

Increasing diversion of prescribed benzodiazepines and Z-drugs to new psychoactive substances

A. Del Rio^{1*}, S. Graziano², R. Tittarelli¹, F. Umani-Ronchi¹

¹Department of Anatomical, Histological, Forensic and Orthopedic Sciences, Sapienza University of Rome; ²National Centre on Addiction and Doping, Istituto Superiore di Sanità, Rome, Italy

Abstract

Over the last few years reports have indicated an increase in the number, type and availability of new psychoactive substances belonging to the benzodiazepine class. These molecules may pose high risks to users, since the majority have never undergone clinical trials or tests so their pharmacology and toxicology is largely unknown. However the new drug scenario emerging from the COVID-19 global pandemic seems to play a role in increasing the diversion of prescribed benzodiazepines and Z-drug. A brief presentation of this phenomenon is hereby presented. The awareness and response activities at national and international levels related to this issue should be enforced. *Clin Ter 2021; 172 (2):e116-118. doi: 10.7417/CT.2021.2296*

Key words: benzodiazepines, Z-drugs, new psychoactive substances, drug diversion

Over the last 2 decades, new psychoactive substances (NPS) have rapidly emerged in the drug market becoming a matter of great concern and a threat to public health. NPS are de novo designed molecules or are created by manipulating already existing psychoactive substances, to mimic or enhance the effects of internationally controlled drugs and then sold through various modes of distribution, including the Internet, ‘head’ or ‘smart shops’, or street-level drug traffickers (1-6). The United Nations Office on Drugs and Crime (UNODC) reported 899 NPS from 2008 to 2019, and the EU Early Warning System formally notified 731 NPS in Europe since 1997 to date (7).

NPS belong to several classes of compounds as synthetic cannabinoids, cathinones, phenethylamines, opioids, tryptamines, arylalkylamines, benzodiazepines, piperazines, plants and extracts, etc. The last 5 years have been characterized by the increase in the number, type and availability of new psychoactive substances belonging to the benzodiazepine class. At the end of 2019 the EU Early Warning System was monitoring 30 new benzodiazepine, 21 of which were first detected in Europe since 2015 (8). These molecules

may pose high risks to users, since the majority have never undergone clinical trials or tests so their pharmacology and toxicology is largely unknown. In some countries, new benzodiazepines have been associated with harms, including poisonings and deaths (i.e. etizolam, flualprazolam) (9).

In early 2020, the need to contain the COVID-19 global pandemic has led to the introduction of severe restrictive measures including closure of non-essential services and border closures. The imperative to “stay at home” has affected all areas of life, including many behaviors linked to drug use and drug supply (10). The disruption in access to and availability of usual drugs of abuse with consequent phenomena of withdrawal syndromes together with the social isolation leading to boredom and anxiety feelings, have determined the increased diversion of prescribed medicines advised for the short-term management of insomnia and anxiety, like benzodiazepines and Z-drugs (Zolpidem, zopiclone and zaleplon) (11).

The non-medical use of benzodiazepines is a well-known phenomenon and represents an increasingly widespread public health problem since its magnitude is difficult to estimate, mainly due to the lack of monitoring and data collection in most countries. A polydrug use pattern, typically in combination with illicit drugs or alcohol, frequently occurs to enhance the drug effects, to get high or to be helpful with the ‘come down’ of stimulants or to relieve withdrawal symptoms. This misuse pattern is associated with an elevated risk of serious health consequences or fatal overdose, especially among high-risk opioid users, who misuse benzodiazepines to increase the effects of opioids or to self-medicate to treat symptoms of psychiatric disorders, negative emotional states, opioid withdrawal symptoms, and the side effects of alcohol and cocaine use (12).

The diversion of benzodiazepines most commonly involve alprazolam, diazepam, and lorazepam that seem to have a wider diffusion than oxazepam, clorazepate and chlordiazepoxide because of their upper abuse potential. In Europe the cases of deaths among the high-risk opioids users are more frequently related to the use of benzodiazepines with rapid onset of action as diazepam, clonazepam, alprazolam, rather than those with a slower one as oxazepam

Correspondence: Prof. Alessandro Del Rio. E-mail:alessandro.delrio@uniroma1.it

and flunitrazepam according also to their availability, legal status and costs (13,14).

Zolpidem, zopiclone and zaleplon, commonly known as Z-drugs are non-benzodiazepine hypnotic drug with pharmacology similar to benzodiazepines (15).

Compared to benzodiazepines, Z-drugs show a lower rate of misuse about one third that of benzodiazepines. Moreover, the phenomenon of abuse and diversion of these compounds remains understudied and unexplored because of the difficulties to find data related to the reasons and the frequency of misuse and the abusers' supply sources, even if some cases of abuse, intoxication, overdose and death caused by Z-drugs misuse are reported in the international scientific literature (16).

Intoxications resulting from Z-drugs abuse are mostly related to the concomitant use with other CNS depressants (alcohol, benzodiazepines, antidepressants and opioids) and the polydrug use can be considered the major confounding factor to determine the cause of death. Moreover, the interpretation of Z-drugs role in drug related deaths is complicated by factors such as short half-life of these drugs, inter patient variability and presence of co-ingestants. Another challenge arises from objective assessment of drug use in cases of intoxications and fatalities since analytical toxicological screening of benzodiazepines and Z-drugs in biological matrices are poorly performed, even if it is well known that toxicological and forensic data can be crucial in better assessing and classifying the role of a psychoactive substance especially when serious adverse events occur (17-21).

The diversion of prescribed benzodiazepines and Z-drugs is also involved in date-rape or drug-facilitated sexual assaults (DFSAs), in which the forcible or covert administration of central nervous system depressants is used to alter the victim's behavior leading to a weakness or unconscious state and are often associated with anterograde amnesia. Benzodiazepines, together with alcohol and gamma-hydroxybutyric acid and most recently its precursor gamma-butyrolactone still appear the most used date-rape drugs and chemsex drugs, consciously or unconsciously consumed by victims and perpetrators (22-26).

The benzodiazepine most commonly associated with date rape is flunitrazepam, licensed as a powerful sedative-hypnotic prescription drug in many European countries. Its hypnotic effects occur in 15-30 minutes and are enhanced by the concomitant use of alcohol or other psychoactive substances leading the person to become confused and sleepy up to a complete sedation after a short time (27-28).

In conclusion, even if the diversion of prescribed benzodiazepines and Z-drugs has been previously reported, the new scenario emerging from the COVID-19 global pandemic could play a role in increasing this phenomenon. Serious health consequences, up to fatal overdoses, should be considered not only in the groups most at risk, like high-risk opioid users, but also in the general population. It should be recommended to enforce the awareness and response activities at national and international level related to eventual new trends of diversion of prescribed drugs.

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