

Zolpidem: a masked hero. A reply to ZORRO study

Fabio Lugoboni¹, Rebecca Casari¹, Francesca Fusina², and Lorenzo Zamboni¹

¹Integrated University Hospital of Verona

²Università degli Studi di Padova

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Abstract

The use of zolpidem has been driven by the still-widespread false belief among doctors that, since zolpidem is chemically not a benzodiazepine, it cannot lead to addiction and tolerance. We would like to contribute to better highlight certain characteristics of zolpidem and its potential as a substance of abuse due to the fact that our operating unit, which is entirely dedicated to medication abuse, has described among the most numerous cases of addiction to high doses of benzodiazepines and related hypnotics. - Zolpidem was in fourth place among the 29 molecules present on the Italian market; - We believe it's now time to drop the term "Z-drugs": zolpidem, zopiclone e zaneplon all have different chemical structures, they bind to different receptors and have completely different abuse potentials³. In our case history, both zopiclon and zaneplon were virtually absent, albeit being commonly used in Italy; - Istvan & colleagues highlight the fact that addiction and abuse are prevalent in samples suffering from mental illness. In our case history this hasn't been confirmed: about half of our patients had no history of psychiatric illnesses, nor a history of addiction to illicit substances or alcohol; - Lastly, regarding zolpidem's hazardousness, we would like to report the fact that the drug was significantly preferred by addicts with a positive ADHD test result. In conclusion, the 2000s saw solid confirmation of the effectiveness of partial agonists in the treatment of some common addictions, such as buprenorphine, varenicline, cytisine. This didn't happen for BZs

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Dear Editor,

we have read the article by Istvan & colleagues, which recently appeared on your Journal¹, with great interest. The use of zolpidem has been driven by the still-widespread false belief among doctors that, since zolpidem is chemically not a benzodiazepine, it cannot lead to addiction and tolerance. Indeed, it took almost 30 years from when the drug was introduced for pharmacovigilance authorities of various countries to start taking action, as described by Istvan & colleagues. However, we would like to contribute to better highlight certain characteristics of zolpidem and its potential as a substance of abuse due to the fact that our operating unit, which is entirely dedicated to medication abuse, has described among the most numerous cases of addiction to high doses of benzodiazepines and related hypnotics.

1. Istvan & colleagues hint at the similarities between the regulation policies of flunitrazepam to draw conclusions about zolpidem. Italy has enacted the most restrictive regulations in the world on flunitrazepam, although this didn't avoid that use and abuse would overflow towards other molecules, starting from lormetazepam. Indeed, of 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 were due to lormetazepam. Zolpidem was in fourth place among the 29 molecules present on the Italian market².
2. We believe it's now time to drop the term "Z-drugs": zolpidem, zopiclone e zaneplon all have different chemical structures, they bind to different receptors and have completely different abuse potentials³.

In our case history, both zopiclon and zaneplon were virtually absent, albeit being commonly used in Italy.

3. Lormetazepam, towards which most prescriptions by French doctors turned, deserves a separate discussion. Reports about its peculiar addictiveness are quite scarce in literature and virtually only come from Italy and Spain, the only countries to our knowledge in which the drug is sold in the form of drops. In our case history, 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 prevalent². This phenomenon is still unclear, but it's so evident in Italy that other countries should beware of introducing such a formula⁴. In Italy, lormetazepam has also shown to be the most abused intravenous drug for heroin addicts⁵.
4. Istvan & colleagues highlight the fact that addiction and abuse are prevalent in samples suffering from mental illness. In our case history this hasn't 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}.
5. Lastly, regarding zolpidem's hazardousness, we would like to report the fact that the drug was significantly preferred by addicts with a positive ADHD test result⁷. This data should be kept in mind by services that handle neurodevelopment.

We would like to conclude with an appeal to those handling policies regarding drug regulations.

The 2000s saw solid confirmation of the effectiveness of partial agonists in the treatment of some common addictions, such as buprenorphine, varenicline, cytisine. This didn't 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 the same problems.

The same could be said about 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 thirty years, there are very few facilities in the world that offer this practice⁸.

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

Conflict of interest: none.

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

Bibliografia.

1. Istvan M, Caillet P, Rousselet M, et al. Change in the regulatory framework for zolpidem: what is the impact on the landscape of the prescription of sedative medications? The French national ZORRO study. *Br J Clin Pharmacol*. 2021 Epub ahead of print. doi: 10.1111/bcp.14753.
2. Faccini M, Tamburin S, Casari R, et al. High-dose lormetazepam dependence: strange case of Dr. Jekyll and Mr. Hyde. *Intern Emerg Med*. 2019 14:1271-8. doi: 10.1007/s11739-019-02101-8.
3. Rousselet M, Feuillet F, Gerardin M, ET AL. The French addictovigilance network clinical assessment: Z-drugs, true false twins. *Expert Opin Drug Saf*. 2017;16:1063-9. doi: 10.1080/14740338.2017.1346084.
4. Costa E, Sterzi E, Tedeschi F, Casari R, ET AL. Can oral formulation increase the risk of lormetazepam abuse? *Intern Emerg Med*. 2020 Epub ahead of print. doi: 10.1007/s11739-020-02538-2.
5. Lugoboni F, Bertoldi A, Casari R, et al. Adult Attention-Deficit/Hyperactivity Disorder and Quality of Life in High-Dose Benzodiazepine and Related Z-Drug Users. *Eur Addict Res*. 2020;26 :274-82. DOI: 10.1159/000507852
6. Lugoboni F, Mirijello A, Morbioli L, ET AL. Zolpidem high-dose abuse: what about the liver? Results from a series of 107 patients. *Expert Opin Drug Saf*. 2019;18:753-8. DOI: 10.1080/14740338.2019.1628216
7. Lugoboni F, Bertoldi A, Casari R, et al. Adult Attention-Deficit/Hyperactivity Disorder and Quality

- of Life in High-Dose Benzodiazepine and Related Z-Drug Users. *Eur Addict Res.* 2020;26:274-82. DOI: 10.1159/000507852.
8. Hood SD, Norman A, Hince DA, et al. Benzodiazepine dependence and its treatment with low dose flumazenil. *Br J Clin Pharmacol.* 2014;77:285-94. DOI: 10.1111/bcp.12023.