

# When Fentanyl Finds an Outlier: Talking With Teenagers About the Danger

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In the United States from 2013 to 2019, the nonmethadone synthetic opioid-involved death rate increased 1040%, from 1.0 to 11.4 per 100 000 (age adjusted), with 51.5% of all 2019 drug overdose deaths linked to synthetic opioids such as fentanyl.<sup>1</sup> Opioid-involved poisoning deaths overall contributed a loss of 0.21 years in life expectancy from 2000 to 2015<sup>2</sup> and undoubtedly contributed to the 2- to 3.5-fold increase in excess mortality in American teenagers and young adults from 2000 to 2017.<sup>3</sup> Emerging data during the coronavirus disease 2019 pandemic suggest further worsening of the opioid crisis.<sup>4</sup>

Medical uses of opioids have come under increased scrutiny among physicians; anesthesiologists in particular have sought to minimize their administration.<sup>5</sup> Nonetheless, opioids in limited amount and over limited duration have benefitted countless patients. Fentanyl requirements are variable and depend on procedure and individual patient sensitivity, the latter a consequence of interacting environmental and genetic factors that set different pain thresholds and alter fentanyl pharmacokinetics and pharmacodynamics. The variability in fentanyl pharmacokinetics is well established,<sup>6,7</sup> but genetic associations gauging fentanyl response sensitivity are only in initial discovery stages and are focused largely on analgesic phenotypes.<sup>8,9</sup>

Central to our story, opioid response phenotypes of respiratory depression and airway compromise are multifactorial, uncommon in children, and most certainly underreported.<sup>10</sup> Fentanyl may be especially dangerous because of its potency, rate of onset, and other ligand-specific factors.<sup>11</sup> Although low-dose intraoperative fentanyl has been associated with lower odds of postoperative respiratory complications than a high dose or none altogether,<sup>12</sup> as little as 0.5  $\mu\text{g}/\text{kg}$  intravenous fentanyl has been associated with respiratory arrest.<sup>13</sup> Secondary drug exposure and comorbidities such as obstructive sleep apnea may exaggerate respiratory sensitivity to fentanyl.<sup>10,13,14</sup> Novel quantitative trait loci have been associated with morphine-induced respiratory depression in mice,<sup>15</sup> but pharmacogenetic understanding of fentanyl-induced respiratory depression and overdose death in humans is limited.<sup>16,17</sup>

With this article, we offer 4 recollections of the experience of a 17-year-old male patient who had no history of drug use or obstructive sleep apnea but who displayed heightened sensitivity to fentanyl after a routine medical procedure. These overlapping perspectives strive to convey the lived experience of opioid-induced respiratory depression and its life-threatening potential outside of medical supervision. Clinicians must be

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vigilant in identifying opioid outliers, namely, those who may be at high risk for abuse, addiction, respiratory compromise, and death, taking every opportunity to educate and prevent such events.

### FROM DR SCOTT TO VINCENT

As a healthy high school senior, you came to our ambulatory surgery center for a short procedure. As your anesthesiologist, I listened as you told me and the operating room nurses about your plans for college next year. Calmly breathing the anesthesia gases, you slid easily into unconsciousness. The procedure was uneventful until, with the procedural stimulus gone, your breathing became slow and shallow, and then obstructed. I opened your airway with a jaw thrust and supported your breathing using my anesthesia mask and bag. Your oxygenation, which had begun to drift downward, immediately returned to normal. We brought you to the postanesthesia care unit (PACU), where you remained safe, but for a full 10 minutes, nurse Ellie and I continued intermittent jaw thrust, mask ventilation, and supplemental oxygen administration. Then, as expected, you stirred and breathed easily on your own.

As I left to care for my next patient, I asked nurse Ellie to keep you in the PACU until I could return. When I did so 30 minutes later, you had recovered and were smiling. You offered that you did not have a sore throat or nausea, which are risks I had mentioned preoperatively and that you remembered. I explained that you had received several sedative and anesthetic medications, including a small dose of intravenous fentanyl, ~0.5 µg/kg, which contributed to your need for additional respiratory support. Lingering nitrous oxide, sevoflurane, and propofol may have contributed, but the main culprit was fentanyl. Your reaction suggested that you are unusually sensitive to its respiratory depressive

effects, that you are an outlier on the bell curve distribution of responders.

I wanted to be certain that you understood the significant dangers of fentanyl because the drug as it is available outside of hospital settings is not pharmaceutical grade nor is it carefully measured or administered by experts with safety protocols in place. It is illicitly manufactured versions of unknown purity, potency, and quantity, offered in unsafe settings, often along with other sedative substances that can work in dangerous synergy. Overdose death is a tragic end and can happen to anyone, so everyone must be on guard and avoid opioid misuse. An outlier could easily die after a curious first try.

I explained to you that someday we will offer comprehensive genetic tests before surgeries and procedures like yours to develop precision anesthesia regimens for optimal patient safety and comfort. During your procedure, without such testing, I watched in real time as your fentanyl sensitivity revealed itself. I glimpsed your future vulnerability. I said that I hoped our conversation became an effective “vaccine” for you amid the opioid epidemic, that other public health crisis currently overshadowed by coronavirus disease 2019.

### FROM NURSE ELLIE TO VINCENT

As your PACU nurse, I was the first face you saw when you woke up. Dr Scott had brought you to the PACU and was assisting your breathing. When he handed off your care to me, we ensured that I could keep your airway open. Before he left, your airway tone had returned and you were breathing well without our help.

As you awakened and became more talkative, I learned that you would soon head off to college. Your dad was sitting by your side, watching carefully as you

recovered and got ready to go home. When Dr Scott gave his straightforward account of what occurred, I thought about the implications for you and all young people leaving home. You said, “That was the best ‘don’t do drugs’ lecture” you ever heard, and I agreed with you, because the talk was connected to your own experience, not just an abstract lecture.

I have my own experience to draw on, so I know. I chose to tell you that my son suffers from the disease of addiction, although not to opioids, because I wanted you to understand that the sensitivity lesson you learned about yourself applies to all substances of abuse. My son has now been clean and sober for 15 years. I was candid with you about his experience with addiction because it is prevalent in too many homes and in too many neighborhoods. It does not discriminate. By sharing my family story, and in being a part of your story, I hoped that you and others might find reason to turn away from drugs.

### FROM VINCENT TO ANYONE READING THIS

During the drive to the surgery center with my dad, I was calm. My parents had told me what to expect. I looked forward to stopping at my favorite restaurant afterward to get something to eat. We checked in and then went to the preoperative room where a nurse asked us questions and told us what to expect. I didn’t need any calming medication. Dr Scott arrived and explained the anesthesia.

Going into the operating room, I felt fine. The anesthesia mask was on my face and the last thing I remember was a question about which sports I play. I slept through everything. Next thing I knew, I woke up with nurse Ellie alongside my bed and my dad walking into the room. Slowly, I became more alert and heard what they were saying. Nurse Ellie said I am sensitive to anesthesia. When Dr Scott returned

and explained what happened, I was shaken. He told me that my airway partially collapsed after the procedure and he had to hold up my jaw so I could breathe. I learned the anesthesia included a small dose of fentanyl. Dr Scott explained that if such a small dose of this opioid could slow my breathing dramatically and collapse my airway, what would something like heroin do to me? I learned that whereas many people are not harmed by small doses of opioids, I am different. If I have just a little of these drugs, I could die. Knowing this frightened me, especially because I will go away to college soon. If I ever experiment with drugs on purpose or accidentally, I could have a major problem. Without saying it word for word, Dr Scott warned me to stay away from all opioids and never to experiment with them because I could die quickly. I felt afraid hearing this, but I began to think about everything I could do to stay safe. It was important for me to hear this right after I survived an encounter with fentanyl. Without a doubt, that was the best “say no to drugs” warning I ever received!

### FROM DAD TO VINCENT

On our way to the hospital, I told you, yours was going to be a routine, “piece of cake” procedure. Honestly, I was thinking more about your and your siblings’ college tuitions than anything else. Shortly after our arrival, the admitting nurse prepared you and told us the procedure would take ~20 minutes. Dr Scott came in and reviewed the anesthesia plan. Away you went to the operating room. I thought to myself, “This will be an easy, uneventful day.”

You were waking up as I entered the recovery room. Nurse Ellie mentioned that you have a low tolerance for anesthesia and warned that you need to be careful when you go away to college. That got my attention. “Dr Scott wants to talk with both of you before you go,” she said. “Hmmm ... what is this about?” I wondered.

Dr Scott told us he would have felt remiss if he did not discuss the morning’s events in detail. He explained that you received, among other anesthetic drugs, a small dose of fentanyl. You were extremely sensitive to it. Your breathing rate slowed and your airway began to have issues. This was not a major concern while you were being closely monitored and treated by professionals in a medical setting, he explained. The issue, however, is if you were not in such a setting. I knew what Dr Scott was getting at: if you even try an opioid one time, your risk of death is real. I could tell that you were surprised. I was probably more in shock.

I’ll tell you why. Over my last few years with the Pennsylvania State Police, I’ve mainly investigated human trafficking cases. The victims, often young women, are targeted because of their histories of addiction to opioids, like fentanyl and heroin. Many have told us that traffickers would supply them with opioids and assault them when they no longer wanted to have sex for money. One woman told my partner and me that she still shot Kensington-procured fentanyl into her neck every day. Every day! Many times, I thought how thankful I was that my 3 children were insulated from that dangerous world. But, of course, none of us are completely insulated from it. Vincent, you learned that day of your procedure that you must be more careful than most.

Having researched opioids for many years, Dr Scott has a special interest in individual variability. Opioids are associated with real and profound dangers for everyone and for some people in particular. Their abuse causes sadness for many, as nurse Ellie attested. In my work as a police officer, I have dealt with too many victims suffering the horrors of addiction. And you, Vincent, with

your newly understood opioid sensitivity, have an undeniable grasp of your vulnerability. Together, we need to share our cautionary tale and keep finding ways to talk to teenagers, outliers or not, about the dangers of fentanyl and opioids overall.

In 2020, there were 1214 overdose deaths in the City of Philadelphia, just 3 fewer fatalities than the most such cases recorded in any previous year.<sup>18</sup> Fentanyl was present in 84%.

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### ABBREVIATION

PACU: postanesthesia care unit

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