

# Surge in Adverse Events for Prescription Opioids and Opioid Overdose Treatments during the COVID-19 Pandemic

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**Abstract** - The opioid epidemic is one of the most pressing public health issues of our time, with hundreds of deaths daily due to opioid overdose. This research investigates the number of reported adverse events related to the use of prescription opioids and opioid overdose treatments during the COVID-19 pandemic, lending further insight into the impact the COVID-19 pandemic has had on the opioid epidemic. We hypothesized that adverse events for both prescription opioids and opioid overdose treatments rose during the COVID-19 pandemic, due to isolation and lack of access to healthcare services. Using data from the Food and Drug Administration Adverse Event Reporting System (FAERS), we analyzed the number of adverse drug events (ADE) in the years 2020 and 2021 compared to 2019, specifically for the medications Naloxone(G), Naloxone Hydrochloride(G), Oxycodone(G), Oxycodone Hydrochloride(G), and Oxycontin(P). We also analyzed the most commonly reported types of adverse reactions and the age of the reporters. The data reveals an alarming spike in the number of ADEs attributed to Naloxone(G) from 2019 to 2020, increasing by 148% and then another 29% in 2021. Similarly, the number of ADEs reported for Naloxone Hydrochloride(G) nearly rose four-fold from 66 to 246. For the prescription opioid Oxycodone(G), there was a 78% increase in ADEs from 2019 to 2020. More concerning, there was a 434% spike in the number of ADEs for Oxycodone Hydrochloride(G) and more than thirteen-fold the number of cases in 2020 than 2019 for Oxycontin(P). Finally, we found the most commonly reported reactions were “overdose,” “drug dependence,” “drug withdrawal syndrome,” and “drug abuse”; the 18–64-year-old age group reported the majority of the cases. These results highlight the need to increase focus on the opioid epidemic, specifically monitoring the use of prescription opioids.

**Keywords:** opioid, adverse events, naloxone, oxycodone, oxycontin

## 1. Introduction

Opioids are one of the most frequently prescribed drugs in the United States of America, with 32% of American adults being prescribed an opioid in 2016, 2017, and 2018 [1]. Throughout history, opioids have been used to help alleviate pain [2], with companies such as Purdue Pharma producing OxyContin to help increase the number of opioids. However, opioids have also been widely known for their addictive potential, causing the opioid epidemic to be one of the most pressing public health issues in recent years. In 2017 alone, there were more than 191 million opioid prescriptions dispensed to American patients [3], for an adult population of 252 million in the United States that year [4]. In the past decade, the number of adverse events related to opioids has exacerbated severely, with overdose deaths rising an astounding 32% during the rise of Covid-19 [5]. Given the spike in opioid-related deaths during the COVID-19 pandemic, we investigated the number of reported adverse events related to the use of the opioid overdose medication naloxone, as well as prescription opioids, before and during the pandemic. We specifically observed adverse events from Naloxone(G), Naloxone Hydrochloride(G), Oxycodone(G), Oxycodone Hydrochloride(G), and Oxycontin(P), where G designates a generic drug and P designates a brand-name drug. Using data from the US Food and Drug Administration Adverse Event Reporting System (FAERS), we analyzed the number of adverse drug events (ADE) during the pandemic years of 2020 and 2021, compared to the year immediately preceding the pandemic. As well, we collected data on the type of reactions recorded and the age of the reporter. Since reports of adverse events lend insight into the opioid epidemic, the objective of this study was to observe the impact COVID-19 had on the number of yearly reported adverse events for naloxone and oxycodone/oxycontin. By observing adverse event reports for naloxone, a potent opioid antagonist, we can assess trends in the frequency of opioid overdose and the burden of opioid abuse during the rise of COVID-19. In light of rising opioid overdose cases, fentanyl and other synthetic opioids have been considered the main drivers for the increase in overdose reports [6]. However, the focus on fentanyl and other synthetic opioids may be overshadowing an ongoing problem with prescription opioids. By investigating reports related

to oxycodone and oxycontin, we get a deeper look into the number of adverse events related to prescription opioids, which can help identify whether more attention is needed towards the use of prescription opioids in addition to synthetic opioids.

## 2. Methods

We used the FDA Adverse Event Reporting System (FAERS), which contains adverse event reports, medication error reports, and product quality complaints from both consumers and healthcare professionals [7]. In the database, data can be categorized by received year, reaction, product name, generic name, age group, sex, and reporter type. We gathered the necessary FAERS data by searching for Naloxone(G), Naloxone Hydrochloride(G), Oxycodone(G), Oxycodone Hydrochloride(G), and Oxycontin(P) individually and examined the reports by received year, reaction, and age group. We conducted paired t-tests to analyze the statistical significance of the observed differences in monthly adverse events, between the pre-pandemic year 2019 and the pandemic years 2020 and 2021; we set a cutoff for statistical significance of  $p < 0.05$ . We performed the paired t-tests by putting the ADEs for each month in a Microsoft Excel sheet and calculating the number of ADEs per month. Then we performed the paired t-tests for the difference between monthly reported adverse events for the pre-pandemic year and post-pandemic year. Finally, we recorded cumulative ADE data for each pharmaceutical for the entire history of the database from 1968 to the present and analyzed the proportion of cumulative adverse events that occurred in 2020 and 2021.

## 3. Results

For the medication Naloxone(G), there were 166 ADEs reported in 2020. The ADEs in 2020 for Naloxone(G) account for almost 25% of the total ADEs reported for Naloxone in all years; in other words, the adverse events in 2020 alone accounted for almost one-quarter of all adverse events reported for Naloxone over the time period 1968-2021. Similarly, in 2021, there were 214 ADEs reported; together, the ADEs in 2020 and 2021 account for over 54% of the total ADEs reported for Naloxone in all years. Comparing the data from 2019 to 2020, we found a dramatic 147.8% increase in ADEs reported related to Naloxone(G) (Fig. 1). To ensure that this trend was isolated to the pandemic, we compared the percentage increase from 2018 to 2019 to that from 2019 to 2020, and found a 123.7% larger increase during 2019 to 2020 than 2018 to 2019. As well, a paired T-test comparison of adverse events in 2019 versus 2020 yielded a p-value  $< 0.0005$ , and a paired T-test comparison of adverse events in 2019 versus 2021 yielded a p-value  $< 0.003$ , indicating statistical significance. We also looked at the adverse reactions reported in the database, finding the most common reaction to Naloxone(G) was “Toxicity to Various Agents,” which comprised 20.03% of the cases. Other reactions that were frequently reported included: “overdose,” “drug dependence,” and “drug ineffective,” which together accounted for 42.49% of the total reported cases. We finally looked at the age groups which reported the ADEs for Naloxone(G), finding that 53.65% of all ADEs occurred in the 18–64 year-old age group, the most out of any age group. It also needs to be put into consideration that a significant number of people, 28.9%, did not specify their age.

For the medication Naloxone Hydrochloride(G), we found a substantial amount of ADEs reported in 2020 and 2021. In 2020, there were 237 reported ADEs, which was 17.01% of the total reports for all years, and in 2021, there were 181 ADEs reported, which was 13.3% of the total reports for all years. In total, the adverse events for Naloxone Hydrochloride(G) in 2020 and 2021 accounted for 32.23% of the total ADE cases reported for the years 1968-2021. We found a significant 259% increase in ADEs from 2019 to 2020, and a 221% increase in ADEs from 2019 to 2021 (Fig. 2). A paired T-test comparing ADEs for 2019 versus 2020 yielded a p-value  $< 0.001$ , and a paired T-test comparing ADEs for 2019 vs 2021 yielded a p-value  $< 0.0002$ , indicating statistical significance. When sorting the data according to the reactions reported, we found the most common adverse reactions were “drug withdrawal syndrome,” “overdose,” and “drug ineffective,” which were 24.48% of the cases when added together. Additionally, “drug dependence” was 5.67% of the total reported ADEs. When sorting the data according to age groups, we found the 18-64 year old group reported 38.77% of the ADEs, the most out of all age groups. However, 44.22% of the reports did not have a specific age.

For the prescription opioid Oxycodone(G), we found 4,523 cases were reported in 2020 and 6,553 cases were reported in 2021. When adding the cases for 2020 and 2021, we found 40.6% of the total cases for 1968-2021 happened during the

pandemic years of 2020 and 2021. Comparing the pandemic data with 2019, we found a 77% spike from 2019 to 2020 and a 157% increase from 2019 to 2021 (Fig. 3). To ensure this was not a pre-existing trend, we looked at the increase in ADEs from 2018 to 2019, and from 2017 to 2018. Based on the data, there was only a 19.47% increase in ADEs from 2018 to 2019, and a 38.9% increase from 2017 to 2018. While the pre-pandemic data demonstrate an increase in ADEs, the trend was not nearly the magnitude of that from 2019 to 2020, and from 2019 to 2021, suggesting that the pandemic greatly accelerated the increase in ADEs. We also performed paired t-tests for Oxycodone(G), finding a p-value < 0.006 when comparing 2019 to 2020, and a p-value < 0.05 when comparing 2019 to 2021. Therefore, the trend was statistically significant. When examining the type of reaction, we found the most commonly reported ADEs were “drug dependence,” “drug abuse,” “toxicity to various agents,” and “overdose,” which added up to 58.13% of the total cases. We also found 50.94% of the cases were reported from the 18-64 year old age group; however, 35.61% of the reports did not specify age.

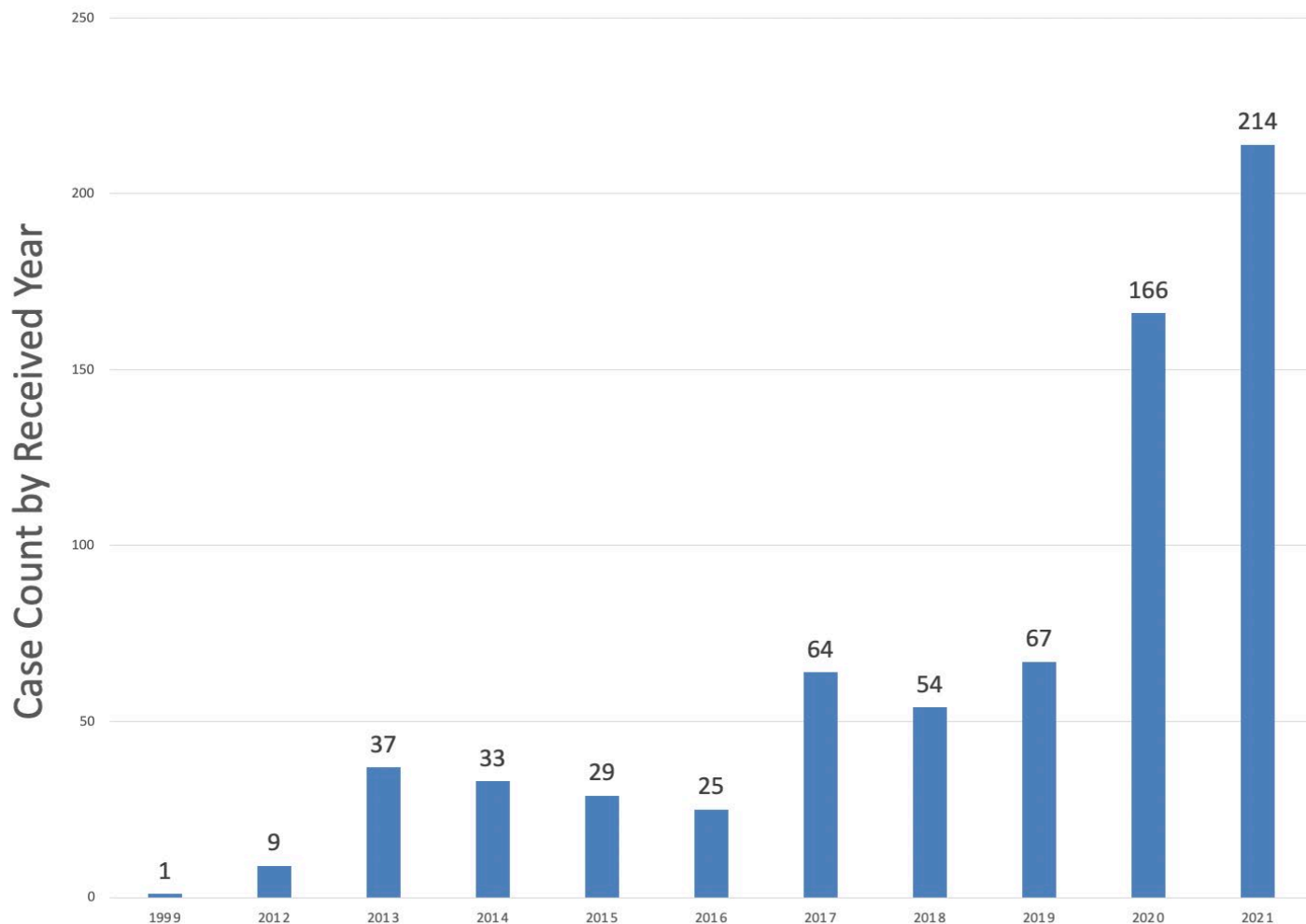


Fig. 1: Yearly number of reported adverse events attributed to Naloxone(G) in the FAERS database

For the prescription opioid Oxycodone Hydrochloride(G), we found 21,530 reports of adverse events in 2020 and 57,293 reports of adverse events in 2021. From 2019 to 2020, there was an alarming 434% spike in cases. A paired T-test comparing 2019 versus 2020 yielded a p-value < 0.03, confirming statistical significance. While there was an astounding 1320% increase from 2019 to 2021, the data did not yield a statistically significant result as the p-value > 0.05. As well, there was a spike in cases during 2018, as 2018 accounted for 14.07% more cases than the previous year 2017, and accounted for 14.5% more cases than the next year 2019 (Fig. 4). However, a paired T-test comparing monthly adverse events in 2018 versus 2019 yielded a p-value > 0.05, indicating statistical insignificance. We also observed the type of reactions recorded and found “drug dependence” was the most common adverse reaction, accounting for 49.13% of the

total ADEs reported. Other highly reported reactions included: “overdose,” “drug withdrawal syndrome,” and “drug abuse,” which in total accounted for 45.16% of the total ADEs reported. Finally, the 18-64 year-old group reported the most adverse events. However, 77.04%, a significantly large portion, did not specify their age.

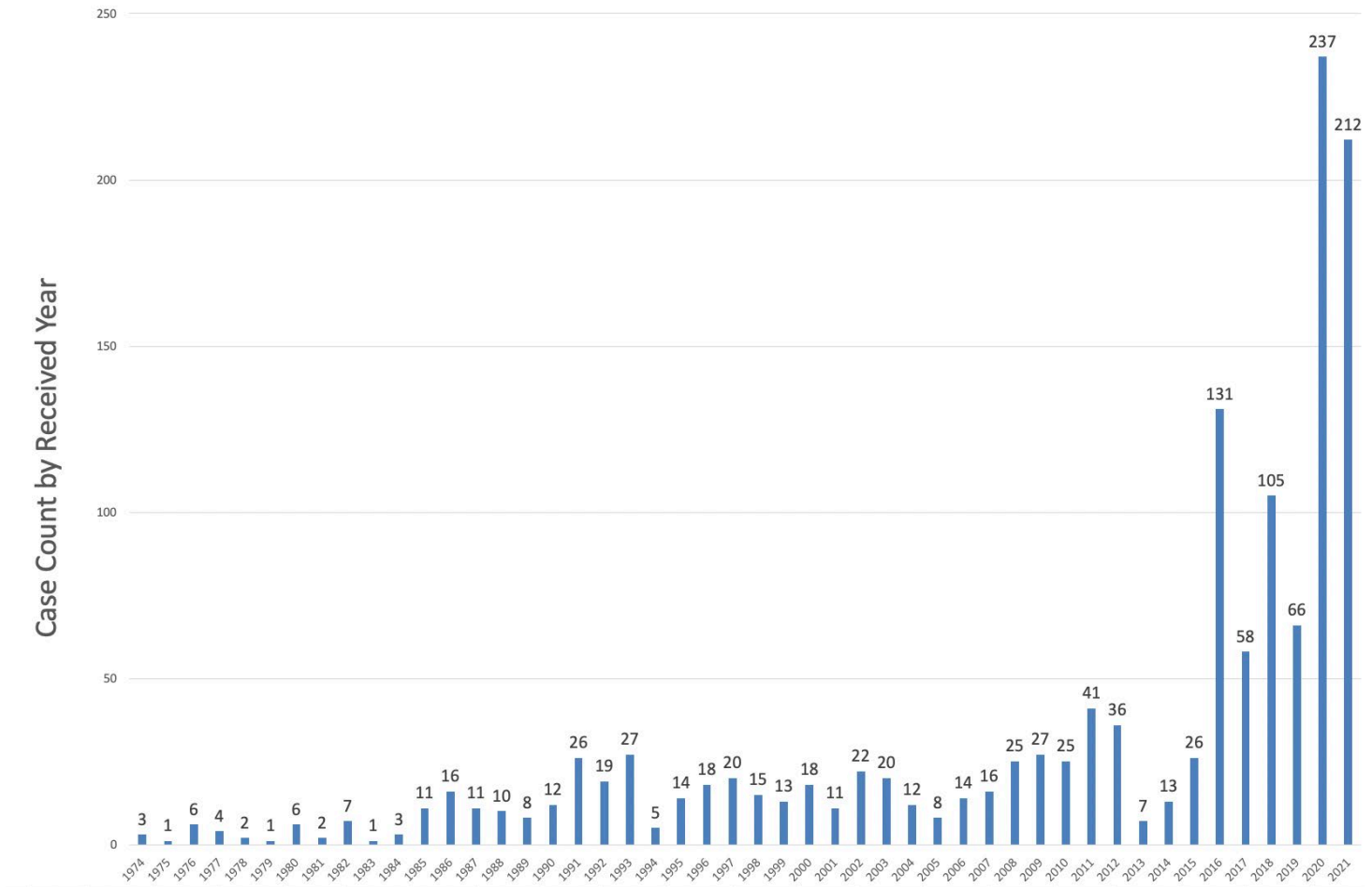


Fig. 2: Yearly number of reported adverse events attributed to Naloxone Hydrochloride(G) in the FAERS database

For the prescription opioid Oxycontin(P), we found 16,895 reports of adverse events in 2020; in 2021, there were a significantly high 48,670 reports of adverse events. From 2019 to 2020, there was a shocking 1,239.8% increase in cases; in other words, there were more than thirteen-fold the number of cases in 2020 than in 2019. Using a paired T-test comparing 2019 versus 2020, a p-value <0.02 was yielded, suggesting statistical significance. While from 2019 to 2021 there was a 3,759.63% increase in ADEs reported, the data did not yield a statistically significant result as the p-value > 0.05. Similar to the results gathered from Oxycodone Hydrochloride(G), there was a significant spike in ADEs reported during 2018. Of all cases reported over the time period 1968-2021, 19.28% of the cases occurred during 2018 alone, which was around 5% more than the number of cases that happened during 2020 (Fig. 5). However, a paired T-test comparing monthly adverse events in 2018 versus 2019 yielded a p-value > 0.05, suggesting statistical insignificance. Observing the types of reaction recorded, the most commonly reported adverse reaction was “drug dependence” and “overdose,” which accounted for 83.46% of the total ADEs reported. Like with all other medications analyzed, the 18-64 year old age group reported the most cases; however, 84.19% of the reporters did not specify their age.

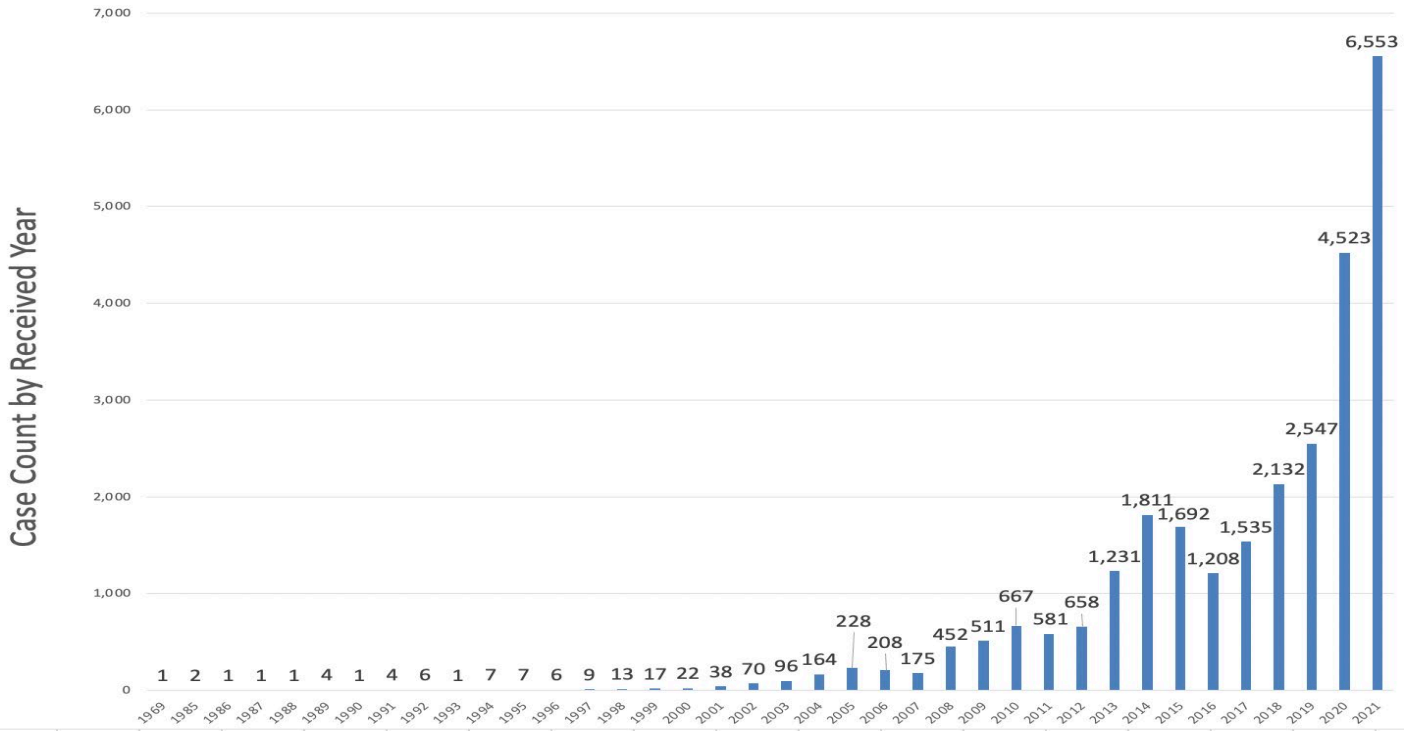


Fig. 3: Yearly number of reported adverse events attributed to Oxycodone(G) in the FAERS database

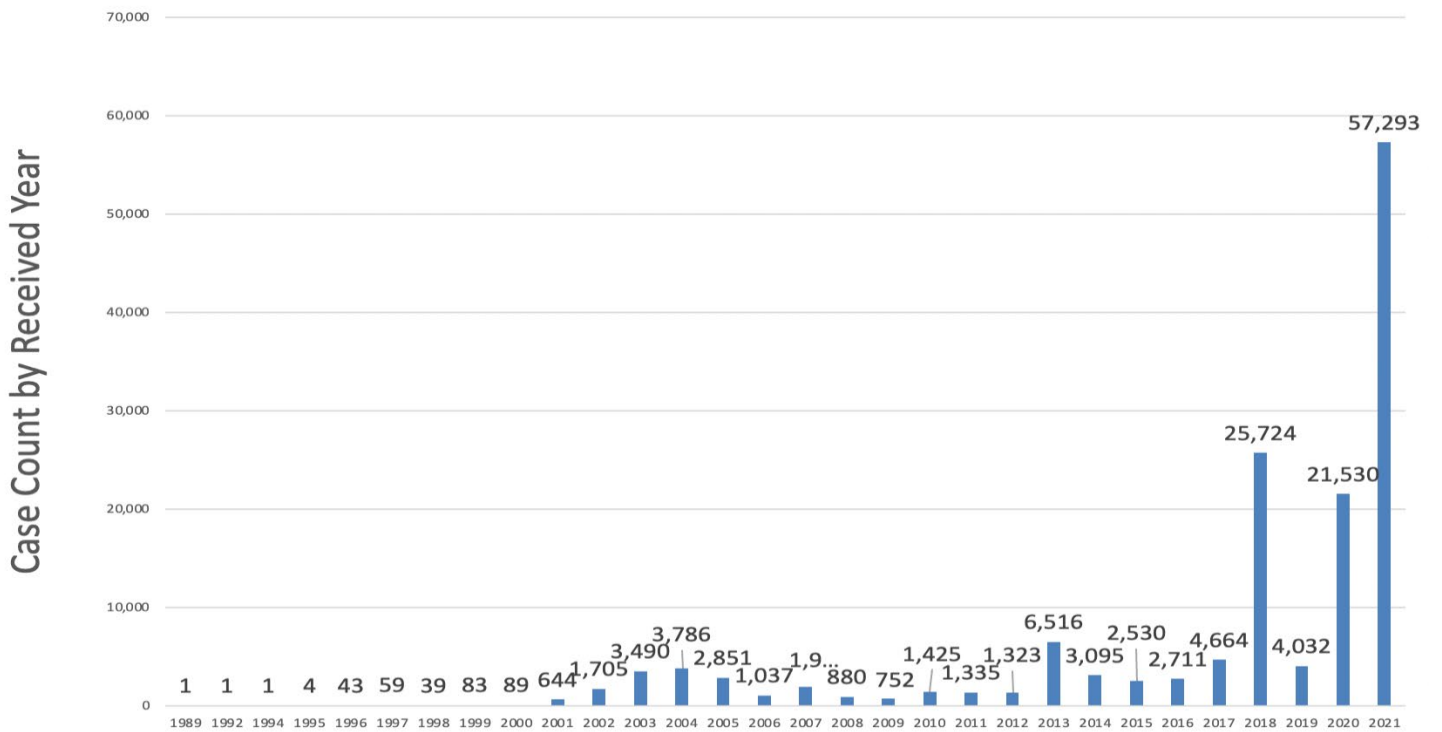


Fig. 4: Yearly number of reported adverse events attributed to Oxycodone Hydrochloride(G) in the FAERS database

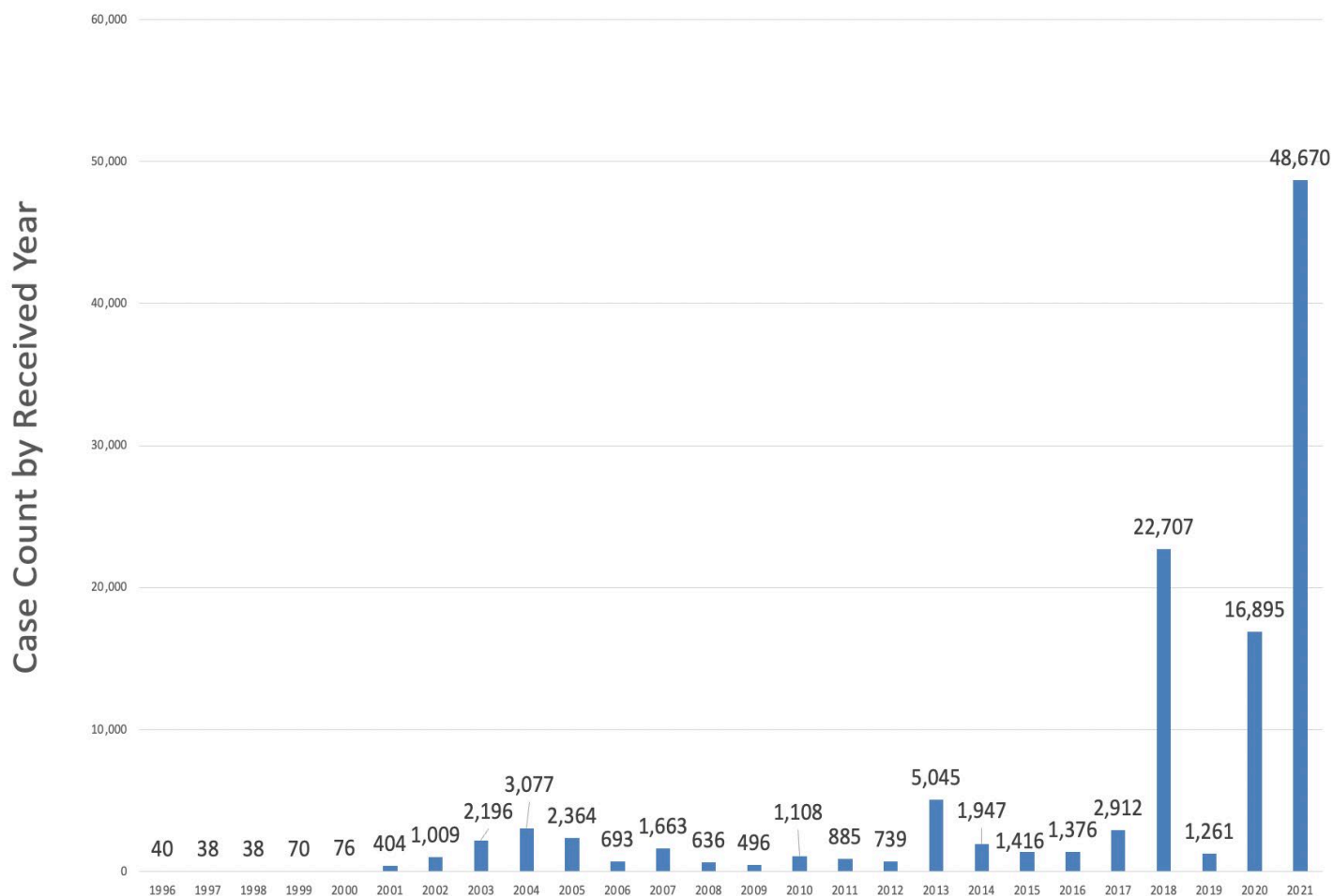


Fig. 5: Yearly number of reported adverse events attributed to Oxycontin(P) in the FAERS database

#### 4. Conclusion:

In summary, our analysis of the FAERS database reveals an alarming spike in ADEs related to naloxone, oxycodone, and oxycontin as a result of the COVID-19 pandemic. In our results, we also found the most reported reactions were “overdose,” “drug dependence,” “drug withdrawal syndrome,” “drug ineffective,” and “drug abuse.” The 18-64 year old age group reported adverse events most frequently, however, many reporters did not specify their age.

There are several explanations for the increase in reported ADEs for naloxone. One explanation was an increase in drug abuse during the pandemic. The American Psychological Association revealed that there was an 18% increase in overdoses in the early months of the pandemic compared to the amounts during the same months in 2019 [8]. Because naloxone is used to rapidly reverse opioid overdose [9], with adverse events reported to happen 45% of the time based on a Norwegian study [10], an increase in naloxone adverse events likely signifies a higher incidence of opioid overdose and subsequently a higher frequency of naloxone use. Therefore, the pandemic brought about a spike in opioid overdose cases, causing an increase in the use of naloxone and the adverse events from the naloxone product. The data from the American Psychological Association helps support the claim there was an increase in opioid overdoses during the pandemic. Another explanation is naloxone became more available/used during the past two years; however, an increase in naloxone availability is unlikely to account for the entire increase in naloxone adverse events. A third explanation is that there is increased awareness about the FAERS database during the pandemic, which leads to a larger number of reports; however,

when examining the reports from 2019 to 2020 for all drugs reported in the database, there was only a meager 1.3% increase in reports. Therefore, the reason there was a larger amount of ADEs reported for naloxone during the pandemic was most likely not due to increased awareness about the FAERS database.

The increase in ADEs for oxycodone/oxycontin suggests an increase in the abuse of prescription opioids. There are several explanations for the increase in the use of prescription opioids. One explanation is the effects the COVID-19 pandemic has on decisions, including larger drug use. According to William Stoops, a professor at the University of Kentucky, due to isolation at home during the pandemic, people have made more unhealthy decisions [8]. One of these decisions includes using opioids more frequently, causing the use of prescription opioids to increase. Another explanation is increased awareness of the FAERS database during the pandemic. However, considering the 1.3% increase in reports for all drugs in the database from 2019 to 2020, the increase in ADEs for oxycodone/oxycontin due to this reason is unlikely.

The large increase in ADEs for oxycodone/oxycontin, which suggests an increase in abuse of prescription opioids, is extremely alarming. According to an American study, when comparing the amounts of overdoses attributed to opioids 12 months before September 2019 and 12 months before September 2020, there was a 33.9% increase in reported overdoses from months before September 2019 to months before September 2020. The increase was heavily attributed to fentanyl and other synthetic opioids, which were found to have a 53.1% increase in overdoses from 12 months before September 2019 to 12 months before September 2020 [11]. Data from the CDC also suggests the increase was heavily attributed to synthetic opioids, with the spike of all opioids deaths and synthetic opioid deaths being mostly the same [12]. However, according to the FAERS database, there was a 78.45% spike in ADEs attributed to Oxycodone(G), which suggests a high increase in the use of prescription opioids during the pandemic. Considering the large spike in ADEs for oxycodone and oxycontin, it is clear the use of prescription opioids is still an ongoing problem, which currently is overshadowed by the accelerated usage of fentanyl during recent years. Since 2012, there has been a decline in prescriptions of opioids, with 2020 being the least prescriptions given in the past 17 years [13]. Despite fewer prescriptions, the use of prescription opioids has still gone up alarmingly, which is concerning as there is still heavy use of prescription opioids despite attempts to alleviate the use of them. According to a study conducted by the CDC from 2008 to 2011, 64% of prescription opioids are attained by family, friends, or drug dealers [14]. Considering the decline in prescriptions but increase in instances of overdose, people are more frequently getting prescription opioids in ways that are not from prescription, which raises concern as there is less attention towards prescription opioids and more towards synthetic opioids despite it being an ongoing and alarming problem.

The reported increase in ADEs for naloxone and prescription opioids, suggesting higher drug abuse during the pandemic, runs parallel to the declining life expectancy of the US in recent years. The life expectancy in the US declined 1.5 years from 2019 to 2020, which was the largest drop since World War 2 [15]. The drop in life expectancy was due to a multitude of reasons, primarily due to the rise of COVID-19. However, also drug abuse influenced the decrease in life expectancy, as there has been a decrease in life expectancy since 2015 [16]. Considering the drop in life expectancy due to opioid overdose, clearly the opioid epidemic has had severe consequences, specifically considering the high increase in adverse events related to opioids during the pandemic. This report provides an overview of the impact the COVID-19 pandemic has had on adverse events and the use of opioids, specifically revealing alarming numbers related to prescription opioids. Going forward, it is essential that prescription opioids and other opioids are monitored more strongly so the opioid epidemic does not continue to get worse and lead to more deaths.

## References

- [1] "One-third of Americans have received an opioid prescription in the past two years," *NORC at the University of Chicago*, 27-Sep-2018. [Online]. Available: <https://www.norc.org/NewsEventsPublications/PressReleases/Pages/one-third-of-americans-have-received-an-opioid-prescription-in-the-past-two-years.aspx>.
- [2] "Opioid basics," *Centers for Disease Control and Prevention*, 16-Mar-2021. [Online]. Available: [https://www.cdc.gov/opioids/basics/index.html#:~:text=Opioids%20are%20a%20class%20of%20drugs%20used%20to%20reduce%20pain.&text=Prescription%20opioids%20can%20be%20prescribed,\)%2C%20morphine%2C%20and%20methadone.](https://www.cdc.gov/opioids/basics/index.html#:~:text=Opioids%20are%20a%20class%20of%20drugs%20used%20to%20reduce%20pain.&text=Prescription%20opioids%20can%20be%20prescribed,)%2C%20morphine%2C%20and%20methadone.)
- [3] "Prescription opioids," *Centers for Disease Control and Prevention*, 29-Aug-2017. [Online]. Available: <https://www.cdc.gov/opioids/basics/prescribed.html>. [Accessed: 09-Apr-2022]. "Population estimates by age, sex, race and Hispanic origin," *Census.gov*, 08-Oct-2021. [Online]. Available: <https://www.census.gov/newsroom/press-kits/2018/estimates-characteristics.html>.

- [4] “Population estimates by age, sex, race and Hispanic origin,” *Census.gov*, 08-Oct-2021. [Online]. Available: <https://www.census.gov/newsroom/press-kits/2018/estimates-characteristics.html>.
- [5] J. C. Baumgartner and D. C. Radley, “The drug overdose toll in 2020 and near-term actions for addressing it,” *Commonwealth Fund*, 16-Aug-2021. [Online]. Available: <https://www.commonwealthfund.org/blog/2021/drug-overdose-toll-2020-and-near-term-actions-addressing-it#dataandmethods>.
- [6] “Understanding the opioid overdose epidemic,” *Centers for Disease Control and Prevention*, 17-Mar-2021. [Online]. Available: <https://www.cdc.gov/opioids/basics/epidemic.html>.
- [7] “FDA Adverse Event Reporting System (FAERS) public dashboard,” *U.S. Food and Drug Administration*. [Online]. Available: <https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard>.
- [8] A. Abramson, “Substance use during the pandemic,” *Monitor on Psychology*, 01-Mar-2021. [Online]. Available: <https://www.apa.org/monitor/2021/03/substance-use-pandemic>.
- [9] “Naloxone,” *SAMHSA*. [Online]. Available: <https://www.samhsa.gov/medication-assisted-treatment/medications-counseling-related-conditions/naloxone#:~:text=Naloxone%20is%20a%20medication%20approved,heroin%2C%20morphine%2C%20and%20oxycodone>.
- [10] I. Buajordet, A.-C. Næss, D. Jacobsen, and O. Brørs, “Adverse events after naloxone treatment of episodes of suspected acute opioid overdose,” *European Journal of Emergency Medicine*, vol. 11, no. 1, pp. 19–23, Feb. 2004.
- [11] D. Ciccarone, “The rise of illicit FENTANYLS, stimulants and the fourth wave of the opioid overdose crisis,” *Current Opinion in Psychiatry*, vol. 34, no. 4, pp. 344–350, Jul. 2021.
- [12] J. C. Baumgartner and D. C. Radley, “The spike in drug overdose deaths during the COVID-19 pandemic and policy options to move forward,” *Commonwealth Fund*, 25-Mar-2021. [Online]. Available: <https://www.commonwealthfund.org/blog/2021/spike-drug-overdose-deaths-during-covid-19-pandemic-and-policy-options-move-forward>.
- [13] “U.S. opioid dispensing rate maps,” *Centers for Disease Control and Prevention*, 10-Nov-2021. [Online]. Available: <https://www.cdc.gov/drugoverdose/rxrate-maps/index.html>.
- [14] “Physicians are a leading source of prescription opioids for the highest-risk users,” *Centers for Disease Control and Prevention*, 10-Apr-2014. [Online]. Available: <https://www.cdc.gov/media/releases/2014/p0303-prescription-opioids.html>.
- [15] “Life expectancy in the U.S. declined a year and half in 2020,” *Centers for Disease Control and Prevention*, 21-Jul-2021. [Online]. Available: [https://www.cdc.gov/nchs/pressroom/nchs\\_press\\_releases/2021/202107.htm](https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/202107.htm).
- [16] M. Devitt, “CDC data show U.S. Life Expectancy continues to decline,” *AAFP Home*, 10-Dec-2018. [Online]. Available: <https://www.aafp.org/news/health-of-the-public/20181210lifeexpectdrop.html>.