



Lormetazepam in oral solution: a formulation at risk of high-dose use

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Faccini et al. [1] studied the prevalence of high-dose use of benzodiazepines (BZDs), in particular lormetazepam (LMZ), among patients admitted for detoxification during a period of 15 years at an Italian tertiary center. They analyzed a sample of 882 patients, 79% of whom abused one BZD and 21% abused more than one BZD. The numbers of subjects abusing BZDs seem rather low for a tertiary center of a country of about 60 million people, considering that these data were collected over a period of 15 years, which means about 74 patients a year on average. This result seems to confirm that the potential for abuse has been dramatically portrayed in the scientific literature and by the media, despite the fact that recreational BZD abuse is uncommon and that rate of abuse of BZDs is low in relation to the number of people using them [2]. The reinforcing effects of benzodiazepines vary and are considerably weaker than those of other drugs of abuse such as other sedative hypnotics, stimulants and opiates [2]. On the other hand, the reinforcing effects of BZDs are stronger than those of drugs recognized as having little abuse potential, such as chlorpromazine [2].

Faccini et al. [1] reported a history of substance-use disorder (SUD) in 52.8% of the sample, with similar prevalence

among LMZ abusers and those who abused other BZDs. Thus, findings from the literature suggesting that BZDs are commonly abused by polysubstance abusers is confirmed. It should be noted that Faccini et al. [1] analyzed a heterogeneous sample which included subjects with poly-drug abuse, subjects with one-drug abuse, as well as subjects with one single BZD abuse. It would be interesting to examine larger and more homogeneous samples with regards to substance abuse patterns.

Unfortunately, only BZD abuse was investigated, although: (1) even the DSM-5 [3] noted that sedatives, hypnotics, and anxiolytics are at risk of abuse; (2) the vast majority of psychotropic medications have their issues related to the occurrence of withdrawal during the tapering or after the discontinuation [4, 5]; (3) several psychotropic medications (e.g., SSRI and SNRI) may trigger craving at tapering or discontinuation [4, 6, 7]. Indeed, the most informative question to ask about a drug's potential for abuse is not whether anyone abuses it, but whether those with no abuse history are likely to do so. People in the throes of addiction may find ways to abuse a great variety of substances, including benzodiazepines, antidepressants, anti-convulsants, and atypical neuroleptics.

An analysis by year of the number of patients admitted to the tertiary care unit was run and the authors concluded that LMZ has progressively become the main BZD of abuse from 2003 ($n = 3$) to 2018 ($n = 70$) with a peak in 2015 ($n = 94$) [1]. These results do not show that high-dose BZD abuse is emerging and the peak in 2015 does not seem like an epidemic. Pharmacoepidemiology data would be necessary to provide more information.

The single or main drug of abuse was LMZ ($n = 630$), followed by lorazepam ($n = 125$) and alprazolam ($n = 111$) [1]. Problems with alprazolam were reported before [8] and BZDs were not the same in terms of their association with tolerance, abuse and dependence [9].

LMZ oral solution was abused significantly more frequently (96.7%), while tablets were more commonly used by other BZD abusers (65.4%) [1]. This issue seems very important: most of those who abused LMZ abused it in oral

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solution form (only a small percentage abused it in pills). Since LMZ dissolves in alcohol, the oral solution form is an alcoholic solution. Thus, these patients not only used BZDs, but also alcohol in a fairly high dose, as noted by the authors. Since this might have serious clinical implications [10], it would be interesting to have more information on alcohol use disorder among LMZ oral solution abusers and among LMZ pill abusers. However, numbers were too low in this study to be informative. Studies in larger samples might provide further insight on this issue. It would also be interesting to ascertain whether patients are abusing LMZ or alcohol. The presence of alcohol in the oral solution of LMZ is the only factor which differentiated LMZ from other BZDs, and there is nothing unique about LMZ. It is another full-agonist benzodiazepine that can be abused under certain circumstances. In summary, this study does not provide evidence that BZD abuse is a large problem. On the contrary, it is not. The real problem is the oral solution of LMZ which should be either banned or restricted to patients not prone to developing alcohol use disorder and, more generally, not prone to developing SUDs.

These findings also calls for a more careful appraisal of the subtle psychological effects of various medications, including behavioral toxicity and iatrogenic comorbidity [11, 12].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statements on human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent None.

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