

## Commentary

# The Real Deal: A Commentary and Examination of Xylazine Use and Unintended Consequences

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## INTRODUCTION

In 1972, the Food and Drug Administration (FDA) granted regulatory approval for xylazine hydrochloride, a sedative intended for use in animals. This particular drug continues to hold significance for veterinarians specializing in the care of large animals such as horses, cattle, and deer. It is not only calming for these animals but also provides needed pain relief.<sup>1</sup> Despite this useful application of the drug itself, as often happens with legal drug supplies, illicit uses become commonplace and result in unintended consequences—in this case, devastating ones. Within this commentary, we examine the current state of the science as pertains to xylazine and the various uses of the illicit supply line, and we explore possible answers to the directions the substance use disorder field may have at their disposal to address this ever-mounting set of calamitous circumstances. In addition, we provide possible directions on what next steps may be appropriate to address these multiple dangers.

## COMMENTARY

More than half a century after its approval for use in animals, the chemical xylazine, a non-opioid agent, is increasingly being found in the illicit drug supply, mixed with other drugs like fentanyl and heroin, among others. Because it is not currently a controlled substance, it is easily obtainable online and is cheap, making it easy for illicit drug distributors to use it to thin out their more expensive drug supply. Many users of illicit drugs may not even realize xylazine is in their supply, combined with fentanyl, other opioids, or even stimulants like methamphetamine or speed.<sup>2</sup> Nevertheless, deaths attributable to these deadly combinations have risen dramatically in recent years.<sup>3</sup> The sad part of this dilemma is that the true severity of this phenomenon started more than a decade ago, and its relentlessness was ignored for years.<sup>4</sup> As an illustration, a study carried out in Puerto Rico over sixteen years ago revealed that 22% of the participants, whose syringes indicated the presence of xylazine, claimed not to have intentionally used xylazine.

This suggests the possibility of xylazine being an unidentified additive within the unregulated drug distribution during that period.<sup>5</sup> Additionally, the US Food and Drug Administration has reported instances of illicit xylazine usage in 48 out of the fifty states within the United States.<sup>6</sup> In 2022, xylazine was reported in eight of the nine Canadian provinces, with the vast majority of the cases being reported in British Columbia and Ontario.<sup>7</sup>

In recent years, within the United States as well as other countries, xylazine has appeared in doses that are used intentionally but, in more and more cases, unintentionally.<sup>8</sup> In a review of over fourteen hundred records, Ball et al<sup>8</sup> found both types of use across nine countries, although the authors indicated that death by such use had not reached the calamitous numbers and deadly results we have witnessed in the last couple of years, as also researched by others.<sup>9-12</sup> Analyzing 1,400 records, as discussed in Ball et al<sup>8</sup> study, revealed a set of 17 articles and 2 abstracts that met the inclusion criteria. They identified a total of 98 patients among reports ranging from 1979 to 2020 and across nine countries, with the most common types of xylazine exposure reported being unintentional exposure and intentional misuse or abuse. Typical indications upon initial observation encompassed hypotension, bradycardia, drowsiness, and lethargy, whereas occurrences of apnea requiring intubation and fatalities were less commonly documented. Kacinko et al<sup>9</sup> studied how often and how much xylazine was present over 2.5 years (January 2019-June 2021) in cases of driving under the influence (DUID) and medico-legal death investigations (MDI). This investigation encompassed the identification of other substances found in conjunction with xylazine. Out of more than 170,000 cases subjected to xylazine screening, a substantial 97% were categorized as MDI cases. Throughout the duration of the study period, the occurrence and geographical distribution of xylazine exhibited an upward trajectory. Overall, 2.8% of DUID and 2.1% of MDI cases screened positive for xylazine with concentrations of 5.1-450 ng/mL (mean=36 ng/mL) and 5.0-11,000 ng/mL (mean=41 ng/mL), respectively.

## **XYLAZINE—THE EFFECTS**

Medical use of xylazine was studied for use in humans as an antihypertensive agent but was not approved by the FDA because it was found to cause bradycardia, permanent hypotension, reduced cardiac output, and depression of the central nervous system (CNS).<sup>13</sup> There is also a clear link to severe skin ulcers and abscesses, which can lead to infections, rotting tissue, and amputations.<sup>6</sup> While the precise origin of the injuries remains uncertain, it is evident that they can be much more harmful compared to those resulting from other injectable substances.<sup>14</sup> Xylazine wounds often begin as small superficial lesions with a white or purple center and a dark red fluid discharge. These wounds initially appear innocuous but will become more severe if left untreated.<sup>14</sup> As the prevalence of xylazine has increased in the unregulated drug supply, there have been subsequent increases in the number of hospitalizations for skin wounds associated with substance use.<sup>15</sup> Additional effects associated with xylazine use include dry mouth, drowsiness, hypertension, and tachycardia, followed by hypotension, bradycardia, and hyperglycemia. If taken in high doses along with other CNS depressants, it can intensify the effects of the other drugs, which can complicate overdose identification and treatment.<sup>16</sup>

Yet another severe concern is that there is no approved or medically sanctioned antidote for xylazine overdose in humans. The possible exception is that if xylazine is used with opioids (as it often is), naloxone may reverse the effects of the opioid portion of the overdose and is therefore recommended by experts.<sup>17,18</sup> As deaths attributable solely to xylazine are not included in the Centers for Disease Control and Prevention's (CDC) national statistics on fatal overdoses, it is feared that these occurrences are widely underestimated.

## **INTERVENTION AND PREVENTION**

Xylazine is not readily identified by routine immunoassay toxicology screens (blood and urine) and therefore may be under-detected and overdoses involving xylazine may be underdiagnosed due to its rapid elimination from the body (half-life of 25-50 minutes).<sup>6</sup> There have been reports of individuals combining xylazine with speedball (i.e., an opioid used with a stimulant) to offset unintended effects of the individual components of the mixture. Research conducted by Choi et al<sup>19</sup> reached the conclusion that xylazine intensifies the life-threatening repercussions of opioids, suggesting that aggravated cerebral hypoxia may underlie the mechanism responsible for opioid-overdose fatalities associated with the presence of xylazine. Because of these reports, it would be beneficial to screen for opioid use or abuse *via* a method other than toxicology, specifically to identify the potential risk of an overdose. One such instrument is the Substance Abuse Subtle Screening Inventory (SASSI-4), which produces a screening outcome score for prescription drug use (Rx Scale) that indicates likely abuse and an overall screening outcome for high or low probability of any type of substance use disorder (SUD).<sup>20</sup> The Rx score was validated against the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnoses of opioid and sedative SUD with an overall accuracy rate of 94%.<sup>21</sup> The questions on the Rx scale specifically address non-medical use of prescription medication; thus, this

score could be used as a predictor of potential opioid overdose as well as such use when in combination with xylazine.

In July 2023, the US White House unveiled an unprecedented national response strategy with the aim of addressing the escalating concern surrounding the combination of fentanyl with xylazine. This strategy centers around six key principles for action that the federal government intends to pursue: 1) Testing 2) Data Collection 3) Implementation of Evidence-Based Prevention, Harm Reduction, and Treatment Measures 4) Supply reduction 5) Scheduling 6) Research.<sup>22</sup> While they will be pursuing these steps, they also acknowledge that it will require a whole-of-society effort to save lives, and their plan includes practical steps states and individuals can take to help address this issue.<sup>23</sup> These governmental responses will open up funding sources to support professionals and service providers in the uphill battle against this deadly drug. It is imperative that the fight against xylazine use move swiftly, as the drug supply on the streets is very volatile. Governmental agencies, community non-profits, service providers, and private institutions all need to work together as agents of change in these efforts going forward.

## **CONFLICTS OF INTEREST**

The authors declare that they have no conflicts of interest.

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