE. UU. y Puerto Rico. Los datos de población se obtuvieron del Censo de los EE. UU. y de la Encuesta Comunitaria Americana. Los análisis de datos se realizaron utilizando Microsoft Excel, versión 2410. Para cada opioide, se calcularon la distribución media y la desviación estándar (DE) para los Estados Unidos continentales. La distribución media en Puerto Rico se comparó con la distribución media en los EE. UU. utilizando un intervalo de confianza del 95%. Se realizaron pruebas de análisis de varianza (ANOVA) para evaluar las diferencias en la distribución de cada opioide a través de los años (2018, 2020 y 2022) dentro de los EE. UU. continentales. Todas las estadísticas descriptivas y los cálculos de ANOVA se realizaron con significancia estadística determinada en p < 0.05. Resultados: De 2018 a 2023, la distribución de la meperidina disminuyó en ambas regiones, pero decreció más bruscamente en los EE. UU. continentales (82.6%) en comparación con Puerto Rico (43.5%). Los niveles de distribución superaron seis desviaciones estándar por encima de la media de EE. UU. en 2023. Las distribuciones de fentanilo y morfina fueron consistentemente más bajas en Puerto Rico que en los EE. UU. continentales. Conclusión: Hubo una distribución desproporcionadamente alta de meperidina en Puerto Rico en comparación con los Estados Unidos continentales a lo largo de los años estudiados.

# Acknowledgments \_\_\_\_

Translation from English to Spanish was performed by Lori Suddarth M.Ed. Learning and Technology, ACICP Tier 4. Minor data entry and minor editing performed by Scott Suddarth.

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