

# Zolpidem: a masked hero. A reply to ZORRO study

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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 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 potentials<sup>3</sup>. 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

## Zolpidem: a masked hero. A reply to ZORRO study

Dear Editor,

we have read the article by Istvan & colleagues, which recently appeared on your Journal<sup>1</sup>, 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 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 market<sup>2</sup>.
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 potentials<sup>3</sup>.

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 prevalent<sup>2</sup>. This phenomenon is still unclear, but it's so evident in Italy that other countries should beware of introducing such a formula<sup>4</sup>. In Italy, lormetazepam has also shown to be the most abused intravenous drug for heroin addicts<sup>5</sup>.
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<sup>2,6</sup>.
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 result<sup>7</sup>. 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 practice<sup>8</sup>.

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.

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