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High-dose lormetazepam dependence: strange case of Dr. Jekyll and Mr. Hyde

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Abstract
High-dose benzodiazepine (BZD) abuse is emerging as a substance use disorder (SUD). The aim of the study is to explore the impact of high-dose lormetazepam (LMZ) abuse and the characteristics of patients affected by this SUD in a tertiary referral addiction unit. We have retrospectively evaluated 1112 patients admitted to the Addiction Medicine Unit, Verona University Hospital, Italy for detoxification from high-dose BZD dependence. LMZ was the most common BZD, with an increasing prevalence from January 2003 to June 2018. Socio-demographic (more women; higher age and education) and clinical features (higher daily diazepam dosage equivalent, BZD abuse duration, age of first BZD intake; BZD prescribed more frequently for sleep disorders; less frequent history of other SUDs, previous/active alcohol, previous opioids abuse; more frequent overall major psychiatric diseases and major depression; less-frequent bipolar disorders and other psychoses, personality disorders, and more than one psychiatric disease) of LMZ vs. other BZD abusers significantly differed. 96.7% LMZ abusers took oral solution, while two-thirds of other BZD abusers took tablets. Oral solution, BZD abuse duration and prescription of BZD for sleep disorders increased, while history of other SUDs, previous/active alcohol and active cannabinoids SUD reduced the risk of high-dose LMZ vs. other BZDs abuse. The large prevalence of high-dose LMZ abusers in Italy may be strongly related to the availability and characteristics of oral formulation that may transform the innocuous Dr. Jekyll tablets into an evil Mr. Hyde. Restriction to the market of LMZ oral formulation might reduce the risk of high-dose abuse.

Keywords Benzodiazepine (BZD) · Lormetazepam · Abuse · Addiction · Oral solution · Substance use disorders (SUDs)

Introduction

Benzodiazepines (BZDs) are positive allosteric modulators of the gamma-amino-butyric acid type A (GABA-A) receptor that are prescribed for anxiety disorders, insomnia, epilepsy and other off-label conditions, and stand among the most widely-used pharmaceuticals worldwide [1, 2].

Guidelines and expert opinions suggest BZDs should be prescribed for short-term treatments [1, 3]. Among patients taking BZDs, 6–76% become long-term users [4], 15–44% experience moderate-to-severe withdrawal symptoms upon discontinuation [5], and 3–4% develop misuse or dependence [1].

High-dose BZD dependence is an emerging substance use disorder (SUD) [2, 6] associated with poor quality of life [7, 8] and multifocal cognitive dysfunction [9]. The prevalence of high-dose BZD dependence in Switzerland was estimated to be 0.16% of the adult population [10], but there are no data from other countries.

Single BZDs differ for pharmacodynamic and pharmacokinetic profiles, and their risk for high-dose abuse [11, 12]. Lormetazepam (LMZ) shows a remarkable selectivity for the GABA-A receptor α1 subunit [13] that causes the sedative-hypnotic effect of BZDs [14], and is marketed in Europe for the short-term treatment of insomnia. LMZ is an intermediate-acting BZD in tablet formulation, but the plasma peak concentration and bioavailability are higher and the peak time is shorter for oral solution [15-17]. LMZ is metabolized to LMZ glucuronide (86%, inactive) and *N*-demethylated LMZ (< 6%, active).

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We have previously reported that LMZ is the most widely used active principle in high-dose BZD users in Italy [5, 7, 8, 18, 19].

To offer new information on LMZ high-dose addiction, we explored a large population of high-dose BZD abusers admitted for detoxification from January 2003 to June 2018 in an Italian tertiary referral addiction unit and compared the socio-demographic and clinical features of LMZ vs. other BZDs abusers.

Subjects and methods

Patients

We have retrospectively evaluated data from 1112 patients (544 women, 568 men) aged > 18 years admitted (January 2003—June 2018) to the Department of Medicine, Addiction Medicine Unit, Verona University Hospital, Italy, a nationwide tertiary referral center for detoxification from high-dose BZD dependence with slow flumazenil infusion [5, 19]. High-dose BZD dependence was defined according to DSM-IV-TR criteria [20] with daily BZD intake exceeding at least five times the maximum daily recommended dose (i.e., > 50 mg daily diazepam dose equivalent, DDDE), and/or an otherwise problematic use, such as mixing BZDs, escalating dose, using BZDs for recreational purposes, or obtaining BZDs illegally [6, 7]. We included Z-drugs (i.e., zolpidem, zopiclone, and zaleplon), which are chemically distinct from BZDs, but they bind to the same GABA-A receptor complex, in particular to the α1 subunit, and their effects are similar to that of BZDs. BZD dose was standardized as DDDE (mg) according to conversion tables [19, 21].

The inclusion/exclusion criteria were: (a) age ≥ 18 years, (b) high-dose abuse of BZDs or Z-drugs, (c) misuse lasting > 6 months, (d) no acute drug intoxication, (e) no contraindications to slow flumazenil infusion.

The study was conducted according to the Declaration of Helsinki and approved by the ethics committee of the Verona University Hospital. All the patients gave written informed consent to the study.

Assessment procedures

Socio-demographic (sex, age, education, employment, marital status) and clinical variables (main BZD of abuse, other BZDs of abuse, DDDE, BZD abuse duration, age of first BZD intake, BZD formulation, reason for BZD prescription, other active SUDs, history of other SUDs, coexisting major psychiatric diseases) were collected for all the patients.

High-dose BZD dependence and coexisting psychiatric diseases were diagnosed with a clinical interview based on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders [22] and the Diagnostic Interview for DSM-IV Personality Disorders [23].

Statistical analysis

All tests were carried out with the IBM SPSS version 20.0. The normality of variable distribution was analyzed with the skewness-kurtosis test. Continuous variables were explored with t test in case of normal distribution, while the non-parametrical Mann–Whitney U test was applied when the distribution was not normal. Pearson's χ^2 test with Yates correction for continuity was applied to dichotomous variables. A logistic regression model analysis was used for exploring the influence of socio-demographic and clinical covariates on the main BZD of high-dose abuse (binary dependent variable: LMZ, 1; other BZDs, 0), and the results were expressed as odd ratios (ORs) and 95% confidence intervals (CIs). The goodness of fit of the logistic regression model was assessed using the Hosmer and Lemeshow test [24]. $p < 0.05$ (two-tailed) was taken as the significance threshold for all the tests.

Results

In our sample, 882 patients (79%) abused of a single BZD, while 230 (21%) abused of two or more BZDs. The single or main active principle of abuse was LMZ in 630 patients (57%), lorazepam in 125 (11%), alprazolam in 111 (10%), zolpidem in 102 (9%), clonazepam in 37 (3%), bromazepam in 31 (3%), diazepam in 23 (2%), triazolam in 21 (2%), and another BZD in 32 (3%; delorazepam, $N = 14$; etizolam, $N = 7$; zopiclone, $N = 5$; flurazepam, $N = 3$; prazepam, $N = 2$; brotizolam, $N = 1$; Table 1). The daily dose and its ratio with the maximum recommended daily dose for the main BZD of abuse are reported in Table 1. Analysis of the number of patients admitted to our Addiction Medicine Unit by year showed that LMZ has progressively become the main BZD of abuse from 2003 ($n = 3$) to 2018 ($n = 70$) with a peak in 2015 ($n = 94$; Fig. 1). Patients were divided into LMZ vs. other BZDs abusers for further analyses.

Among socio-demographic variables, LMZ abusers showed significantly larger number of women, higher age and higher education (grade school 34.9%, high school 44.8%, university 20.3%) in comparison to other BZD abusers (education: grade school 41.3%, high school 37.1%, university 21.6%), while employment and marital status did not differ between the two groups (Table 2).

Clinical variables are reported in Table 3. DDDE, BZD abuse duration and age of first BZD intake were significantly higher in LMZ than other BZD abusers. Oral solution was strikingly and significantly more frequent in LMZ abusers (96.7%), while tablet was more common in other

Table 1 Daily dose of the main benzodiazepine (BZD) of high-dose abuse

Main BZD	Average daily dose (ADD, mg)[a]	Maximum daily dose (MDD, mg)[b]	ADD/MDD ratio[c]
Lormetazepam ($n=630$)	68.6 ± 67.8; 25.0–75.0	2	34.3
Lorazepam ($n=125$)	38.7 ± 93.2; 10.6–39.4	7.5	5.2
Alprazolam ($n=111$)	16.8 ± 13.3; 7.0–20.0	4	4.2
Zolpidem ($n=102$)	480.8 ± 418.8; 200.0–600.0	10	48.1
Clonazepam ($n=37$)	34.1 ± 40.5; 10.0–40.0	8	4.3
Bromazepam ($n=31$)	118.0 ± 167.3; 27.5–100.0	9	13.1
Diazepam ($n=23$)	87.4 ± 68.2; 36.5–125.0	10	8.7
Triazolam ($n=21$)	8.9 ± 10.2; 2.5–14.5	0.25	35.6
Other BZDs ($n=32$)	–	–	–

[a]Data reported as mean ± SD; interquartile range

[b]Recommended maximum daily dose for adult patients according to the package leaflet/information for the user

[c]Ratio between ADD (mean value) and MDD

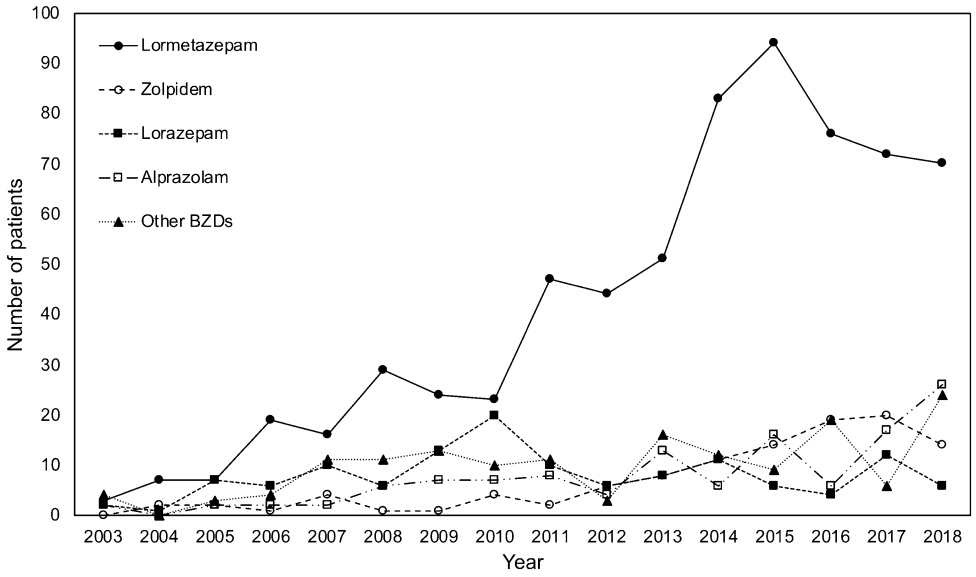

Fig. 1 Number of patients admitted to the Addiction Medicine Unit, Verona University Hospital, Italy for high-dose benzodiazepine (BZD) dependence according to the main BZD of abuse in years 2003–2018. Data for year 2018 were estimated by extrapolation from those admitted from January to June 2018

BZD abusers (oral solution: 31.3%, tablets: 65.4%). No statistical comparison between patients taking LMZ oral solution ($n=609$) vs. LMZ tablets ($n=13$) was performed, because of the disproportion between the two groups that would have reduced the strength of the findings. Reasons for BZD prescription significantly differed, because sleep and anxiety disorders were the main reasons for LMZ and other BZDs prescription, respectively. History of other SUDs, previous or active alcohol abuse and previous opioids abuse were significantly more common in other BZDs vs. LMZ group. Overall, major psychiatric diseases and major depression were significantly more common in LMZ vs. other BZDs group, while bipolar disorders and other psychoses, personality disorders, and more than one psychiatric disease were significantly more common in other BZDs vs. LMZ groups.

The multivariate logistic regression model showed that oral solution (odds ratio, OR = 120.3), BZD abuse duration (OR = 1.004) and prescription of BZD for sleep disorders (OR = 4.7) increased the risk of abusing of LMZ vs. other BZDs (Table 4). Conversely, history of other SUDs (OR = 0.41), previous (OR = 0.23) or active alcohol abuse (OR = 0.26) and active cannabinoids abuse (OR = 0.33) significantly reduced the risk of being LMZ vs. other BZDs abusers, while the remaining covariates were not significant (Table 4).

Discussion

The present report offered new information on high-dose LMZ abusers in a large sample ($n=1112$) of high-dose BZD-addicted patients admitted to an Italian tertiary

Table 2 Socio-demographic characteristics of the patients

Variable	Overall population ($n=1112$)	LMZ abusers ($n=630$)[f]	Other BZDs abusers ($n=482$)[g]	p value[h]
Sex (male/female)[a]	568 (51.1%)/544 (48.9%)	305 (48.4%)/325 (51.6%)	263 (54.6%)/219 (45.4%)	0.042*
Age[b]	44.9 ± 10.9; 37–52	45.5 ± 11.0; 38–52	44.0 ± 10.7; 37–51	0.025*
Education[c]	419/461/232	220/282/128	199/179/104	0.03*
Employment[d]	543 (48.8%)/569 (51.2%)	300 (47.6%)/330 (52.4%)	243 (50.4%)/239 (49.6%)	n.s
Marital status[e]	650 (58.5%)/462 (41.5%)	369 (58.6%)/261 (41.4%)	281 (58.3%)/201 (41.7%)	n.s

*Marks significant comparisons

[a]Data reported as *n* (% of row)

[b]Mean ± SD; interquartile range

[c]Education: grade school/high school/university

[d]Employment: unemployed/employed

[e]Marital status: single or divorced/engaged or married

[f]Patients for whom the main benzodiazepine (BZD) of high-dose abuse was lormetazepam (LZM)

[g]Patients for whom the main BZD of high-dose abuse was different from LMZ

[h]*p* value for LMZ abusers vs. other BZDs abusers comparison

addiction unit as inpatients. We documented that LMZ is the most common (i.e., 57% of patients) active principle in our population of high-dose BZD abusers, and that the number of patients admitted to our addiction unit for high-dose LMZ dependence progressively increased from 2003 to 2018. We also defined the socio-demographic (i.e., more women; higher age and education) and clinical features (i.e., higher DDDE, BZD abuse duration, age of first BZD intake; BZD prescribed more frequently for sleep disorders; less frequent history of other SUDs, previous/active alcohol, and previous opioids abuse; more frequent overall major psychiatric diseases and major depression; less frequent bipolar disorders and other psychoses, personality disorders, and more than one psychiatric disease) of high-dose LMZ vs. other BZD abusers. Nearly all (i.e., 96.7%) of our high-dose LMZ abusers took oral solution, while two thirds of other BZD abusers took tablets. The multivariate logistic regression model indicated that, among variables that were significant in univariate analysis, oral solution, BZD abuse duration and prescription of BZD for sleep disorders increased, while history of other SUDs, previous/active alcohol and active cannabinoids SUD reduced the risk of high-dose LMZ vs. other BZDs abuse.

Data on high-dose BZD abuse are scanty. The striking prevalence of LMZ in comparison to other BZDs in Italian patients confirms previous studies from our group [5,7,8,18,19]. Other authors explored high-dose BZD abusers outside Italy, but they did not report data on single BZDs use [2,6]. A study on 2183 New England veterans with post-traumatic stress disorder and alcoholism, nearly all males and in prevalence aged 41–60 years, documented that 234 received doses of alprazolam, clonazepam, diazepam, or lorazepam that were above those typically recommended [25]. Results from the Luxembourg national health insurance registry showed that hypnotics and the triazolo-BZDs alprazolam and triazolam, which are very liposoluble, had higher risk for high-dose use, the highest risks being with triazolam, but long-term high-dose users were on average older than our patients [12]. Despite the paucity of data worldwide, and the difficulty of comparing our findings to those from New England and Luxembourg reported above [12,25] because of the differences in methods and patient samples, high-dose LMZ abuse seems to be a peculiar SUD with a large prevalence in Italy.

The very large number of high-dose LMZ abusers in our population seems to parallel the consumption of this BZD. The LMZ-defined daily dose (DDD) in 2017 was 13.0/1000 people, with a 9% increase vs. 2016, making LMZ by far the most popular of the 29 BZDs and Z-drugs in Italy (i.e., 29% of all the BZD/Z-drugs DDDs in 2017) [26]. For comparison, the 2017 DDD/1000 people of other commonly prescribed BZDs was 10.2 for lorazepam, 8.7 for alprazolam, 4.1 for zolpidem, 3.3 for triazolam, 2.3 for delorazepam, 1.4 for bromazepam and brotizolam, 1.2 for diazepam, and 0.6 for flurazepam [26]. These figures suggest that the number of LMZ prescriptions in the general population may be the main reason for the higher likelihood of high-dose abuse, but a direct correlation between BZD prescription and high-dose abuse does not completely explain our findings. When considering only more popular BZDs in Italy, the 2017 DDD for LMZ was 1.3 times that of lorazepam, 1.5 times that of alprazolam, and 3.2 that of zolpidem. However, the number of high-dose LMZ abusers in our population was 5.2 times that of lorazepam, 5.7 times that of alprazolam and 6.3 times that of zolpidem abusers, respectively, suggesting that other additional factors might have contribute to our results. A very large and progressively increasing number of DDD of LMZ was reported in Italy [26] and Spain [27], which are

Table 3 Clinical characteristics of the patients

Variable	Overall population ($n=1112$)	LMZ abusers ($n=630$)[g]	Other BZDs abusers ($n=482$)[h]	p value[i]
DDDE (mg)[a,b]	357.9 ± 479.7; 125–450	358.7 ± 351.2; 125–500	356.6 ± 625.0; 100–425	< 0.001*
BZD abuse duration (months)[a]	87.2 ± 87.6; 24–120	89.5 ± 83.5; 20–120	84.3 ± 92.7; 26–120	0.008*
Age of first BZD intake[a]	30.3 ± 10.6; 23–37	31.3 ± 10.5; 23–38	29.0 ± 10.6; 20–35	< 0.001*
Oral BZD formulation[c]				< 0.001*
Tablet	328 (29.5%)	13 (2.0%)	315 (65.4%)	
Solution	760 (68.3%)	609 (96.7%)	151 (31.3%)	
Both	24 (2.2%)	8 (1.3%)	16 (3.3%)	
Reason for BZD prescription[c]				< 0.001*
Anxiety disorders	501 (45.1%)	217 (34.4%)	284 (58.9%)	
Sleep disorders	389 (35.0%)	259 (41.2%)	130 (27.0%)	
Other/more than one reason	222 (19.9%)	154 (24.4%)	68 (14.1%)	
Other active SUDs (yes/no)[d]	311 (28.0%)/801 (72.0%)	171 (27.1%)/459 (72.9%)	140 (29.0%)/342 (71.0%)	n.s
History of other SUDs (yes/no)[d]	587 (52.8%)/ 525 (47.2%)	315 (50.0%)/315 (50.0%)	272 (56.4%)/210 (43.6%)	0.033*
Alcohol[e]	722/214/176	443/95/92	279/119/84	< 0.001*
Opioids[e]	907/163/42	520/79/31	387/84/11	0.008*
Cocaine[e]	799/238/75	436/148/46	363/90/29	n.s
Cannabinoids[e]	860/200/52	490/111/29	370/89/23	n.s
Major psychiatric diseases (yes/no)[d]	1017 (91.5%)/95 (8.5%)	559 (88.7%)/71 (11.3%)	458 (86.7%)/24 (13.3%)	< 0.001*
Major depression (yes/no)[d]	700 (62.9%)/412 (37.1%)	433 (68.7%)/197 (31.3%)	267 (55.4%)/215 (44.6%)	< 0.001*
Other psychoses (yes/no)[d,f]	94 (8.5%)/1018 (91.5%)	42 (6.7%)/588 (93.3%)	52 (8.3%)/430 (91.7%)	0.014*
Personality disorders (yes/no)[d]	112 (10.0%)/1000 (90.0%)	48 (7.6%)/582 (92.4%)	64 (10.3%)/418 (89.7%)	0.002*
More than one disease (yes/no)[d]	111 (10.0%)/1001 (90.0%)	36 (5.7%)/594 (94.3%)	75 (11.9%)/407 (88.1%)	0.008*

SUDs substance use disorders

*Significant comparison

[a]Mean ± SD; interquartile range

[b]Sum of the daily diazepam dose equivalent (DDDE) for all benzodiazepines (BZDs) in case of abuse of two or more BZDs

[c]Data reported as *n* (% of column)

[d]Data reported as *n* (% of row)

[e]Absent/previous/active

[f]Bipolar disorders and other psychoses

[g]Patients for whom the main benzodiazepine (BZD) of high-dose abuse was lormetazepam (LZM)

[h]Patients for whom the main BZD of high-dose abuse was different from LZM

[i]*P* value for LMZ abusers vs. other BZD abusers comparison

the only countries in Europe where LMZ is marketed as oral solution (see below for discussion of the features of this formulation), while other BZDs (e.g., lorazepam, alprazolam, diazepam) are more popular in other countries [28,29].

According to the Eudra Vigilance data of the European Medicine Agency, 48% of the 1656 adverse drug reactions of LMZ are from Italy, suggesting a high likelihood of side effects in this country [30]. However, the different sensitivity of clinicians and health services across European countries to notify adverse events might have contributed to these findings.

Some pharmacodynamic and pharmacokinetic features of LMZ might explain the high percentage of high-dose abusers in our population. LMZ has remarkable selectivity for the GABA-A receptor α1 subunit [13], and α1-containing GABA-A receptors in the ventral tegmental area have been demonstrated to be particularly relevant for BZD addiction in animal models [3,31–33]. The therapeutic window of LMZ is quite narrow, in that the maximum recommended daily dose in adults is 2 mg, accounting for 1–2 tablets or 20 drops of oral solution. The ratio between the average daily dose and the recommended maximum daily dose in our sample was nearly 35 (Table 1), i.e., among the biggest ones in together with zolpidem and triazolam. This finding suggests that LMZ high-dose abusers become progressively unresponsive to this BZD and is in keeping with data from animal models that point to significant decrease in the isoform α1 of the GABA-A receptor leading to BZD-receptor decoupling after prolonged BZD stimulation [32–34]. High lipid solubility of LMZ

Table 4 Results of the multivariate logistic regression model analysis for being LMZ vs. other BZDs high-dose abuser

Significant covariates	OR [95% CI]	*P* value
Oral BZD formulation		
Tablet	1	
Solution	120.3 [58.0–249.4]	< 0.001
BZD abuse duration (months)	1.004 [1.001–1.007]	0.008
Reason for BZD prescription		
Anxiety disorders	1	
Sleep disorders	4.7 [2.7–8.3]	< 0.001
History of other SUDs		
No	1	
Yes	0.41 [0.18–0.92]	0.03
Alcohol abuse		
No	1	
Previous	0.23 [0.11–0.52]	< 0.001
Active	0.26 [0.11–0.60]	0.002
Cannabinoids abuse		
No	1	
Active	0.33 [0.12–0.93]	0.036

Here are reported only covariates that turned out to be significant in the multivariate logistic regression model analysis

BZD benzodiazepine, *CI* confidence interval, *OR* odds ratio, *SUDs* substance use disorders

that results in higher bioavailability may have also contributed to our findings.

Among the data we collected to understand the reason of the great number of high-dose LMZ abusers, the most striking feature is that 96.7% of them took LMZ oral solution, while only a minority took either tablet (2.0%) or both formulations (1.3%). The disproportion between patients taking oral solution and tablets hampered any robust statistical comparison between the two subpopulations of high-dose LMZ abusers. There are, however, a number of hypotheses that may explain the preference for LMZ oral solution and its high addictive risk. LMZ oral solution has higher bioavailability (i.e., 173%), higher plasma concentration (i.e., 138%) and shorter peak time (median t_{max}: 30′), resulting in faster absorption and more rapid effect than tablet formulation (median t_{max}: 90′) [16]. LMZ oral solution pharmacokinetics features increase the risk of abuse, because BZDs with shorter half-life are associated with a greater risk of dependence [3,35]. Another reason for the higher number of high-dose LMZ abusers taking oral solution is the presence of 95% alcohol in this formulation, accounting for 15 mg of alcohol per 20 ml bottle. The LMZ daily dose was on average 68.6 mg (i.e., 1.37 bottles) with an interquartile range (IQR) of 25–75 mg (i.e., 0.5–1.5 bottles) corresponding to 20.5 g (IQR 7.5–22.5 g) of alcohol, which is close to the recommended maximum daily dose for men (i.e., 24 g) and nearly the double of that for women (i.e., 12 g) according to the Italian Ministry of Health [36]. The involuntary intake of alcohol with LMZ oral solution might bring the serum alcohol level close to the 0.5 g/L cutoff to withdraw the driving license in Italy. Alcohol acts as a positive allosteric modulator of the GABA-A receptor on a different binding site than BZDs, and the involuntary contemporary intake of alcohol might contribute to the higher risk of high-dose abuse with LMZ. Finally, the good taste of LMZ solution might favor its direct intake in the mouth without dilution, further increasing fast absorption via sublingual route. In contrast, the taste of other BZD solutions (e.g., lorazepam) is usually reported as unpleasant, thus requiring dilution in water.

The socio-demographic profile of high-dose LMZ abusers was characterized by significantly larger number of women, higher age and higher education than other BZDs abusers. These features are in keeping with those previously reported by our group in a smaller population [37]. Prevalence of females are in accordance with population surveys [27,38–40], and the Luxembourg national health insurance registry [12]. However, socio-demographic characteristics did not survive multivariate analysis as predictors of high-dose LMZ abuse, probably because they covariated with clinical ones.

BZD-related clinical features of high-dose LMZ abusers included higher DDDE, longer BZD abuse duration, higher age of first BZD intake, and higher likelihood that BZD were prescribed for sleep disorders. Higher DDDE and longer BZD abuse duration in LMZ abusers are in keeping with the literature [12,18,37], and the pharmacodynamics features that make LMZ more prone to high-dose abuse (see above). Higher age of first BZD intake may be related to the higher overall age of LMZ abusers, and further support the view of a specific socio-demographic profile of these patients. Not surprisingly, the likelihood that the BZD was prescribed for sleep disorders was high for LMZ, being this BZD indicated as a hypnotic. BZDs are divided into anxiolytic and hypnotic agents on the basis of their pharmacodynamics and clinical effects, but in principle their anxiolytic, hypnotic, muscle-relaxant, and anticonvulsant effects largely overlap [3], and both anxiolytics and hypnotics may be indifferently prescribed for anxiety and sleep disorders in some settings [41,42]. The problem of long-term BZD prescription is widely known [43], despite guidelines recommend BZDs should be used only for short-term treatments [1,3], and more attention should be paid to the information for prescribers. BZD abuse duration and prescription of BZD for sleep disorders survived multivariate analysis as significant predictors of high-dose LMZ abuse.

In our sample, patients with high-dose LMZ abuse showed less-frequent history of other SUDs, previous/active alcohol, and previous opioids abuse. Multivariate analysis documented history of other SUDs, previous/active alcohol and active cannabinoids SUD as negative predictors of high-dose

LMZ abuse. High-dose BZD abusers are known to frequently show poly-drug abuse [44], in particular coexistent alcohol abuse [3], and great care is recommended when prescribing BZDs in patients with other SUDs [45]. Our data add a piece of information to this notion, in that they suggest high-dose LMZ abuse may occur in patients with no other SUDs and underscore that patients, who are not considered particularly prone to SUD, may abuse of LMZ at high doses.

The psychiatric comorbidities of high-dose LMZ abusers included more frequent overall major psychiatric diseases and major depression but less-frequent bipolar disorders and other psychoses, personality disorders, and more than one psychiatric disease. These findings indicate that psychiatric history might be helpful for stratifying the risk of LMZ abuse before prescribing BZDs. However, psychiatric features were not confirmed as significant predictors in multivariate analysis, suggesting that some covariates might have influenced our findings [37]. Moreover, our patients did not undergo routine psychiatric consultation to confirm diagnoses [37], and further studies are needed on this topic.

The main limitation of the present study is its retrospective nature and the little generalizability to other populations outside Italy. Moreover, the cutoff value for daily BZD dose (i.e., > 50 mg DDDE) we chose might have biased towards selection of more LMZ than other BZDs abusers.

In conclusion, we reported a very large number of patients taking LMZ in a population of high-dose BZD abusers referred to a tertiary addiction unit in Italy. Among predictors of high-dose LMZ abuse, the most striking factor was the use of oral solution. These data are at variance with previously published reports from other countries, where oral solution is not marketed. Our findings suggest that some features of LMZ solution may transform an innocuous Dr. Jekyll, i.e., LMZ tablets, into the evil Mr. Hyde, namely LMZ drops. Flunitrazepam was very popular among addicted patients in the 80s and 90s decades of the last century. Some specific restrictions, such as withdrawing oral solution from the market, consistently reduced flunitrazepam abuse and intravenous misuse [46,47]. A similar restrictive measure could be useful for LMZ and should be considered by regulatory authorities.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Statement of human and animal rights The study was conducted according to the Declaration of Helsinki and approved by the ethics committee of the Verona University Hospital.

Informed consent All the patients gave written informed consent to the study.

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