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## Case 37-2017: A 36-Year-Old Man with Unintentional Opioid Overdose

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### PRESENTATION OF CASE

*Dr. Alister M. Martin (Emergency Medicine):* A 36-year-old man with opioid-use disorder was seen in the emergency department of this hospital during the winter because of opioid overdose.

Approximately 4 years before this evaluation, the patient had undergone an unspecified hand surgery. Immediately after the procedure, hydromorphone was administered. After the patient was discharged home, he initially sought out more prescription opioids and then switched to intravenous heroin because he found it to be less expensive and more easily obtained. During the next 3 years, he injected 1 to 2 g of heroin each day.

One year before this evaluation, after the patient lost his job, he attempted to quit using heroin. He began to take methadone, which helped to reduce withdrawal symptoms and cravings, but he stopped taking it after 10 days because he was concerned that weaning off methadone after a period of maintenance treatment would be associated with unacceptable adverse effects. He then resumed heroin use. Six months before this evaluation, the patient again stopped using heroin and was admitted to an inpatient, medically supervised detoxification program for management of withdrawal symptoms. After 2 weeks, he was discharged home.

Approximately 2 months before this evaluation, the patient was released from jail and was admitted to a structured residential rehabilitation program, in which he participated in work therapy, attended regular Narcotics Anonymous meetings, and underwent random, intermittent urine toxicology screenings. He continued in this program and abstained from opioid use until 3 days before this evaluation, when he resumed intravenous heroin use. He obtained the drug, which he believed to be mixed with fentanyl, from a single dealer and began to inject 0.5 g at a time using clean needles and cotton filters. On the day of this evaluation, the patient injected 0.5 g at 10 a.m., followed by another 0.5 g at approximately 1:30 p.m.; he remembered subsequently walking around a park and placing a phone call to a friend to arrange a meeting.

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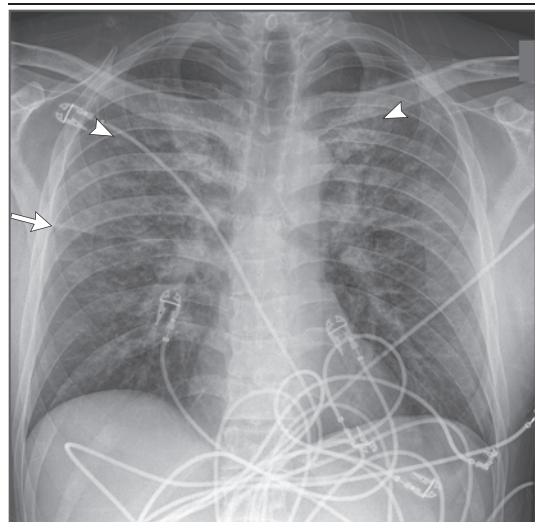
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At 2:44 p.m. on the day of this evaluation, emergency medical services personnel were dispatched to the park, where the patient was found lying on the ground in a puddle of slush. He was unresponsive. The patient's friend was present and reported that when he had found the patient, he had administered intranasal naloxone and then called for emergency medical assistance. First responders from the fire department had administered a second dose of intranasal naloxone before emergency medical services personnel arrived. On examination, the patient appeared cyanotic, and he had a Glasgow Coma Scale score of 3 (on a scale ranging from 3 to 15, with lower scores indicating lower levels of consciousness). The temperature was 35.6°C, the pulse 88 beats per minute, the blood pressure 122/76 mm Hg, the respiratory rate 4 breaths per minute, and the oxygen saturation 80% while he was breathing ambient air. He had pinpoint pupils and shallow breathing. An oropharyngeal airway was placed, and positive-pressure ventilation was initiated with the use of a bag–valve–mask device. The blood glucose level, obtained by fingerstick testing, was 164 mg per deciliter (9.1 mmol per liter; reference range, 70 to 110 mg per deciliter [3.9 to 6.1 mmol per liter]). Several minutes later, the patient woke up, removed the oropharyngeal airway, and was noted to be alert and oriented, with a respiratory rate of 16 breaths per minute. Oxygen was administered through a nasal cannula at a rate of 6 liters per minute, and the patient was transported by ambulance to the emergency department of this hospital.

In the emergency department, the patient reported that the overdose was unintentional, that he had never had an overdose before, that this incident was a “wake-up call,” and that he wanted help with managing his opioid addiction. He had been feeling sad after the recent deaths of his mother and grandmother, and he thought that his relapse in opioid use might have been related to these stressors. He had no history of other medical conditions, took no medications, and had no known allergies. He was a high-school graduate and had worked as an electrician before he became unemployed. He was single and had no children. He had smoked a half-pack of cigarettes daily for the past 4 years and had smoked marijuana when he was younger. He did not drink alcohol or use illicit drugs other than heroin. There was no fam-



**Figure 1. Initial Chest Radiograph.**

A portable anteroposterior radiograph of the chest, obtained at the time of presentation to the emergency department, shows cephalization of the pulmonary vasculature and fluid in the minor fissure (arrow), findings consistent with interstitial pulmonary edema. In addition, there are bilateral faint rediculonodular and patchy airspace opacities (arrowheads), findings that suggest superimposed aspiration.

ily history of depression, bipolar disorder, schizophrenia, dementia, or suicide.

On examination, the patient was alert and fully oriented. His clothes were wet. The temperature was 35.9°C, the pulse 84 beats per minute, the blood pressure 115/69 mm Hg, the respiratory rate 16 breaths per minute, and the oxygen saturation 93% while he was breathing oxygen through a nasal cannula at a rate of 6 liters per minute. The pupils were equal, round, and reactive to light. There were scattered focal crackles in the lungs, and the remainder of the examination was normal. The hemoglobin level, hematocrit, white-cell count, differential count, platelet count, and red-cell indexes were normal, as were blood levels of electrolytes, the anion gap, and results of renal-function tests. The blood glucose level was 165 mg per deciliter (9.2 mmol per liter). Venous blood gas measurements, which were obtained while the patient was breathing oxygen through a nasal cannula at a rate of 6 liters per minute, included a pH of 7.29 (reference range, 7.30 to 7.40), a partial pressure of carbon dioxide of 68 mm Hg (reference range, 38 to 50), a partial pressure of oxygen of less

than 28 mm Hg (reference range, 35 to 50), a bicarbonate level of 32 mmol per liter (reference range, 24 to 30), and a base excess of 2.6 mmol per liter (reference range, 0 to 3.0). An electrocardiogram showed nonspecific ST-segment and T-wave abnormalities and was otherwise normal.

*Dr. Efrén J. Flores:* A portable anteroposterior radiograph of the chest (Fig. 1) revealed cephalization of the pulmonary vasculature and fluid in the minor fissure, findings consistent with interstitial pulmonary edema. There were also bilateral nodular and patchy airspace opacities, findings that suggested superimposed aspiration.

*Dr. Martin:* A diagnosis and management decisions were made.

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#### DIFFERENTIAL DIAGNOSIS

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*Dr. Emily S. Miller:* I am aware of the diagnosis in this case. Although the patient's mental status normalized after treatment with naloxone, he remained hypoxemic and had crackles in the lungs. One plausible cause of these clinical findings is aspiration pneumonitis, which is a chemical burn to the bronchial tree that is caused by inhalation of sterile gastric contents.<sup>1</sup> The patient had recently been unresponsive, with a Glasgow Coma Scale score of 3; during that time, he was unable to protect his airway and was treated with bag-valve-mask ventilation, and he could have aspirated gastric contents. Patients with aspiration pneumonitis typically present with acute dyspnea, crackles, and hypoxemia, although the spectrum of illness ranges from minimal symptoms to life-threatening acute respiratory distress. In contrast, aspiration pneumonia results from inhalation of infectious oropharyngeal secretions and typically has a more indolent course. Patients with aspiration pneumonia present with fatigue, fever, cough, and dyspnea, symptoms similar to those of community-acquired pneumonia. Community-acquired pneumonia is 10 times more likely to occur in people who use intravenous drugs than in people who do not, presumably because drug injection can result in bacteremia and because the rates of tobacco use and human immunodeficiency virus infection are high among people who use injection drugs.<sup>2</sup> Neither aspiration pneumonia nor community-acquired pneumonia was a likely diagnosis in this patient, because he had no reported illness before the overdose.

The findings on radiography were interpreted to be most consistent with pulmonary edema. Taken together, the clinical presentation and imaging findings suggest that the cause of pulmonary disease in this patient was most likely opioid-induced noncardiogenic pulmonary edema.

Noncardiogenic pulmonary edema occurs most commonly in the acute respiratory distress syndrome, although it may arise in numerous clinical situations.<sup>3</sup> Cardiogenic pulmonary edema results from increased pulmonary capillary pressure, whereas the mechanism of noncardiogenic pulmonary edema is thought to be increased permeability of the pulmonary capillary wall. Cardiogenic and noncardiogenic pulmonary edema are associated with similar presentations and may coexist. Clinicians distinguish them on the basis of clinical history; because this patient had a known opioid overdose and did not have risk factors for an acute coronary syndrome, cardiogenic pulmonary edema is an unlikely diagnosis.

The onset of noncardiogenic pulmonary edema after opioid overdose was first described by Osler,<sup>4</sup> and noncardiogenic pulmonary edema occurs as a complication of opioid overdose in approximately 0.8 to 2.4% of cases.<sup>5</sup> It is more frequent in males and in people who have been using heroin for weeks to months, rather than months to years.<sup>5,6</sup> Concurrent cocaine or alcohol use is present in approximately half the patients.<sup>6</sup> The majority of patients who have noncardiogenic pulmonary edema related to opioid overdose have respiratory symptoms immediately after overdose, but the symptoms may be delayed up to 4 hours.<sup>5</sup> Treatment consists of supportive therapy with supplemental oxygen; mechanical ventilation is required in approximately one third of patients.<sup>7</sup> Symptoms resolve within 24 to 48 hours in the majority of patients.<sup>7,8</sup>

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#### DR. EMILY S. MILLER'S DIAGNOSIS

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Opioid-induced noncardiogenic pulmonary edema.

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#### PATHOLOGICAL DISCUSSION

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*Dr. George Eng:* An immunoassay panel that is used to screen for drugs of abuse, including opioids, was performed on a urine sample that had been obtained 16 hours after the patient presented to the emergency department. The immunoassay is

performed on urine, as opposed to blood, because drug metabolites can accumulate in the urine, enhancing the sensitivity of the assay. The urine was negative for the drugs of abuse. The urine creatinine level was 177 mg per deciliter, which confirmed that the sample was not adulterated by dilution. A second urine test that can be used to differentiate among types of opiates (thus helping to distinguish between illicit and prescribed opioid use) was negative for buprenorphine, oxycodone, methadone, and 6-monoacetylmorphine.

The metabolite 6-monoacetylmorphine is unique to heroin and has a substantially longer half-life than heroin itself.<sup>9</sup> The 16-hour interval between the patient's last opioid injection and the collection of the urine specimen may have contributed to the negative results of the urine drug screen. However, because the assay has a very low limit of detection, 6-monoacetylmorphine would most likely have been detected in the urine sample if the patient had used pure heroin the previous afternoon; its absence suggests that the dose contained a substantial amount of a different opioid.

Fentanyl is a synthetic opioid that has been increasingly used as an additive in heroin. It is markedly more potent than morphine or pure heroin, and it usually accounts for only one thousandth of heroin formulations. Incomplete mixing of such minute quantities can lead to lethal dose variance.<sup>10</sup> Fentanyl differs structurally from both morphine and heroin, and the immunoassay that was performed on this patient's urine sample would not detect it. Fentanyl may result in cross-reactivity on an immunoassay for risperidone; the reported rate of such false positive results is 15%.<sup>11</sup> Our laboratory tests for fentanyl include liquid chromatography and mass spectrometry of oral fluid, a type of specimen that is less likely than urine to be adulterated. During a visit to this hospital a few months later, testing of an oral fluid specimen from this patient was positive for fentanyl, which most likely represented recent use of the drug.

#### DISCUSSION OF MANAGEMENT

*Dr. Ali S. Raja:* The rate of death from drug overdose has recently increased markedly in several states. In Massachusetts, the rate increased 35% from 2014 to 2015.<sup>12</sup> The rates of opioid-related emergency department visits and inpatient admis-

sions have also increased.<sup>13,14</sup> In fact, of the 30 states with available data from 2014, Massachusetts had by far the most opioid-related emergency department visits, with 450 visits per 100,000 population.<sup>14</sup>

The prevention of opioid overdoses requires a multifaceted approach. This patient's first exposure to opioids most likely occurred 4 years before his overdose, when he received hydromorphone that had been prescribed by a physician for pain management after hand surgery. Primary prevention of opioid-use disorder involves limiting a patient's exposure to prescription opioids, starting with the first encounter. When pain management is being considered, opioid medications should be used only when other methods, such as nonopioid analgesic agents and physical therapy, have failed. Patients for whom opioid prescriptions are considered should be assessed with the use of a prescription-monitoring program. Finally, if opioids are prescribed, a defined treatment plan should be discussed with the patient. Both the dose and the duration of the first opioid prescription should be limited, since the probability of prolonged opioid use increases linearly with the number of days for which the drug is initially supplied.<sup>15</sup>

Patients who already use opioids should be considered to be at risk for possible overdose, and secondary prevention efforts could be initiated. For example, when patients receive opioids in the emergency department, they could be offered kits that contain naloxone, an opioid antagonist. Patients' friends and family could also be offered kits and training in overdose recognition, so that they can administer naloxone if needed (as in this case). Among patients who already use opioids, there are several risk factors for overdose, including previous overdose, use of opioids without others nearby, concurrent use of sedatives, use of illicit opioids, and recent abstinence from opioids. This patient had used illicit opioids and had recently abstained from opioid use.

This patient's presentation (with a depressed mental status, bradypnea, hypoxemia, and miosis) is typical among patients who present with acute opioid overdose, although concurrent ingestion of stimulants can alter these signs, especially the miosis. When a patient presents with suspected opioid overdose, the airway should be evaluated (and airway support provided, if necessary) and naloxone should be administered. Once the re-



spiratory status has been stabilized, a more thorough physical examination can be performed. During the complete examination, the patient should be fully examined, both for the detection of transdermal patches that may hinder resuscitation efforts because of the continued administration of opioids and for the detection of signs of occult trauma that may have initially been missed.

The goal of the administration of naloxone is to restore adequate ventilation, rather than to reverse all the effects of the opioid and potentially precipitate withdrawal. Naloxone can be administered intravenously, intramuscularly, and subcutaneously, but in patients who are in respiratory arrest, naloxone is often administered nasally (perhaps by a trained bystander) at a dose of 2 mg or 4 mg, which can be repeated, if needed. In patients in the emergency department who have bradypnea but do not have respiratory arrest, a lower dose (0.04 to 0.4 mg) may be administered intravenously to increase the respiratory rate and improve ventilation without reversing all the effects of the opioid.

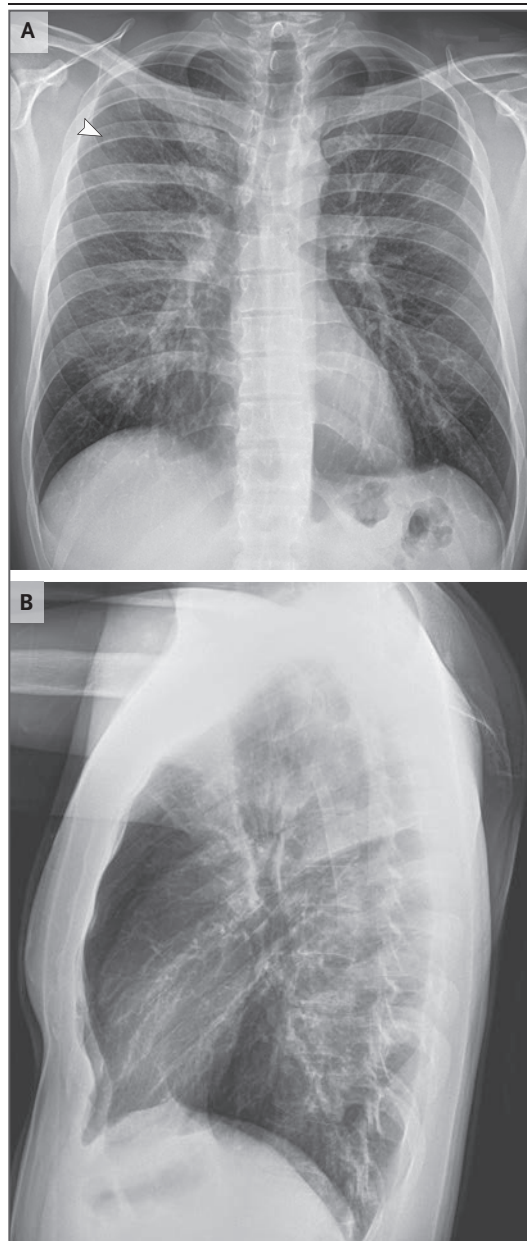
Reversal is only the first step in the management of opioid overdose in the emergency department. In Massachusetts, patients who are resuscitated after an opioid overdose are offered an evaluation for substance-use disorder before discharge, with the goal of helping them to connect with inpatient and outpatient resources for long-term treatment of addiction.

*Dr. Virginia M. Pierce (Pathology):* Dr. Kunzler, would you tell us what happened with this patient in the emergency department and during his hospitalization?

*Dr. Nathan M. Kunzler (Emergency Medicine):* Furosemide was administered, after which the requirement for supplemental oxygen decreased but persisted. The patient was admitted to the hospital; by the next morning, the abnormal findings in the lungs had resolved.

*Dr. Flores:* Posteroanterior and lateral radiographs of the chest showed evidence of resolution of the pulmonary edema (Fig. 2). Scattered nodular opacities persisted, and these findings aroused concern about aspiration pneumonia.

*Dr. Kunzler:* The patient had a single elevated temperature (38.4°C) while he was in the emergency department, but the fever did not persist and the hypoxemia and crackles resolved. Pneumonia was thought to be unlikely, and antibiotic



**Figure 2. Follow-up Chest Radiographs.**

Posteroanterior and lateral radiographs of the chest (Panels A and B, respectively), obtained 20 hours after presentation, show evidence of resolution of the pulmonary edema. Scattered nodular opacities continue to be present (arrowhead), and these findings arouse concern about aspiration pneumonia.

agents were not administered. Treatment with buprenorphine was initiated during the hospitalization, and a follow-up appointment was arranged at a transitional clinic that focused on addiction

treatment for patients without community-based providers. A blood test for antibodies to hepatitis C virus was positive; the result of an assay for hepatitis C viral load, which was pending at the time of the patient's discharge, was 1,120,000 IU per milliliter of plasma.

*Dr. Sarah E. Wakeman:* This patient's history represents a common narrative in the ongoing crisis of deaths related to opioid overdose. Opioid-use disorder can develop after medical or, more commonly, nonmedical exposure to prescription opioids during a vulnerable period. Patients with opioid-use disorder who do not have access to prescription opioids or to addiction treatment can then transition to using heroin or illicit fentanyl.<sup>16</sup> This patient described the beneficial effect of opioid-agonist therapy with methadone. However, he stopped treatment prematurely and began a common cycle of inpatient detoxification, residential treatment, and incarceration, followed by overdose. Each step highlights a missed opportunity for the health care system to intervene: screening and counseling could have been provided when opioids were initially prescribed, immediate access to effective treatment could have been ensured after opioid-use disorder developed, and addiction treatment and harm-reduction services could have been integrated with the medical treatments.

Physicians receive little training in addiction medicine, and therefore, the majority of physicians feel unprepared to care for patients with addiction or even to discuss treatment options with them.<sup>17</sup> As a result, patients are expected to navigate a fragmented treatment system on their own or are referred for detoxification, an intervention that is not effective in helping patients avoid opioid use.<sup>18-20</sup> Evidence shows that inpatient detoxification programs are of limited value and the most effective approach is long-term opioid-agonist therapy with methadone or buprenorphine, which increases treatment retention and reduces ongoing opioid use, health care costs, and mortality.<sup>21-25</sup>

Medications for addiction treatment have traditionally been hard to access, in part because of requirements such as mandatory counseling. When barriers are lowered and such medications become available to the sickest and most marginalized patient populations, treatment initiation and retention increases. Initiation of addiction treatment with buprenorphine or methadone in the

general hospital or emergency department is a strategy that results in higher rates of treatment retention than do detoxification programs or referrals to community treatment.<sup>22-24</sup> Although psychosocial services should be made available to all patients, medication alone effectively reduces ongoing opioid use.<sup>25-27</sup>

Unfortunately, access to opioid-agonist therapy remains limited. Only 1% of specialists in emergency medicine have waivers that allow them to prescribe buprenorphine, and half the counties in the United States do not have a single specialist who can prescribe buprenorphine.<sup>28</sup> Furthermore, pharmacotherapy is part of the treatment plan for relatively few patients, even among those who are admitted to addiction-treatment programs for the use of heroin and other opioids.<sup>29,30</sup>

Why do so few patients receive opioid-agonist therapy? A main barrier to expanding the use of opioid-agonist therapy is stigma perpetuated by the widely held misperception that these medications "replace one addiction with another."<sup>31</sup> Despite the vast amount of data supporting the use of opioid-agonist therapy, physicians are not immune to this stigma. The prevailing societal view that people with addiction have "brought upon themselves the suffering they deserve" may also affect physicians and contribute to the low frequency of offering buprenorphine treatment.<sup>29</sup>

In this case, stigma could have driven the patient's initial decision to stop methadone prematurely. However, his incarceration may have also played a role. Qualitative studies that included people who had been incarcerated showed that fear of forced withdrawal led them to opt against opioid-agonist therapy.<sup>32</sup> In addition, the standard practice of forced withdrawal of opioid-agonist therapy at the time of incarceration results in lower treatment retention in the community after release.<sup>33</sup>

This case comes at a time when the approach to addiction in this country is peculiar. On one hand, there are calls for a public health approach to the crisis of opioid-related deaths. Some hospitals have embraced new models of care, in which they offer addiction consultation and initiate opioid-agonist therapy during hospitalization.<sup>34</sup> On the other hand, people are still being incarcerated for drug-related charges, including positive toxicology screenings that violate terms of probation.<sup>35</sup> Advances in treatment integration are

laudable, but they fall short when people can still be arrested and forcibly withdrawn from effective treatment, which may have happened in this case.

*Dr. Pierce:* Dr. Kunzler, what happened with this patient after discharge from the hospital?

*Dr. Kunzler:* Unfortunately, the patient missed his appointment at the addiction care clinic. He instead tapered the dose of buprenorphine himself and then resumed using heroin when he was unable to obtain buprenorphine on the street. He returned to the emergency department of this hospital a month and a half after discharge because of symptoms of opioid withdrawal; clonidine was administered. A new appointment was scheduled at the addiction care clinic, but the patient missed it. He was subsequently incarcerated and lost to follow-up.

Seven months after discharge, the patient returned to this hospital to establish care with a primary care physician. He reported that he had

recently participated in inpatient and outpatient addiction care programs at another hospital and that he had abstained from heroin use for 6 months. In addition to ongoing treatment of his opioid-use disorder, his care plan includes referral to a specialist for treatment of hepatitis C virus infection.

#### FINAL DIAGNOSES

Unintentional opioid overdose, possibly from heroin mixed with fentanyl.

Opioid-induced noncardiogenic pulmonary edema.

This case was presented at Emergency Medicine Grand Rounds.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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#### LANTERN SLIDES UPDATED: COMPLETE POWERPOINT SLIDE SETS FROM THE CLINICOPATHOLOGICAL CONFERENCES

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