

Fentanyl and Fentanyl Analogs Detected Among Unintentional Opioid Involved Overdose Deaths in Rhode Island: January 2019–December 2021

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INTRODUCTION

Starting in the fall of 2019, Rhode Island (RI) has experienced a significant increase in overdose deaths, with 435 lives lost to unintentional overdoses in RI in 2021.¹ Fentanyl, a highly potent synthetic opioid, continues to drive the overdose epidemic in RI and contributed to over 77% of overdose deaths in 2021. These deaths also include those attributable to fentanyl analogs, which are chemically synthesized fentanyl derivatives, which act on the opioid receptor to produce similar analgesic effects but vary in their individual potency. Some fentanyl analogs (e.g., sufentanil) are approved pharmaceuticals; however, an evolving and expanding list of fentanyl analogs without known medical use (e.g., acetylfentanyl, furanylfentanyl) have been detected in the drug supply in Rhode Island and nationally.² Data on pharmacokinetic and pharmacodynamic properties of fentanyl analogs in humans is limited and much of the available data is derived from animal models and invitro study limiting our knowledge on the safety of these substances.

Fentanyl and fentanyl analogs were first detected in RI in 2013. Due to notable increases in overdose deaths caused by fentanyl and fentanyl analogs they have been a concern in RI for many years.^{3,4} Over time, other potent fentanyl analogs, such as carfentanil, have been detected in RI and neighboring states.⁵ To better address the overdose epidemic, this work aims to better understand the role of fentanyl and fentanyl analogs among unintentional opioid-involved deaths in RI and how the presence of fentanyl analogs has changed over time.

METHODS

We used RI's State Unintentional Drug Overdose Reporting System (SUDORS) to identify opioid overdose deaths that were unintentional or undetermined in intent, and occurred in Rhode Island from January 1, 2019 to December 31, 2021. SUDORS is a standardized Centers for Disease Control and Prevention (CDC) database that collects overdose deaths from states regardless of state-specific testing protocols. Using toxicological data generated at the RI State Health Laboratories, SUDORS records the substances detected at time of death, as well as those contributing to the cause of death as determined by the medical examiner, including

information on fentanyl, specific fentanyl analogs, and select metabolites.

Fentanyl analogs that were not detected during this time-frame and analogs that were detected in fewer than 5 deaths (benzylfentanyl, butyrylfentanyl, cyclopropylfentanyl, furanylfentanyl, and valerylfentanyl) were excluded to comply with Rhode Island Department of Health's (RIDOH) Small Numbers Policy.

Our final analysis assessed the detection and contribution of fentanyl and fentanyl analogs by year of death. Fentanyl analogs present in the analysis included acetylfentanyl, carfentanil, and fluorinated analogs (*p*-fluorofentanyl and *p*-flourobutyryl, which are grouped together in SUDORS despite being separate compounds). A flag was created to identify deaths which involved only fentanyl analogs (in the absence of fentanyl), and those for which no fentanyl/fentanyl analogs were involved. Results were also stratified by other substances detected at the time of death. All analyses were performed in SAS [Version 9.4].

FINDINGS

From January 1, 2019 to December 31, 2021, 965 individuals experienced a fatal opioid-involved overdose in Rhode Island. Of these, fentanyl and/or fentanyl analogs contributed to the cause of death in 86% (*n*=834) of deaths (Table 1). During this period, the proportion of unintentional opioid-involved deaths involving fentanyl or fentanyl analogs has increased from 84% to 89%. In only 2% of deaths (*n*=16) did fentanyl analogs contribute to the cause of death in the absence of fentanyl.

When looking at the role of fentanyl and fentanyl analogs over time, the proportion of deaths in which fentanyl was detected increased from 80% in 2019 to 88% in 2021 (Figure 1). The proportion of deaths in which acetylfentanyl was detected remained relatively constant over time, from 6% in 2019 to 8% in 2020 and 2021 (Figure 2). In contrast, the presence of carfentanil has been declining; with carfentanil detected in 5% of opioid-involved overdose deaths in 2019, 2% of deaths in 2020, and fewer than 1% of deaths in 2021. Deaths in which *p*-fluorofentanyl analogs were detected increased from 0% in 2019, to 1% in 2020, and to 13% in 2021. When looking at the presence of fentanyl

Table 1. Fentanyl and Fentanyl Analogs Detected at Time of Death, Rhode Island, 2019–2021

Substance	N (%)
Acetyl Fentanyl	
Detected	72 (7%)
Cause of Death	44 (5%)
Carfentanil	
Detected	20 (2%)
Cause of Death	20 (2%)
Fentanyl	
Detected	821 (85%)
Cause of Death	818 (85%)
P-Fluorofentanyl	
Detected	52 (5%)
Cause of Death	25 (3%)
Analogs Only (no fentanyl)	
Detected	15 (2%)
Cause of Death	16 (2%)
No Fentanyl or Analogs Present	
Detected	129 (13%)
Cause of Death	131 (14%)
Total Opioid Overdoses	965 (100%)

Source: State Unintentional Drug Overdose Reporting System

Note: Categories are not mutually exclusive. Multiple substances and fentanyl analogs can be detected in the same overdose. For overdoses where no fentanyl or analogs were present, other illicit or prescription opioids were detected or contributed to the cause of death.

analogs with other substances detected at the time of death (such as stimulants, central nervous system depressants, alcohol, and cannabis) no fentanyl analogs appeared to be solely associated with a particular co-exposure.

DISCUSSION

Our findings reaffirm the steadily growing prevalence and danger of fentanyl as it contributes to overdose deaths in Rhode Island. Fentanyl was detected and contributory to the cause of death in the majority of opioid-involved unintentional overdose deaths during the study period. Despite the growing concern of fentanyl analogs present in the drug supply, the results from this analysis indicate that most fentanyl analogs captured by SUDORS were either not detected, were found in fewer than 5 overdoses, or, if present, co-occur in the presence of fentanyl. Using all opioid overdose involved deaths occurring between 2019 and 2021, only 2% of deaths were attributed to fentanyl analogs in the absence of fentanyl. These results are promising for interventions such as fentanyl tests strips which rely on the presence of fentanyl and/or specific analogs to return a positive result.

Figure 1. Proportion of Unintentional Opioid Overdose Deaths Where Fentanyl Was Detected, Rhode Island, 2019–2021

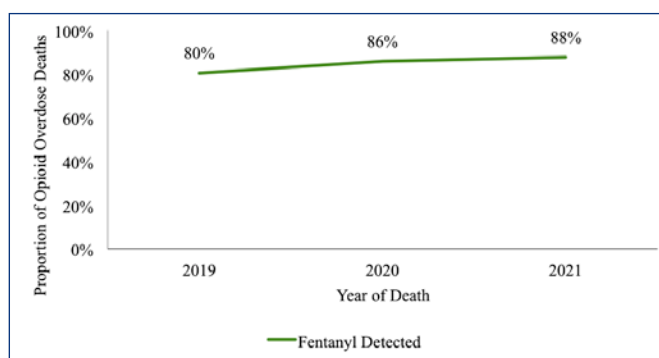
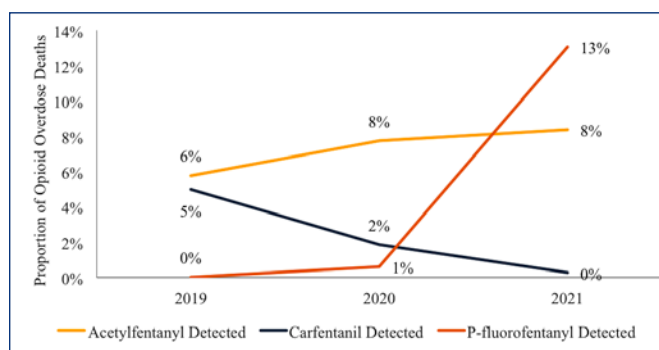


Figure 2. Proportion of Unintentional Opioid Overdose Deaths Where Fentanyl Analogs Were Detected, Rhode Island 2019–2021



While carfentanil was of concern locally due to having a potency ten thousand times that of morphine,⁶ it is encouraging to see its sharp decline in RI since 2019 as it was detected in fewer than 5 opioid-involved overdose deaths in 2021. Acetyl fentanyl and *p*-fluorofentanyl, while increasing in prevalence, are more often detected among overdoses and in combination with fentanyl, rather than contributing to death according to medical examiner assessment. These findings align with trends observed among non-fatal overdoses in Rhode Island, as *p*-fluorofentanyl was first detected in non-fatal toxicology data starting in November 2020 and continued to appear in samples throughout 2021.⁷ Similarly, acetyl fentanyl was detected in an average of 4% of non-fatal overdoses during a similar timeframe.⁷

Other studies have found that drug classes, such as stimulants, have been found to be increasingly contaminated with fentanyl over time⁸; contributing to the growing burden of polysubstance overdose deaths.⁹ This should be taken into consideration when promoting harm reduction practices, as individuals may be hesitant to utilize tools such as fentanyl test strips or naloxone in situations where they intend to use substances other than opioids or in combination with opioids. This concern is further supported by local data from

testRI, which has detected fentanyl in substances that were sold as non-opioids, including crystal meth, crack cocaine, and powder cocaine.¹⁰

This study is subject to several limitations. First, a standard analysis for fentanyl analog confirmation among overdose deaths did not exist prior to June of 2021. Samples from suspected opioid overdoses that screened positive for fentanyl and were confirmed by tandem mass spectrometry were not required to be analyzed for fentanyl analogs. Testing for analogs was only performed for overdose deaths in which fentanyl was indicated by ELISA but undetected through confirmatory analysis. As such, the presence of fentanyl analogs in overdose deaths is likely higher than reported; however, due to the testing protocol, the proportion of deaths in which fentanyl analogs contributed to the cause of death in the absence of fentanyl is as reported. Second, new fentanyl analogs appear in the drug supply more quickly than the test panel can be updated. There are likely analogs that were missed due to a lag in updating the test panel. Third, SUDORS does not contain information on all fentanyl metabolites (including norfentanyl) so it is possible the true proportion of deaths where fentanyl was present is higher than shown.

Further studies are planned that utilize data from SUDORS to better understand the role of fentanyl and/or fentanyl analogs with polysubstance use and describe the presence of other substances detected and contributing to the cause of death. Additional work is also planned to utilize results from RI's biosurveillance system to compare toxicology data obtained from non-fatal opioid overdoses to the fatal opioid overdoses reported by SUDORS.

The findings from this work reaffirm the steadily growing prevalence and danger of fentanyl in RI, with over 89% of opioid overdose deaths in 2021 involving fentanyl and/or fentanyl analogs. These results emphasize the need to continue promoting harm reduction practices through efforts such as naloxone distribution and training, dissemination of fentanyl test strips, and continued education on the role of fentanyl in the drug supply, as well as more innovative approaches such as establishing harm reduction centers in the state.

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