Simultaneous use of non-benzo sleeping pills and anti-epilepsy drugs increases drug overdose deaths

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With an alarming rise in the number of prescriptionss filled for non-benzo sleeping/z-drugs and anti-epilepsy gabapentinoids over the last two

decades, researchers at Columbia University Mailman School of Public Health aimed to fill in the gap in knowledge in the proportion of overdose deaths involving those medications and learn more about their co-usage with other substances across U.S. demographics categories. They found that the proportion of overdose deaths involving these drugs increased more than three-fold between 2000 and 2018, coinciding with exponential prescription increases since their introduction into the market. Until now there was little data on overdose deaths involving non-benzodiazepines and gabapentinoids. The findings are published in *The Lancet Regional Health - Americas*.

More than 67 percent of those who died from overdoses with these drugs between 2000 and 2018 had also opioids in their system indicating that using more than one substance is the norm.

"These drug classes were introduced as less dangerous alternatives to opioids and benzodiazepines, creating perceptions among physicians and patients of their supposed increased safety, even without guidelines or data to back up such perceptions and leading to increases in prescribing," said Silvia Martins, MD, Ph.D., professor of epidemiology at Columbia Mailman School, and senior author. "Approved for short-term treatment of insomnia, they were touted as safe alternatives to the popular benzodiazepines when introduced to the market as less prone to abuse or dependence. Yet, recent evidence suggests that this alternative may also be as harmful as the product it intended to replace partially. We felt it was critical to further explore and especially determine the dangers of their co-usage."

Using data from the National Center for Health Statistics, the researchers calculated overdose death rate per 100,000 persons for every year between 2000 and 2018.

Between 2000 and 2018, 788,135 persons died with an overdose code as

the underlying cause of death. Of those, 587,884 persons had any T or specific code for the drug involved among their multiple causes of death. In turn, 21,167 among those had a T42.6/T42.7 ICD code, which include gabapentinoids and z-drugs, among their multiple causes of death.

There were more intentional overdoses and a greater proportion of women, a greater share of whites, and those with higher educational background, who died from an overdose between 2000 and 2018 with a T code of T42.6/T42.7 ICD compared to the population of overall overdose casualties.

In addition to being prescribed to avoid or replace benzodiazepines and opioids, gabapentinoids are often offered off-label for such conditions as anxiety and insomnia. "The rise in gabapentin prescriptions roughly accompanies the involvement of z-drugs and gabapentinoids in overdose deaths, which suggests they can be playing a role in those deaths. The literature also has shown increasing deaths with gabapentin co-using with other substances including alcohol," noted Martins.

Prescription opioids and benzodiazepines are the most common medication classes involved in drug-related emergency department visits and drug overdose deaths in the U.S. When taken in excess, both benzodiazepines and prescription opioids promote respiratory decline.

Despite the introduction of z-drugs and gabapentinoids aiming to replace benzodiazepines and opioids as safer alternatives to treat insomnia and pain, there exists sufficient evidence that users of one often intake the intended replacement as well, a dangerous and often fatal practice, according to the researchers.

"The positive news is that clinicians garnered some awareness about the risks of opioids after the catastrophic consequences of their widespread use, and prescriptions have decreased notably over the past 10 years,"

said Vitor Tardelli, of the Universidade Federal de São Paulo, and Centre for Addiction and Mental Health, Toronto, as well as a former Columbia Mailman school student. "Drug monitoring initiatives have already been implemented successfully to reduce prescribing of benzodiazepines as well." However, he also points out that unfortunately, illegal markets have been gaining importance as a source of benzodiazepines—often with unclear potency.

"Rates of concurrent overdose deaths with opioids and benzodiazepines are startling and the involvement of gabapentinoids and z-drugs suggests they could add risk to non-medical users of benzodiazepines and opioids rather than minimize it. As such, gabapentinoids and z-drugs should always be prescribed with caution and patients should be monitored closely," observed Tardelli.

"Clinicians and primary care doctors should take a thorough history of potential risky behaviors prior to prescribing these drugs and educate their patients about potential interactions between gabapentinoids and z-drugs with opioids, alcohol, and other sedative drugs," said Martins

More information: Vitor S. Tardelli et al, Overdose deaths involving non-BZD hypnotic/sedatives in the USA: Trends analyses, *The Lancet Regional Health - Americas* (2022). DOI: 10.1016/j.lana.2022.100190

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