

## Naloxone Over the Counter: Increasing Opportunities and Challenges for Health Providers

On November 15, 2022, the US Food and Drug Administration (FDA) issued a request for data from manufacturers of naloxone to support a switch from prescription to over-the-counter (OTC) formulations.<sup>1</sup> Specifically, the FDA said that a nasal spray and an auto-injector could potentially be safe and effective for OTC distribution. On December 26, 2022, the FDA granted a priority review to Harm Reduction Therapies, a pharmaceutical nonprofit, to market an OTC formulation of naloxone.<sup>2</sup> We commend the FDA for these efforts. In this Commentary, we conclude that the far wider availability of naloxone, which would occur with the anticipated approval by the FDA for OTC distribution, would pose both opportunities and challenges for health providers.

Naloxone is an opioid receptor antagonist that rapidly reverses or blocks the effects of opioids, restores normal respiration and heart rhythm, and reverses the potentially fatal effects of an overdose. The side effects are generally minimal and consist of mostly those symptoms related to opioid withdrawal. In some cases, naloxone can precipitate noncardiogenic pulmonary edema, with rates ranging from 0.2%-3.6%,<sup>3</sup> typically within 4 hours of administration.<sup>4</sup> Despite the low absolute risks of pulmonary edema associated with the administration of naloxone, we believe that

health providers should be aware that the lifesaving benefit vastly exceeds the risk.

The United States accounts for <4.5% of the world's population but accounts for >13% (or 2.1 million) of the more than 16 million opioid addicts, as well as >20% of the more than 500,000 deaths worldwide.<sup>5</sup> From April 2020 to April 2021, the United States experienced 100,306 deaths from drug overdoses, a 28.5% increase from the prior year, with 75,673 of those deaths attributed to opioids.<sup>6</sup> Synthetic opioids, primarily fentanyl and natural and semi-synthetic opioids, are major contributors.<sup>7</sup> In addition, illicitly manufactured fentanyl is often added to other recreational drugs because of its low cost and increased potency; thus, the risk of fatal overdose increases for all users, especially first-time or occasional users. It is sobering to note that about 6 of 10 fentanyl-laced illegal drugs sold on the street now contain a potentially lethal dose of fentanyl.<sup>8</sup>

About 1 in 5 patients prescribed opioids for chronic pain have overdosed, and more than half take other prescription drugs that may cause overdose, as well as abuse alcohol. Many patients who are prescribed high doses of opioids have witnessed overdoses, but <3% have naloxone available for immediate use.<sup>7</sup> Health providers should counsel all their patients who use drugs, and their families, to have a naloxone nasal spray or auto-injector in the household. Cost could be cited as a potential barrier, but the average retail price of naloxone is under \$100, far less expensive than the approximately \$400 for epinephrine auto-injectors for emergency treatment of anaphylaxis.<sup>9,10</sup> In addition, Harm Reduction Therapies stated in its press release that the company would donate 10% and sell the remainder to drug stores and health providers for cost, or about \$18 per dose.<sup>2</sup>

Patients for whom the benefit-to-risk ratio is positive include, but are not limited to, the 22.5 million people, or about 8.5% of the US population aged 12 years or older, who need professional treatment for an illicit drug or alcohol use disorder.<sup>11</sup> Two-thirds of patients who are participating in syringe service programs, detoxification, or opioid treatment programs previously had witnessed an overdose, but only 17% had naloxone available to them at the time.<sup>11</sup> Ideally, health care providers in substance use disorder

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treatment programs should include nasal or auto-injector naloxone in their treatment program, both teaching how to use it as well as providing it upon discharge from the program. Health providers should also prescribe naloxone for any patient who is prescribed a high-dose or long half-life opioid, whether for pain or any other condition. In the United States, over 142 million patients are prescribed opioids, yielding a prescribing rate of approximately 43.3 per 100 persons.<sup>12</sup> Compared with a daily dose of 20 morphine milligram equivalents (MME) or less, a daily dose of 50 or more MME doubles the risk of opioid overdose death, and at 90 MME, the risk of opioid overdose death increases tenfold. Although naloxone is included in the recommendations by the US Centers for Disease Control and Prevention, the drug is currently prescribed to <1 in 70 patients prescribed high-dose opioid prescriptions.<sup>12</sup> In addition, we urge all emergency medicine providers to counsel and provide naloxone to any patient presenting with an opioid overdose, including accidental.

We also encourage health providers at college-based student health services to initiate campaigns across their campuses to increase naloxone availability and distribution as well as provide guidance to students about the overall safety and life-saving benefits of emergent use of naloxone. Fortunately, opioid addiction and overdoses are rarer on college campuses than among young adults in the general population. Nonetheless, on March 11, 2022, 6 football players from the US Military Academy at West Point in New York traveled to south Florida on spring break and accidentally overdosed on fentanyl-laced cocaine. Emergency medical responders found them in cardiac arrest and immediately administered naloxone. Of the 6, 2 died and the other 4 recovered after 2 of them were admitted to the hospital in critical condition.<sup>13</sup>

It also seems beneficial to have nasal or auto-injector naloxone available wherever there are portable defibrillators, especially because the drug could be life saving for those who have cardiac arrest due to opioid toxicity.

Naloxone access laws to increase availability and access are presently under the control of each individual state.<sup>14</sup> We believe that all state medical societies should advocate for less restrictive naloxone access laws. It may also be worthwhile for medical societies to require prescribing physicians to counsel patients on the availability, efficacy, safety, and relatively low cost of OTC naloxone, when available.

While the United States has been more reactive than proactive with the epidemics of COVID-19<sup>15</sup> and gun violence, especially among young Black men<sup>16</sup> and school children,<sup>17</sup> now is the time to become more proactive, especially in the fight against opioid-related deaths. As of today, the epidemic of drug overdose deaths due to opioids is second only to COVID-19 in the United States in potentially avoidable premature deaths. Health providers should counsel patients who use drugs, as well as their families, to have a nasal spray or auto-injector of naloxone in the household. Health providers should more widely provide naloxone, and increasing the distribution to emergency personnel could avert >20% of opioid overdose deaths.<sup>18</sup>

In conclusion, we propose a call to action for all health providers and state medical societies to ensure the widest distribution and easy availability of naloxone, including over the counter, which is likely to be FDA-approved very soon. As Sir Richard Doll so eloquently stated, “Death in old age is inevitable but death before old age is not.”<sup>19</sup>

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