Proceedings of the 11th World Congress on New Technologies (NewTech'25)
Paris, France - August, 2025
Paper No. ICBB 139
DOI: 10.11159/icbb25.139

Increase in Adverse Event Reporting for Methadone During the COVID-19 Pandemic

Nysa Anand
Normal Community High School
3 Callahan Ct, Bloomington, United States
nysaanand19@gmail.com

Abstract **-** The objective of this study was to examine the trends in adverse event reporting for methadone before, during, and after the COVID-19 pandemic. This study utilized the FDA Adverse Event Reporting System to analyze methadone adverse event reports and compare these trends with those of all medications. The study finds that 18.8% of all methadone-related adverse event reporting occurred in 2021, with 21,257 out of 22,447 adverse event cases classified as serious adverse events, and 10,109 resulting in death. There was a 320.9% increase in reported adverse events for methadone between 2012 and 2013, marking the first major uptick in methadone adverse event reports. Overall, there was a 1297% increase in reported adverse events for methadone across the decade of 2011 to 2021. The trend in adverse event reporting for methadone did not match the trend in adverse event reporting across all medicines. There was a 61.9% increase in reported adverse events for methadone between 2020 and 2021, while the increase in reported adverse events across all medicines was only 5.7% over this same period. The study additionally finds that 51.2% of reported cases for methadone adverse events were from men. Additionally, the greatest proportion of reported adverse events for methadone involved drug dependence, making up 21.8% of all reported adverse events for methadone. The results highlight that increases in reported adverse events for methadone during the COVID-19 pandemic are unique to methadone, and cannot be attributed to a general increase in reporting of adverse events across all pharmaceuticals. Further research could examine trends in adverse event reporting in other substances used to treat opioid use disorder, and potential solutions to counteract increased opioid usage in times of widespread infectious disease.

Keywords**:** adverse events, COVID-19 pandemic, methadone, opioid use disorder

1. Introduction

Opioids have been used to manage acute, terminal, and chronic pain from the earliest human times. In 3400 B.C., the euphoric effects of the opium poppy (Papaver somniferum) were recognized under the term “joy plant” [1]. Ancient Greece utilized the characteristics of this plant in the 8th century B.C., describing preparations of sedatives and hypnotics [2]. Later, opium was recorded to be held over the nose as a form of painkiller during the earliest forms of Western surgery [1]. More recently, however, opioid usage has developed some increasingly concerning consequences. Nearly 727,000 deaths in the United States were caused by opioid overdoses between 1999-2022 [3]. On October 16th, 2017, the United States Government declared the opioid epidemic a public health emergency under section 319 of the Public Health Service Act, and this declaration was most recently renewed in June 2024 [4].

Today’s opioid epidemic is characterized by a spike in overdose deaths related to the misuse of prescription and illegal opioids and has impacted the United States immensely. The use of opioids has increased by approximately 10 times over the 20-year period from 1997 to 2017 [5]. Deaths by opioids continue to rise; an estimated 224 people died daily in the United States from opioid overdose in 2022 [3].

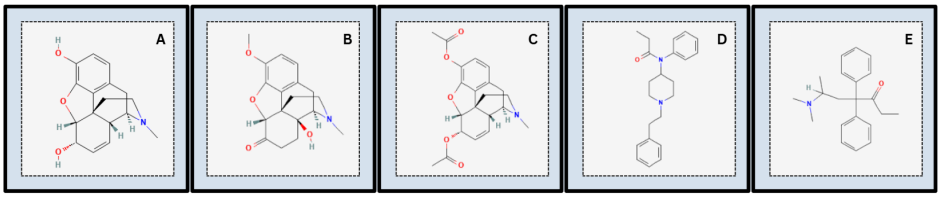

Figure 1. Chemical structures of (A) morphine; (B) oxycodone; (C) heroin; (D) fentanyl; (E) methadone

Opioids are a class of natural, semi-synthetic, and synthetic drugs, such as heroin, oxycodone, methadone, morphine, and fentanyl (Figure 1), which are defined as medications that bind to opioid receptors [6]. In signaling pathways, opioid receptors function as painkillers, inhibiting the transmission of pain neurotransmitters and inducing analgesia [2]. However, the involvement of opioids in long-term treatment plans has become increasingly controversial. As these medications have become more accessible in pain treatment, opioid addiction and abuse have become more frequent. The surge in opioid usage can partially be attributed to commercial marketing strategies to physicians who prescribe these products.

Despite being intended as a treatment for chronic non-cancer pain, opioid usage has many common side effects, the most prominent being constipation and nausea [1]. Other common side effects include sedation, dizziness, vomiting, physical dependence, and respiratory depression [1]. When an individual takes a higher dosage of an opioid than their body can handle, an opioid overdose occurs [6]. Opioid overdose can induce deadly symptoms [6]. These symptoms include unconsciousness, difficulty breathing, discolored skin, nails, or lips, and constricted pupils [6]. An overdose can be intentional or unintentional, and it usually results from multiple drugs being mixed [6]. For example, overdose deaths in adolescents have been on the rise due to lethal doses of fentanyl being mixed into counterfeit pills [6]. Additionally, prolonged usage of opioids has some adverse consequences, including tolerance, hyperalgesia, hormonal effects, and immunosuppression [1]. Prolonged opioid usage leads to a loss of analgesic potency, meaning that the dosage must continually increase to achieve the same level of effectiveness as time goes on, inducing a dependency on opioids [1].

Aside from tolerance, another primary cause of dependency on opioids lies in opioid receptor structures and receptor signaling cascades [2]. In conventional opioid receptor signaling, the primary opioid receptors are mu (MOR), delta (DOR), kappa (KOR), and nociceptive (NOPR) opioid receptors [2]. In these signaling pathways, when opioids bind to mu-opioid receptors, they create a signal in the brain's ventral tegmental area (VTA), triggering a release of dopamine, which induces euphoric feelings of pleasure [7]. Repeated use of opioids causes the brain to associate these feelings with taking the opioid, leading to opioid cravings and in most cases, addiction [7].

To understand the impact of opioids, it is critical to examine the basics of conventional pain-signaling pathways [8]. Pain transmission begins with detecting chemical, thermal, or mechanical stimuli that trigger signals to travel through Aδ- and C-fibers, which are specialized pain fibers, to the spinal cord and eventually the brain [8]. Once the brain receives these signals, serotonin and norepinephrine are released, and the signals are then sent back down via the locus coeruleus and nucleus raphe magnus to help reduce pain at its source [8]. Serotonin release activates opioid-releasing neurons to block pain, and norepinephrine release triggers receptors in the spinal cord to aid in reducing pain [8]. Meanwhile, glutamate and N-methyl-D-aspartate (NMDA) receptors serve to transmit and amplify pain signals, respectively [8]. Repeated release of these pain signals over-activates these receptors, leading to long-term, chronic pain [8].

Transduction processes of conventional opioid receptor signaling rely on G protein-coupled receptor-transducer (GPCR) interactions involving G-proteins and GPCR kinases [2]. Opioid receptors may express a multitude of Gα subtypes, one, for example, being the Gαi/o inhibitory protein family [2]. Gαi/o can decrease the level of cellular cyclic adenosine monophosphate (cAMP), which hinders the effects of the cAMP signaling cascade [2]. For example, calcium channels are closed, preventing positively charged calcium from entering the cell [2]. Meanwhile, the G protein-gated inwardly rectifying potassium (GIRK) channels are opened, which enables positively charged potassium to leave the cell [2]. Additionally, SNAP receptors (SNAREs), which are protein complexes, are inhibited [2]. These processes are a result of the reduced cAMP production, which collectively leads to reduced presynaptic release of neurotransmitters and inhibits the transmission of pain signals throughout the body, hence causing analgesia [2].

Methadone is a long-term opioid agonist that is most well-known for its role in opioid maintenance therapy and treatment [8]. It is an analgesic for acute and chronic pain management [8]. Its longer half-life in comparison to most clinically used opioids as well as its ability to attach to mu, delta, and kappa opioid receptors, make it an effective opioid agonist [8]. Methadone is a synthetic, easily manufacturable, and cost-effective substance that has unique pharmacological properties, enabling it to differentiate itself from mainstream opioids such as fentanyl and morphine [8]. One property includes high lipid solubility, which leads to increased bioavailability and prolonged impact [8]. After repeated administration, methadone still has an analgesic effect after 8-12 hours and inhibits serotonin and norepinephrine reuptake in the central nervous system [8]. Additionally, methadone has many routes of administration, such as buccal, topical, neuraxial, and intravenous routes, and can be administered most effectively through oral or nasal pathways [8].

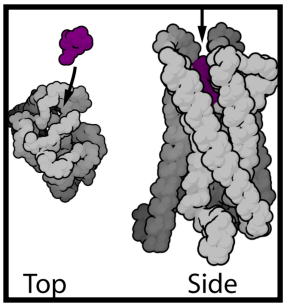

Figure 2. A mu-opioid receptor is bound to a ligand/opioid signal (Wikimedia Commons 2007).

In methadone signaling pathways, the opioid agonist binds to mu-opioid receptors (Figure 2), resulting in signaling transduction and cascades very similar to those of conventional opioids, reducing the presynaptic release of neurotransmitters, and inhibiting the transmission of pain signals, and causing analgesia [8]. However, methadone inhibits serotonin and norepinephrine reuptake as well, enabling the neurotransmitters to continue to block and reduce pain by sending further messages between nearby cells rather than being absorbed by a presynaptic nerve [8]. Additionally, methadone blocks the NMDA and glutamate receptors, reducing the transmission and amplification of pain signals, and it prevents the nervous system from being overstimulated by pain, reducing the risk of hyperalgesia and chronic pain [8]. These collective factors enable methadone to be an extremely effective analgesic, especially in opioid-tolerant patients [8].

However, as an opioid agonist, methadone has many adverse consequences that are similar to those of standard opioids, including respiratory depression, euphoria, nausea, sedation, miosis, physical dependence, and tolerance [8]. Methadone is a strong central nervous system (CNS) depressant, and when combined with other CNS depressants, such as alcohol, it can cause significant negative CNS effects [8]. Methadone is also a federally designated Schedule II drug [8]. Since methadone has a steady plasma concentration, it does not offer pleasurable sensations and the typical drug craving associated with standard opioids like heroin, morphine, and oxycodone [8]. However, it does create strong sedative effects that can lead to euphoric feelings [8].

As with the long-term use of all agonists, methadone has a high chance of resulting in physical dependence [8]. Physical dependence is a term used to refer to changes in the nervous system's function caused by prolonged opioid binding to receptors, leading to receptor-mediated adaptations over time [8]. These changes can cause the body to rely on the drug to function normally, and stopping or reducing drug usage results in withdrawal symptoms, such as anxiety, agitation, restlessness, hyperhidrosis, and tachycardia [8]. Additionally, after chronic exposure to opiates, the MOR receptors become desensitized to the methadone binding, leading to tolerance [8]. Because of this occurrence, over long-term periods, methadone intake leads to a decreased drug response in the body, requiring an increase in dosage to achieve an effective analgesic effect [8].

Because methadone has been seen to be an effective analgesic and plays a critical role in opioid maintenance, it is crucial to understand the impact of the pharmacological adverse effects and consequences of methadone usage. The objective of this research is to investigate reported adverse events for methadone and trends in adverse event reports in the pre-pandemic, pandemic, and post-pandemic eras.

2. Methods

This study aims to investigate and perform an analysis of reported adverse events for methadone and trends in adverse event reports in the pre-pandemic, pandemic, and post-pandemic eras by employing a combination of statistical analysis and data extraction from the FDA Adverse Event Reporting System (FAERS) Public Dashboard. The pre-pandemic era is defined as the period from 2011 to 2019. The pandemic era is defined as the period from 2020 to 2021, with peak pandemic conditions in 2021. The post-pandemic era is defined as the period beginning in 2022 and beyond.

The FAERS is a web-based platform that allows the general public to access data reported to the FDA on human adverse events associated with pharmaceuticals. The FAERS Public Dashboard contains all reports of adverse events from

both mandatory reporters (pharmaceutical manufacturers) and voluntary reporters (healthcare professionals and consumers) for all medicines approved for use in the United States.

The FAERS public dashboard was searched using the term “methadone”, and data on case count by received year, serious cases including death, case count by reaction, and case count by sex were collected. A serious adverse event is defined by the FAERS Public System as one that is life-threatening or that requires hospitalization.

3. Results

3.1. Overall Trends

Methadone has had FDA approval for the treatment of opioid addiction since 1972, but adverse events reported for methadone began to increase substantially in 2013 (Figure 3). Between 2012 and 2013, the first major increase in reported adverse events for methadone occurred, with a percent increase of 320.9%.

There were a total of 2,606 adverse event reports for methadone in 2020 and a 61.9% increase in methadone adverse event reports between 2020 and 2021. There was a spike in adverse event reports for methadone in 2021, during the COVID-19 pandemic, with a total of 4,219 cases reported that year. There were a total of 2,259 adverse event reports for methadone in 2022, a 46.5% decrease in methadone adverse event reports between 2021 and 2022. Overall, there was a 1297% increase in reported adverse events over the decade from 2011 to 2021.

The trend in reported adverse events for methadone from 1998 to 2024 does not match the overall trend for reported adverse events for all pharmaceuticals collectively in the FAERS database (Figure 4), meaning that methadone exhibited unique increases in reported adverse events over this timeframe. The 320.9% increase in reported adverse events for methadone from 2012 to 2013 is specific to this medication; by comparison, the increase in reported adverse events for all medicines from 2012 to 2013 was 14.9%. The 61.9% increase in reported adverse events for methadone from 2020 to 2021 is also specific to this medication; by comparison, the increase in reported adverse events for all medicines from 2020 to 2021 was 5.7%. While the number of reported adverse events for all medications steadily increased over the decade from 2011 to 2021, the increase was not nearly as dramatic as that for methadone. While methadone demonstrated a 1297% increase in reported adverse events from 2011 to 2021, all medications together demonstrated a 197% increase in reported adverse events over the same time period. There was no clear spike in total reported adverse events for all medications during the COVID-19 pandemic.

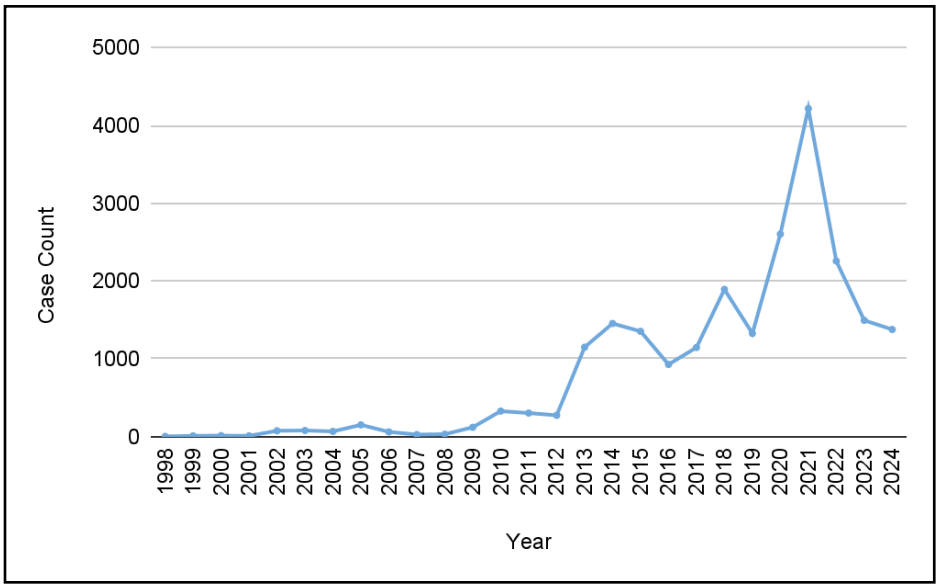

Figure 3. Total Reported Adverse Events for Methadone vs. Year (1998-2024)

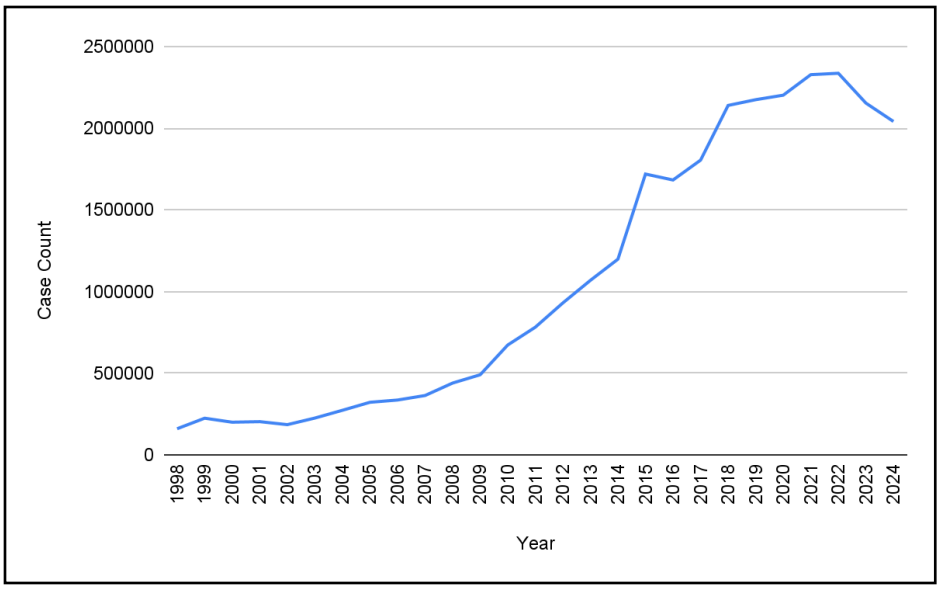

Figure 4. Total Reported Adverse Events for All Medications vs. Year (1998-2024)

3.2. Serious Adverse Events

The FAERS Public System indicates that 18.8% of all methadone-related adverse event reports occurred in 2021. Additionally, of the 22,447 adverse event cases reported for methadone over all years, 21,257 were classified as serious adverse events. This means that 94.6% of all reported adverse events for methadone are serious adverse events (this includes death). Of the 22,447 adverse event cases reported for methadone over all years, 10,109 resulted in death. This means that 45.0% of all reported adverse events for methadone resulted in death.

3.3. Demographic Trends

Notably, when adverse events are classified by sex, men account for a greater proportion of reported adverse events for methadone than women (Figure 5). Men make up 51.21% of reported adverse event cases, women make up 36.08% of reported adverse event cases. The remaining 12.71% of adverse event reports did not specify the sex of the individual. This differs from total adverse reports across all medications, in which women made up 53.22% of reported adverse event cases.

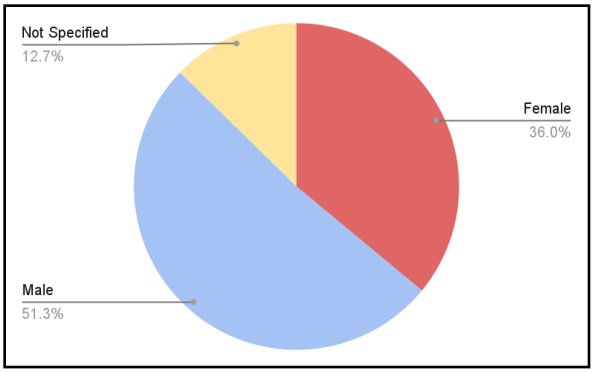

Figure 5. Percent Cases of Reported Adverse Events for Methadone by Sex

3.4. Reaction-Type Trends

When adverse events are classified by reaction type, the greatest proportion of reported adverse events for methadone, 21.8%, involved drug dependence (Figure 6). Toxicity to various agents, drug abuse, and overdose were also frequently reported adverse events for methadone.

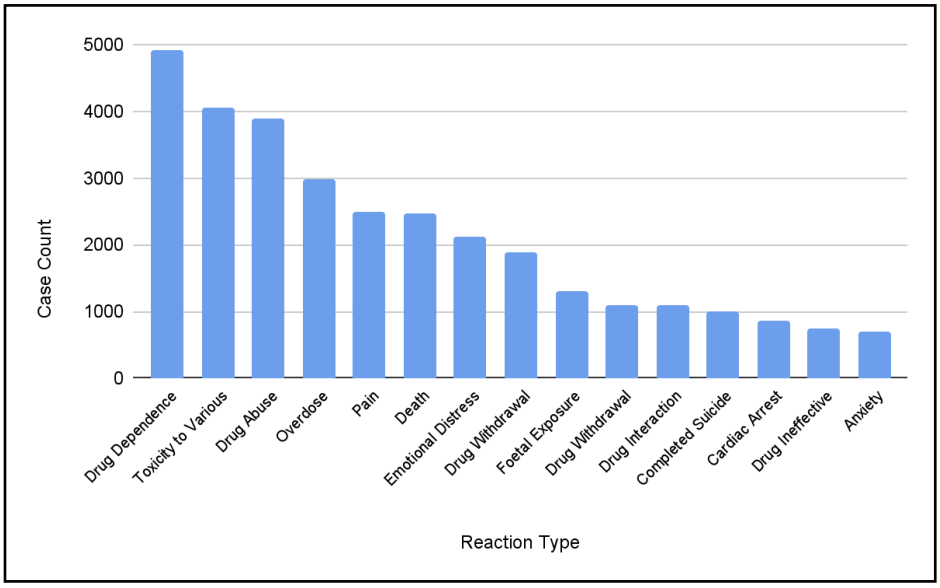

Figure 6. Case Count by Reaction Type of Methadone Adverse Events

4. Discussion

The results of the study highlight that the increases in reported adverse events for methadone in 2013 and 2021 cannot be attributed to an overall increase in reporting of adverse events for all pharmaceuticals. In 2021, the number of reported adverse events for methadone was 14 times the number of reported adverse events for methadone from a decade earlier. In contrast, the number of reported adverse events for all medicines in 2021 was 3 times the number of reported adverse events for all medicines from a decade earlier. This indicates that there was a clear spike in reported adverse events for methadone during the COVID-19 pandemic. Still, there was no clear spike in reported adverse events for all medicines during the COVID-19 pandemic. This means that the increase in reported adverse events for methadone during the COVID-19 pandemic was unique to methadone, indicating that there is a high probability of external factors influencing the increase in usage of methadone. In 2013, the initial rise of reported methadone adverse events was suggestive of an opioid addiction crisis, seven years before the COVID-19 pandemic. It is important to note that this rise in reported methadone adverse events occurred nearly 18 years after the approval of Oxycodone and 14 years after the first wave of the opioid epidemic. When the COVID-19 pandemic hit, the methadone adverse events spiked, suggestive of a sudden and troubling worsening of the third wave of the opioid epidemic.

4.1. Strengths and Limitations

A strength of the FAERS system is that it allows public participation in adverse reporting, which aids in monitoring adverse events, as compared to adverse reporting being limited solely to health professionals. The system also enables the general public, doctors, and patients to access reports promptly. Additionally, as this study utilized anonymous information from the FAERS Public Dashboard, the data was free in the public domain, allowing for ethical research practices.

However, the FAERS Public Dashboard does have some limitations. The system may contain incomplete reports, inaccurate reports, or duplicate reports. As the data in this system relies on reported adverse events, some information can be inaccurate as adverse events may go completely unreported. Finally, the reporting of an adverse event associated with the use of a drug does not necessarily prove that the drug caused the event. Adverse events are often correlated with many external variables that may depend on environmental, patient-specific, or behavioral factors.

Despite these limitations, the present study still suggests that methadone adverse events showed concerning trends both before and during the COVID-19 pandemic

4.2. Related Scholarly Works

There was an increase in the permitted amount of methadone take-home doses for the treatment of Opioid Use Disorder (OUD) by the US Substance Abuse and Mental Health Services Administration (SAMHSA) at the start of the COVID-19 Pandemic [9]. A study of 183 patients at a single methadone clinic in Spokane, Washington examined the impacts of this policy change and revealed that the mean number of methadone take-home doses increased from 11.4 take-home doses per 30 days to 22.3 take-home doses per 30 days after SAMHSA relaxed the rules on methadone prescriptions [9]. All individuals with OUD were given similar access to methadone take-home doses regardless of individual demographics, so an individual's demographics did not influence their access to OUD treatment [9]. Another study conducted in 8 opioid treatment programs across the state of Connecticut, with an average of 837 individuals with OUD in each program, indicated similar results [10]. This suggests that the increase in the number of take-home doses was most likely not unique to Spokane, Washington, or any specific geographic area. There was a 16,700% increase in the percentage of patients receiving 28-day take-home doses [10]. Additionally, 75.2% of patients transitioned into telehealth and there was an 84.1% decrease in in-person individual counseling; this indicates that there were many individuals who lost the added value of seeing their doctors in person, and some individuals who completely lost the guidance of their healthcare experts in treating OUD and managing their methadone dosages [10].

This increase in the ease of accessibility to methadone, coupled with the decrease in professional supervision, allows for the increased potential of misuse. Multiple treatment programs within the studied clinics stated that patients were experiencing difficulties due to the COVID-19 pandemic, and healthcare professionals expressed concerns about the new SAMHSA guidelines [10].

However, the studies conducted in Washington and Connecticut found that there were no negative impacts on the treatment of OUD associated with this increase in take-home dose prescriptions [9]. These studies report that the SAMHSA exemption and increase in take-home doses resulted in improved patient satisfaction [9]. These findings directly contrast with the current study's findings from the FAERS Dashboard, which indicates that there was a clear spike in methadone adverse event reporting in 2021 during the COVID-19 pandemic that was unique to methadone in comparison to all medicines.

During a worldwide pandemic, infection control measures may cause many unintended consequences, such as an increase in access to synthetic opioids such as methadone due to the SAMHSA exemption. With this increase in accessibility, there was also an increase in unsupervised prescriptions of methadone due to control measures preventing individuals from meeting with doctors in person. With a limited amount of supervision for individuals in possession of methadone, there were increased chances of misuse, which may account for the spike in adverse event reporting during the COVID-19 pandemic. This discrepancy in findings could be attributed to differences in study design and methodology, sample populations, or other factors not accounted for in the existing studies, which should be explored through further research.

One possibility for future research within the range of methadone usage during the COVID-19 pandemic could include examining data sets with the number of prescriptions for methadone that were filled over this time. Another avenue for research includes analyzing the reported adverse events for other medicines used to treat addictions to other substances and OUD before and during the COVID-19 pandemic, providing a deeper understanding of the opioid epidemic during this period overall. Finally, it would be interesting to examine the potential solutions to counteract the increasing misuse of opioids, such as methadone, during times when infectious diseases become more imminent. This could include events similar to the pandemic itself, but is not limited to widespread events and can be later researched on smaller-scale events, such as in a local community.

5. Conclusion

In conclusion, the opioid epidemic is an imminent public health crisis, resulting in major negative impacts across the nation. Synthetic opioids such as methadone, along with a multitude of other treatments, have been implemented in an attempt to overcome opioid addiction. The findings of this study demonstrate a significant spike in adverse event reporting unique to methadone in comparison to all medications during the COVID-19 pandemic, based on data in the FAERS Database. This emphasizes the need for caution in OUD treatment practices and regulation, especially during times of disrupted healthcare access and increased risk of misuse, such as the global pandemic. Despite the uncertainty in the cause of this spike, it is

important to acknowledge the increase in accessibility to methadone and the decrease in supervision during this period. Future research could potentially explore how similar disruptions in access to opioids may influence adverse event reporting and OUD treatment, and research should determine ways to minimize the impact of these disruptions.

Acknowledgements

I would like to express my gratitude to Dr. Sujata K. Bhatia for her invaluable guidance and mentorship throughout the development of my research. Her support played a crucial role in helping me grow, both as a student and a researcher, as well as in the success of this study. I would also like to give special thanks to my parents for their continuous encouragement and support, which helped make this research possible.

References

[1] R. Adlaka, R. Benyamin, R. Buenaventura, S. Datta, S. E. Glaser, N. Sehgal, A. M. Trescott, and R. Vallejo, "Opioid Complications and Side Effects," *Pain Physician*, vol. 11, no. 2, pp. 105-120, 2008 [Online]. Available: https://painphysicianjournal.com/current/pdf?article=OTg1&journal=42.

[2] T. Che and B. L. Roth, "Molecular basis of opioid receptor signaling," *Cell*, vol. 186, no. 24, pp. 5203-5219, 2023. [Online]. Available: https://doi.org/10.1016/j.cell.2023.10.029.

[3] U.S. Centers for Disease Control and Prevention, "Understanding the opioid overdose epidemic | overdose prevention," Centers for Disease Control and Prevention, Nov. 1, 2024. [Online]. Available: https://www.cdc.gov/overdose-prevention/about/understanding-the-opioid-overdose-epidemic.html.

[4] U.S. Federal Communications Commission, "Focus on opioids," *Connect2Health FCC*, 2024. [Online]. Available: https://www.fcc.gov/reports-research/maps/connect2health/focus-on-opioids.html.

[5] E. A. Shipton, E. E. Shipton, and A. J. Shipton, "A review of the opioid epidemic: What do we do about it?" *Pain and Therapy*, vol. 7, no. 1, pp. 23-26, 2018. [Online]. Available: https://doi.org/10.1007/s40122-018-0096-7.

[6] U.S. National Institute on Drug Abuse, "Opioids," *National Institute on Drug Abuse*, Nov. 22, 2024. [Online]. Available: https://nida.nih.gov/research-topics/opioids#work.

[7] T. P. George and T. R. Kosten, "The neurobiology of opioid dependence: Implications for treatment," *Science & Practice Perspectives*, vol. 1, no. 1, pp. 13-20, 2002. [Online]. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC2851054/.

[8] E. N. Aroke, G. Lai, S.J. Zhang, "Rediscovery of methadone to improve outcomes in pain management," *Journal of PeriAnesthesia Nursing*, vol. 37, no. 4, pp. 425-434, 2022. [Online]. Available: https://doi.org/10.1016/j.jopan.2021.08.011.

[9] S. Amiri, O. Amram, P. J. Joudrey, R. Lutz, V. Panwala, and E. Socias, "The impact of relaxation of methadone take-home protocols on treatment outcomes in the COVID-19 era," *The American Journal of Drug and Alcohol Abuse*, vol. 47, no. 6, pp. 722–729, Oct. 20, 2021. [Online]. Available: https://doi.org/10.1080/00952990.2021.1979991.

[10] S. Brothers, R. Heimer, and A. Viera, "Changes in methadone program practices and fatal methadone overdose rates in Connecticut during COVID-19," *Journal of Substance Abuse Treatment*, vol. 131, p. 108449, Dec. 2021. [Online]. Available: https://doi.org/10.1016/j.jsat.2021.108449.