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LETTER TO THE EDITOR

Zolpidem: A masked hero. A reply to ZORRO study

We have read the article by Istvan and colleagues, which recently appeared on your Journal,[1] with great interest. Among doctors, the use of zolpidem has been driven by the still-widespread false belief that, since zolpidem is not chemically a benzodiazepine, it cannot lead to addiction and tolerance. Indeed, it took almost 30 years from when the drug was introduced on the market for pharmacovigilance authorities of various countries to start taking action in regulating its use, as described by Istvan and colleagues. However, due to the fact that our operating unit, which is entirely dedicated to the abuse of medications, has treated an extremely high number of cases of addiction to high doses of benzodiazepines and related hypnotics, we would like to contribute to better highlighting certain characteristics of zolpidem and its potential as a substance of abuse.

In their paper, Istvan and colleagues hint at the similarities between the regulation policies of flunitrazepam and zolpidem to draw conclusions about zolpidem's use. Italy has enacted the most restrictive regulations in the world on flunitrazepam, although this did not avoid that its use and abuse would overflow towards other molecules, starting from lormetazepam. Indeed, of the about 1400 cases of hospitalization for addiction to high doses of benzodiazepines and the like in our institution, none were due to flunitrazepam, while more than half of them were due to lormetazepam. Zolpidem was in fourth place among the 29 molecules present on the Italian market.[2]

Furthermore, we believe the term "Z-drugs" to be inappropriate: zolpidem, zopiclone, and zaneplon all have different chemical structures, they bind to different receptors, and they have completely different abuse potentials.[3] Indeed, both zopiclon and zaneplon were virtually absent from the cases that were brought to the attention of our institution, albeit both molecules being commonly used in Italy.

Lormetazepam, which is vastly prescribed by French doctors, deserves a separate discussion. Reports about its peculiar addictiveness are quite scarce in literature and virtually only come from Italy and Spain, which to our knowledge are the only countries in which the drug is sold in the form of drops. Of the cases we treated, 99% of the abusers that were hospitalized for addiction to lormetazepam were addicted to its soluble formula, unlike all other molecules for which tablets were found to be the most addictive.[3] This phenomenon is still unclear, but it is so evident in Italy that other countries should beware of introducing such a formula.[4] In Italy, lormetazepam has also shown to be the most abused intravenous drug for heroin addicts.[5]

Istvan and colleagues also highlight the fact that addiction and abuse are prevalent in populations suffering from mental illnesses. In our experience, this has not been confirmed: about half of our patients had no history of psychiatric illnesses, nor a history of addiction to illicit substances or alcohol.[2,6]

Lastly, regarding zolpidem's hazardousness, we would like to report the fact that zolpidem was significantly preferred by addicts with a positive ADHD test result.[5] These data should be kept in mind by institutions and services that study and handle neurodevelopmental issues.

We would like to conclude with an appeal regarding drug regulation policies.

The 2000s saw a solid confirmation of the effectiveness of partial agonists in the treatment of some common addictions, such as buprenorphine, varenicline, and cytisine. This did not happen for BZs despite the fact that some drugs (e.g., abecarnil) have been the subject of research for years. The pharmaceutical market has pushed the use of molecules such as zolpidem, which are similar to benzodiazepines and have thus gained significant market share, but that have often shown to have the same problems.

The same could be said about the therapies that are offered to those suffering from addiction to high doses of BZs and zolpidem. Although studies on slow-infusion flumazenil have proven to be the most promising for 30 years, there are very few facilities in the world that offer this practice.[7]

We hope that these points will stimulate a discussion about the most common off-label pharmaceutical usage in the world: that of BZs.

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The authors would like to remember Malcolm Lader (1936–2020), our mentor for pharmacological research about benzodiazepines and their misuse.

COMPETING INTERESTS

There are no competing interests to declare.

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