



## The Dangerous Combination of Opioids and Benzodiazepines

On August 31, 2016, the Food and Drug Administration (FDA) issued a press release regarding the class-wide changes for the labeling of products to inform health care providers and patients about the risks of combining opioids and benzodiazepines. These changes require the FDA's strongest warning for drug product labeling and patient Medication Guides to be added to nearly 400 products which include opioid analgesics, opioid-containing cough products, and benzodiazepines. The boxed warnings will provide information about the serious risks of concomitant use of the medications including extreme sleepiness, respiratory depression, coma, and death.<sup>1</sup>

More recently, a retrospective cohort study of Medicare Part D claims data was performed on patients taking opioids and benzodiazepines concomitantly to evaluate the exposure-response association between the days with concurrent prescription opioid and benzodiazepine use and the risk of overdose.

This study found that during the first 90 days of concomitant use of opioids and benzodiazepines, there was a 5-fold increase in the risk of opioid-related overdose. This

risk of overdose was nearly double in patients on days 91 to 180 of concomitant use than the risk of overdose in patients taking only an opioid. Other factors that increased the risk of overdose included utilizing multiple prescribers and the following comorbid conditions: chronic kidney disease, chronic obstructive pulmonary disease, depression, and a history of stroke or transient ischemic attack.<sup>2</sup>

At the March 12, 2019 DUR Board meeting, data on the Nebraska Medicaid population were reviewed. Between March 1, 2018 and May 31, 2018, there were 1,771 patients identified as taking an opioid and benzodiazepine concomitantly. DUR Board members agreed that policy needs to be in place to prevent the concomitant use of opioids and benzodiazepines, especially in patients utilizing multiple prescribers.

According to the Nebraska Pain Management Guidance Document: *Benzodiazepines are potentially addictive drugs that may produce physical dependence, amnesia, emotional blunting, psychomotor retardation, and synergistic respiratory depression when combined with opioids.*

*Anxiety, although initially ameliorated by benzodiazepines taken short term, often returns to near baseline levels with chronic use. Patients may be reluctant to taper off of these medications fearing the exacerbation of anxiety that usually accompanies the dose-reduction process. Unlike opioids, abrupt withdrawal from high doses of benzodiazepines can result in seizures and death.*

*The detoxification resembles alcohol withdrawal in terms of symptomatology and risk. Some patients will need medically supervised residential treatment to successfully discontinue benzodiazepines. Withdrawal: The longer the treatment, the higher the dosage, the shorter the half-life, or the faster the taper, then the more likely the patient will have withdrawal symptoms. Even small doses of benzodiazepines taken chronically may produce uncomfortable symptoms if discontinued abruptly.<sup>3</sup>*

In October of 2018, HR 6 (The Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act or the SUPPORT for Patients and Communities Act) became law, as passed by Congress. This law requires all Medicaid programs to implement a claim review automated process that monitors when an individual enrolled under the State plan is concurrently prescribed opioids and benzodiazepines.

Nebraska Medicaid, the Nebraska DUR Program and the Managed Care Organizations (Nebraska Total Care, UnitedHealthcare, and WellCare of Nebraska) will be putting measures into place to prevent drug overdoses related to the concomitant use of opioids and benzodiazepines.

## References

1. FDA News Release August 31, 2016 <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518697.htm>
2. Hernandez I, He M, Brooks MM, Zhang Y. Exposure-Response Association Between Concurrent Opioid and Benzodiazepine Use and Risk of Opioid-Related Overdose in Medicare Part D Beneficiaries. *JAMA Netw Open*.2018;1(2):e180919. doi:10.1001/jamanetworkopen. 2018.0919
3. Nebraska Pain Management Guidance Document. DHHS. 1st Edition, October 2017. <http://dhhs.ne.gov/publichealth/PDMP/Documents/Nebraska%20Pain%20Management%20Guidance%20Document%20v4.0.pdf>. Accessed March 26, 2019.

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