Introduction:
Naloxone is a potent opioid antagonist and is used commonly within the hospital and in the prehospital setting for rapid reversal of opioid overdose. Multiple case reports have documented the phenomenon of Narcan-induced pulmonary edema (NIPE) which is thought to occur secondary to increased sympathetic tone from a catecholamine surge after administration of the drug, leading to increased blood flow to the pulmonary circulation, overload of the circuit, and subsequent capillary leak. Researchers in the 1970s administered morphine followed by naloxone to anesthetized dogs, and noted subsequent increases in heart rate, cardiac output, mean arterial pressure, and myocardial oxygen demand presumed secondary to increased sympathetic outflow driven by naloxone’s rapid reversal of opioid effects. Sporadic patient cases have been present across literature since the 1980s. Previous, the thought was that this adverse outcome was dose-dependent, however recent literature has found otherwise. There were no differences in pulmonary edema, aspiration pneumonia or pneumonia between those who received high, medium or low doses of naloxone. Reports have also been documented of this adverse event occurring in children. This emphasizes the importance of awareness especially among emergency medical providers to remain vigilant for respiratory distress symptoms following naloxone administration and the value of an observational period.

Case Report:
A 26-year-old female with a history of mild intermittent asthma presented to the ER via ambulance after being found down on her living room floor. She endorsed using Ecstasy that evening and stated she occasionally uses ecstasy at concerts. EMS had found the patient lying supine in her home, unresponsive with pinpoint pupils, and provided two doses of Narcan 2mg intranasally. Patient exhibited depressed, irregular respirations therefore breathing was assisted with a bag-valve mask after Narcan was given. Within minutes of Narcan administration, EMS noted the patient to become alert and begin breathing normally. Her oxygen saturation was noted at 95% and she was placed on 4 liters nasal cannula for comfort, and transferred to our Emergency Department. Shortly after arrival, ED staff noted her oxygen saturations were dipping into the 60s, with visible external cyanotic skin changes. Her heart rate was in the 130s, respiratory rate 25, blood pressure 155/91, mental status was appropriate, however. She was immediately started on non-rebreather 15L oxygen with improvement in her oxygen saturation to 100%. Her lungs were notable for bibasilar crackles, with bedside ultrasound demonstrating diffuse B-lines. Portable chest X-ray showed changes consistent with bilateral interstitial edema (Figure1). Only medical history was intermittent asthma, therefore this was presumed to be acute noncardiogenic flash pulmonary edema. Given persistent tachypnea, she was transitioned to bilevel positive airway pressure and given IV furosemide 20mg.

Her notable initial labwork included: arterial blood gas pH 7.29, PCO2 48, PAO2 50, O2 Saturation 80%; WBC 31.3, potassium 2.7, lactic acid 4.1, RUDS + amphetamines, + cannabinoids. Rapid COVID/Flu were negative.

She was given 3g Unasyn for empiric coverage of possible aspiration pneumonia. After ED shift change, oncoming providers noted the patient to become ex-
extremely tachypneic up to 70 times a minute, with worsening sinus tachycardia up to 170 BPM. Intubation was discussed, however the patient remained setting well on BIPAP with excellent mentation; she was interactive and actually did not seem particularly distressed despite her critical vitals.

Figure 1: Patient’s chest x-ray shortly upon arrival concerning for developing pulmonary edema

Repeat chest X-ray (Figure 2) within 10 hours of presentation showed changes with more infiltrative development in lower lungs.

Figure 2: Patient’s chest X-ray later in emergency room course with more prominent lower lobe infiltrates

Given her concerning respiratory status, she was evaluated and accepted by the medical ICU team. There she was started on scheduled Lasix and valium. Within 4 hours of arriving to the ICU, she was noted to meet 4/4 SIRS criteria: temperature 102.4, HR 160-170s, RR 50-70s, BP 80/50s.

Decision was made to intubate, however afterwards, she became hypoxic again to the 60s requiring manual bagging. She was paralyzed with vecuronium, however despite maximizing ventilatory settings, she was unable to maintain oxygen saturations. Therefore, she was taken for V-V ECMO cannulation.

She remained hypotensive requiring pressors. This was attributed to sedation as well as possible aspiration pneumonia. She also had an acute drop in hemoglobin (14.5 → 10.3, in 5 hours) and was given 2 unit packed red blood cells.

An Echocardiogram performed after ECMO initiation showed reduced systolic function of 25-30% with severe global hypokinesis. No pericardial effusion.

Within 24 hours, the patient was transferred to tertiary center for further care and ECMO management. Her blood cultures ended up resulting positive for Strep pneumonia after she was transferred.

Her outside hospital course was notable for an episode of atrial fibrillation requiring amiodarone, placement of intra-aortic balloon pump with successful weaning of vaspressors 24 hours later.

The IABP was weaned within 48 hours. She was taken off of ECMO in 12 days. She was extubated 6 days later with eventual discharge home after a total hospital length of stay of 25 days. Her blood and sputum cultures have never repeated positive but she completed 7 days of antibiotics. Additionally, two repeat echocardiograms demonstrated improving ejection fraction with a final of 70%.

Discussion

There are several variables affecting this case presentation that add complexity to our ability to understand the precise pathophysiology underlying the patient’s presentation. Narcan induced flash pulmonary edema is theoretically noncardiogenic in nature. Therefore, her reduced ejection fraction contradicts with the classic pathophysiology. Her being otherwise healthy previously, and the quick recovery in her ejection fraction as shown by subsequent echocardiograms suggest there could be a reversible cardiomyopathy underlying her acute decompensation. This could possibly have been tachycardia induced secondary to her concurrent MDMA and amphetamine use which was exacerbated by the naloxone-induced catecholamine surge.

Sepsis could also have contributed to the patient’s picture. This was demonstrated by blood cultures positive for Streptococcus pneumoniae taken at our institution prior to transfer. However, interestingly after one dose of antibiotics, she was transferred without repeat cultures ever resulting positive at the outside hospital, including blood and sputum. Her chest X-ray pattern of bilateral airspace opacities is more consistent with pulmonary edema than community acquired pneumonia.

The literature does describe cases of pulmonary edema following MDMA use though the literature here
is scantier. Cases we’ve read, described onset of pulmonary edema within hours of use and during the period of acute intoxication with MDMA possibly secondary to a neurogenic trigger. Cases of amphetamine induced pulmonary edema have also been described. We hypothesize that this patient suffered an unintentional co-ingestion, as the MDMA she attempted to purchase was likely laced with other substances including amphetamines seen on her RUDS and fentanyl which resulted in her respiratory depression and altered mental status. While amphetamines or MDMA could have resulted in cardiogenic or noncardiogenic pulmonary edema, the timing of this patient’s decompensation, as well as her otherwise intact mental status seems to suggest a causal relationship with Narcan. She was brought to the ED right after naloxone administration with an acute critical change in her vital signs: RR 25, O2 60s, HR 130s.

Regardless of the ultimate etiology of the patient’s presentation, her recovery and discharge home without need for inpatient rehabilitation emphasizes the reversibility and transient nature of the pathology. This case reinforces the need for Emergency physicians to be aware of the profound hemodynamic consequences which may accompany acute toxicidromes brought on by recreational drugs, as well as health care interventions which may be taken to mitigate their effects. Aggressive management can mitigate the worst outcomes, and being aware of potential adverse effects is the first step in treatment.

References
3. https://www.uptodate.com/contents/naloxone-drug-information?topicRef=300&source=see_link#references

Received: 25.03.2023
Revised: 13.06.2023
Accepted: 27.06.2023