Understanding the link between nicotine use and misuse of 'benzos'

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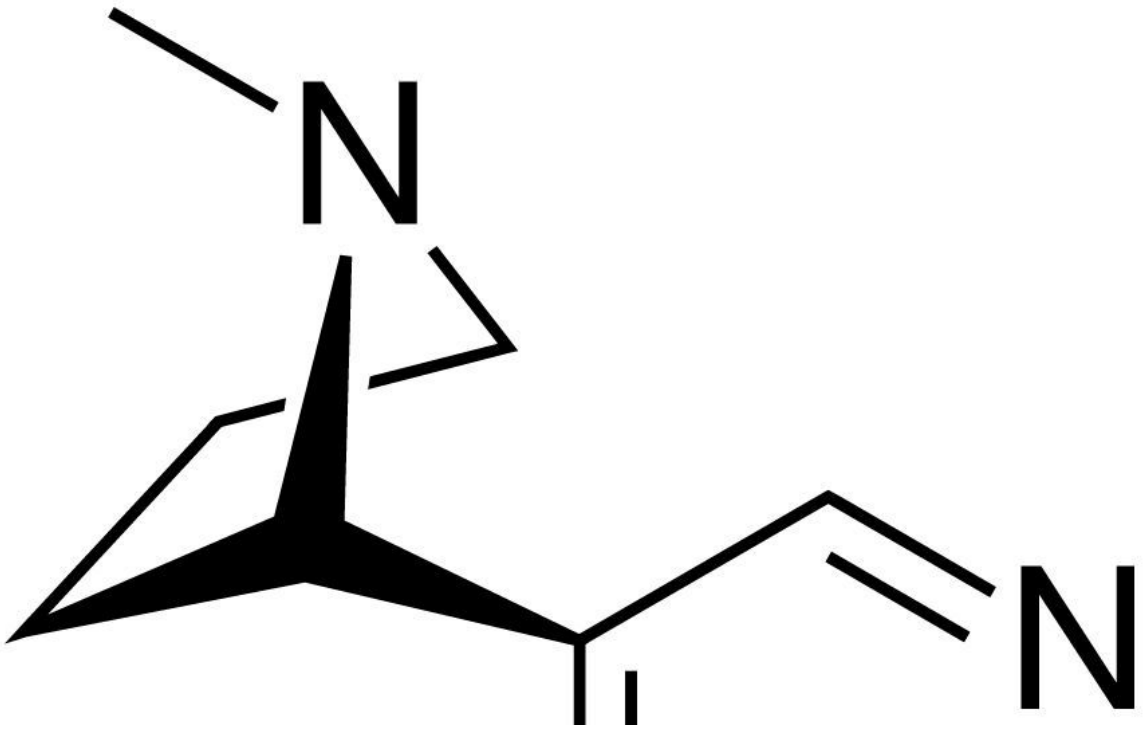

Nicotine, alternate molecular skeletal 2D rendering showing the 3D conformation of its ring at lowest energy in actual space. Credit: Public Domain

Studies have correlated a relationship between smoking or vaping nicotine with misuse of other substances, such as alcohol and prescription drugs. Lately, misuse of prescription benzodiazepines (such as alprazolam or Xanax, and diazepam or Valium) has also been linked

to nicotine use. These connections have all been statistically derived—researchers did not directly study human interaction with these drugs.

Now, however, evidence of how nicotine "sets up" a craving for benzodiazepines—often called "benzos"—in animal laboratory studies has been published in the open access journal *eNeuro*. Georgetown University Medical Center investigator Alexey Ostroumov, Ph.D., led the study, which he conducted with colleagues at the University of Pennsylvania before joining Georgetown where he continues this research focus.

"Our findings in rats show that nicotine increases the use of another drug," says Ostroumov, an assistant professor in the department of pharmacology & physiology. "Rats exposed to nicotine drank more of a solution that contained benzodiazepine. Rats without nicotine exposure were less interested in the benzodiazepine solution." Benzodiazepines, prescribed for severe anxiety and other conditions, also include the tradenames Ativan, Klonopin, Tranxene, Versed, among many others.

To investigate the mechanisms of increased benzodiazepine consumption, the research team focused on the brain pathway that is critical for use of all addictive substances, including nicotine and benzodiazepines.

This pathway originates in the ventral tegmental area (VTA), which sends dopaminergic neurons throughout the brain. VTA is considered an integral part of the brain's rewards system that is involved in reinforcing behavior, thus, the VTA is thought to play the major role in motivation, reward and addiction behaviors.

Ostroumov emphasizes that this pathway is probably most important in establishing addiction to other substances in nicotine users, but not in

maintaining ongoing addiction. "We believe that nicotine-induced adaptations in this brain pathway increase the risk for future misuse of other addictive substances, including benzodiazepines," he says.

In their experiments, investigators observed that nicotine-treated rats had reduced dopamine neuron activity in response to benzodiazepine. Similar results have frequently been observed in humans, where blunted dopamine signaling reliably predicts elevated use of various addictive substances.

"This association between blunted dopamine responses and nicotine-induced benzo intake supports the idea that when the brain doesn't sense enough gratification from a substance, people may take more of it to compensate," Ostroumov explains.

By looking into mechanisms of this VTA modification, researchers found a protein, KCC2, that is downregulated by nicotine. Thus, upregulating KCC2 appears as a potential remedy to mitigate the effect of nicotine on benzodiazepine consumption. Researchers boosted KCC2 in the brain with a synthesized chemical (CLP290). They found that, indeed, CLP290 restored normal functioning of VTA neurons. In rats treated with nicotine, CLP290 decreased consumption of the benzo solution to pre-nicotine levels.

Ostroumov says there is much more research to do to define therapeutic potential of KCC2 in substance misuse. "But rat studies provide evidence that human smoking and vaping can likely contribute to the misuse of drugs, including benzodiazepines."

Provided by Georgetown University Medical Center

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