International Journal of Risk & Safety in Medicine 32 (2021) 295–320
DOI 10.3233/JRS-210014
IOS Press

Mono- and poly-therapy with benzodiazepines or Z-drugs: Results from a tertiary-care Addiction Unit study

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Received 1 March 2021
Accepted 13 May 2021

Abstract.
BACKGROUND: Using benzodiazepines (BZDs) or Z-drugs in poly-therapy is a critical issue.
OBJECTIVE: Identifying factors influencing the use of BZDs/Z-drugs in poly- vs mono-therapy in patients with or without substance use disorders (SUDs).
METHODS: 986 inpatients were analysed. Socio-demographic and clinical variables were collected. BZD/Z-drug doses were compared via the Defined Daily Dose (DDD) and standardized as diazepam dose equivalents. Mann-Whitney, Chi-square, Fisher test, hierarchical multivariate regression analyses were run referring to the whole sample and to subjects with current SUDs, lifetime SUDs, current and lifetime SUDs, non-SUDs.
RESULTS: In the whole sample the variance of being mono- vs poly-therapy users was explained by BZD/Z-drug formulation, DDD, duration of treatment, age of first BZDs/Z-drugs use ($\Delta R^2 = 0.141$, $p < 0.001$). Among those with current SUDs ($\Delta R^2 = 0.278$, $p = 0.332$) or current and lifetime SUDs ($\Delta R^2 = 0.154$, $p = 0.419$), no variables explained the variance of being mono-vs poly-therapy users. Among lifetime SUDs subjects, the variance of being mono- vs poly-therapy users was explained by BZD/Z-drug formulation and age of first BZD/Z-drug use ($\Delta R^2 = 0.275$, $p < 0.001$). Among non-SUDs subjects, the variance of being mono- vs poly-therapy users was explained by DDD and duration of treatment ($\Delta R^2 = 0.162$, $p = 0.001$).
CONCLUSIONS: Tablets, high drug doses, long duration of treatment, and early age of first use were more likely associated to poly- than mono-therapy. This suggests that patients have different clinical features and a pharmacological prescription should be tailored to them also based on the variables here analysed.

Keywords: Mono-therapy, poly-therapy, poly-pharmacy, substance use disorder, benzodiazepine, Z-drug

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1. Introduction

Benzodiazepines (here abbreviated as BZDs) and non-benzodiazepine receptor agonists (here abbreviated as Z-drugs) are currently prescribed with prevalence rates in the general population ranging from 2% to 17% for BZDs [1–3] and from 2% to 9% for Z-drugs [2,4]. BZDs and Z-drugs are used in mono-therapy or in poly-therapy; prevalence rates in the general population range from 23% to 44% [5,6] for mono-therapy and from 9% to 29% [2,4,5,7] for poly-therapy.

Of course, mono- and poly-therapy users differ for clinical features. Poly-therapy users are more prevalent than mono-therapy users when the duration of the treatment is longer or the dose is higher [4,6,8,9]. Poly-therapy users have higher rates of adverse events, toxicity, harmful drug-to drug interactions, and increased risk of mortality, including the one due to suicide, than mono-therapy users [10–12]. Poly-therapy users are highly represented among Substance Use Disorder (SUD) patients, with 34.6% using more than one BZD and 20% using both BZDs and Z-drugs [9].

Unfortunately, the investigation of the potential factors influencing the risk of using BZDs or Z-drugs in poly-therapy rather than in mono-therapy has not received enough attention. A recent study conducted in the general population found that current depressive symptoms and obesity are associated with two-fold increased risk of BZD/Z-drug use in poly-therapy than in mono-therapy [13] while no studies have been run among SUDs patients.

In this framework, we examined mono-therapy and poly-therapy users with the aim of identifying socio-demographic and clinical characteristics influencing the risk of using BZDs or Z-drugs in poly-therapy, versus mono-therapy, in patients with or without SUDs.

2. Methods

2.1. Participants

BZD/Z-drug dependent patients consecutively admitted at the Addiction Unit (AU) of the Verona University Hospital (Verona, Italy) from January 2003 to June 2019 were screened. Subjects had to meet the following inclusion criteria: 1. age ≥ 18 years; 2. a diagnosis of BZD/Z-drug dependence according to the DSM-IV-TR criteria [14] lasting from at least 180 days [3] (the DSM-IV-TR diagnosis of dependence is based on at least 3 dependence criteria while the DSM-5 diagnosis of substance use disorder is based on at least 2 substance use disorder criteria which may include both abuse and dependence criteria according to the DSM-IV-TR); 3. a BZD/Z-drug daily consumption > 5 times the maximum daily dose recommended (i.e., 50 mg daily diazepam dose equivalent) [15,16].

Written informed consent was obtained from all eligible patients. The study protocol fully adhered to the guidelines of the Ethic Committee of the Verona University Hospital.

2.2. Procedure

Socio-demographic (i.e., age, sex, marital status, education, working activity) and clinical data (i.e., smoking status, BZD/Z-drug used, BZD/Z-drug average daily dose in the last 180 days, duration of BZD/Z-drug use, age of BZD/Z-drug first use, formulation of BZD/ Z-drug used) were collected via a set of interview-based screening questions already used in the past [17]. Psychiatric disorders were assessed via the Structure Clinical Interview for DSM-IV – Patient Version (SCID-I-P) [18]. The SCID-I-P showed excellent validity and reliability [18]. The Italian version is consistent with the English one [19].

Personality disorders were assessed via the semi-structured Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV) [20]. The DIDP-IV showed good inter-rater and test-retest reliability [20].

2.3. Statistical analyses

The Kolmogorov–Smirnov test was run to test normality of data [21]. Given that data were non-normally distributed, Mann-Whitney matched pairs test was used to compare rank means of continuous variables [22]. Chi-square tests or Fisher test, when more than 20% of cells had expected frequencies less than 5 [23], were run to compare rates.

BZD/Z-drug doses were compared via the Defined Daily Dose (DDD) (i.e., the therapeutic daily dose according to the World Health Organization) [24], BZD/Z-drug dose was standardized as diazepam dose equivalents according to conversion tables [25,26].

Subjects were stratified based on the number of BDZs/Z-drugs used. Mono-therapy users were defined as those who used only one BZD or Z-drug, poly-therapy users were defined as those who used more than one BZD or Z-drug [27]. The comparisons between mono- and poly-therapy users were run for the whole sample as well as separately for groups of patients with current SUDs, lifetime SUDs, current and lifetime SUDs, or without SUDs. Since tobacco smoking appears to be different to other substances in terms of tolerance, time spent to have it or to dispose of the effect, hazardous use, perceived difficulty quitting, and toxic effects [28,29], cigarette smoking was not considered as a SUD.

Hierarchical multivariate regression analyses were run to identify predicting variables influencing the risk of using BZDs or Z-drugs in mono-therapy or in poly-therapy for the whole sample as well as separately for the groups described above. Mono-therapy vs poly-therapy users was used as reference. The entry order of predicting variables was the following for all regressions (this methodological choice was taken to increase the comparability of the results): sex, working activity, education, lifetime alcohol use, current and lifetime barbiturate use were entered at Step 1 as adjusting variables; duration of BZD/Z-drug use and diazepam equivalent were entered respectively at Steps 2 and 3 since they significantly differed between mono- and poly-therapy users in one out of the five comparisons taken into account (i.e., the whole sample, patients with current SUDs, patients with lifetime SUDs, patients with current and lifetime SUDs, patients without SUDs); daily dose, which significantly differed between mono- and poly-therapy users in 2 out of 5 comparisons, was entered at Step 4; DDD, which significantly differed between mono- and poly-therapy users in 3 out of 5 comparisons, was entered at Step 5; age of first BZD/Z-drug use, which significantly differed between mono- and poly-therapy users in 4 out of 5 comparisons, was entered at Step 6; formulation of BZD/Z-drug used (i.e., tablets or drops), which significantly differed between mono- and poly-therapy users in all comparisons, was entered at Step 7. Two-sided signicance level was set at $p \leq 0.05$. Analyses were performed via SPSS, version 21 (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 1,112 BZD/Z-drug users were consecutively enrolled at the AU of the Verona University Hospital (Verona, Italy) from January 2003 to June 2019. Among them, 126 were excluded because using both tablets and drops ($n = 109$) or had missing data on the formulation information ($n = 17$).

A total of 986 subjects were analysed, 515 (52.23%) were males and 471 (47.77%) females, the mean age was 44.95 ± 10.83 years. Table 1 shows demographic and clinical characteristics of the whole sample. Most of the subjects were unmarried, had a high school degree, and were employed. A total of 112 (11.36%) subjects had a current SUD, 231 (23.43%) a lifetime SUD, 183 (18.56%) both current

Table 1
Demographic and clinical variables. Total sample (n = 986)

	n (%)
DEMOGRAPHIC VARIABLES	
Marital status	
Married	284 (28.80%)
Unmarried	508 (51.52%)
Cohabitant	90 (9.13%)
Widower	14 (1.42%)
Missing	90 (9.13%)
Education	
Primary school	55 (5.58%)
Secondary school	290 (29.41%)
High school	392 (39.76%)
Graduation	192 (19.47%)
Missing	57 (5.78%)
Working status	
Employed	488 (49.49%)
Unemployed	275 (27.89%)
Housewife/retired/invalid	198 (20.08%)
Missing	25 (2.54%)
CLINICAL VARIABLES	
Substance use disorder	
Current substance use disorder	112 (11.36%)
Alcohol use	75 (7.61%)
Cocaine use	25 (2.55%)
THC use	16 (1.62%)
Heroin use	6 (0.61%)
Barbiturates use	4 (0.40%)
Lifetime substance use disorder	231 (23.43%)
Alcohol use	138 (13.99%)
Cocaine use	113 (11.46%)
THC use	89 (9.03%)
Heroin use	74 (7.51%)
Barbiturates use	0 (0.00%)
Current and lifetime substance use disorder	183 (18.56%)
Alcohol use	124 (12.58%)
Cocaine use	142 (14.40%)
THC use	119 (12.07%)
Heroin use	107 (10.85%)
Barbiturates use	5 (0.51%)
No substance use disorder	460 (46.65%)
Smoking status	
Current smokers	637 (64.60%)
Past smokers	75 (7.61%)
Non smokers	255 (25.86%)
Missing	19 (1.93%)

Table 1 (Continued).

	n (%)
Current psychiatric disorder	
Present	901 (91.38%)
Absent	84 (8.52%)
Missing	1 (0.10%)
Type of current psychiatric disorder	
Anxiety/depressive disorders	767 (77.79%)
Personality disorders	116 (11.76%)
Eating disorders	6 (0.61%)
Psychotic disorder	5 (0.51%)
ADHD	4 (0.40%)
Obsessive compulsive disorder	3 (0.30%)
Other	19 (1.93%)
Missing	94 (9.53%)
BZD used	
Lormetazepam	580 (58.82%)
Lorazepam	142 (14.40%)
Alprazolam	118 (11.97%)
Clonazepam	42 (4.26%)
Bromazepam	39 (3.95%)
Triazolam	39 (3.95%)
Diazepam	34 (3.45%)
Delorazepam	21 (2.13%)
Flurazepam	12 (1.22%)
Etizolam	9 (0.91%)
Flunitrazepam	4 (0.40%)
Oxazepam	3 (0.30%)
Temazepam	2 (0.20%)
Brotizolam	2 (0.20%)
Prazepam	2 (0.20%)
Ketazolam	–
Z-drugs used	
Zolpidem	107 (10.85%)
Zoplicone	3 (0.30%)
Other BZD/Z-drugs not specified	3 (0.30%)
Formulation of BZD/Z-drugs used	
Tablets	298 (30.22%)
Drops	688 (69.78%)

Note ADHD: attention deficit hyperactivity disorder; BZD: benzodiazepine; Z-drugs: non-benzodiazepine receptor agonists.

and lifetime SUDs, 460 (46.65%) did not report SUDs. Cocaine and alcohol had the highest rates of current/lifetime use. The majority were current smokers (n = 637, 64.60%) and had at least one current psychiatric disorder (n = 901, 91.38%).

Among BZDs, lormetazepam had the highest rate of use, followed by lorazepam, and alprazolam. Among Z-drugs, zolpidem had the highest rate of use.

Table 2
Comparison between mono-therapy users (n = 846) and poly-therapy users (n = 140). Chi-square and Fisher test

	Mono-therapy users		Poly-therapy users			
	n	*n* (%)	*n*	*n* (%)	Chi-square$_{(df)}$	*p*
DEMOGRAPHIC VARIABLES						
Marital status	774		122			
Married		247 (31.91%)		37 (30.33%)	$0.15_{(3)}$	0.985
Unmarried		437 (56.46%)		71 (58.20%)		
Cohabitant		78 (10.08%)		12 (9.84%)		
Widower		12 (1.55%)		2 (1.63%)		
Education	801		128			
Primary school		48 (5.99%)		7 (5.47%)	$1.15_{(3)}$	0.764
Secondary school		252 (31.46%)		38 (29.69%)		
High school		340 (42.45%)		52 (40.62%)		
Graduation		161 (20.10%)		31 (24.22%)		
Working status	824		137			
Employed		431 (52.30%)		57 (41.60%)	$6.26_{(2)}$	**0.044**
Unemployed		232 (28.16%)		43 (31.39%)		
Housewife or retired or invalid		161 (19.54%)		37 (27.01%)		
CLINICAL VARIABLES						
Substance use disorder	846		140			
Current		95 (11.23%)		17 (12.14%)	$3.18_{(3)}$	0.364
Lifetime		192 (22.70%)		39 (27.86%)		
Lifetime and current		155 (18.32%)		28 (20.00%)		
Absent		404 (47.75%)		56 (40.00%)		
Smoking status	830		137			
Current smokers		547 (65.90%)		90 (65.69%)	$4.02_{(2)}$	0.134
Past smokers		59 (7.11%)		16 (11.68%)		
Non smokers		224 (26.99%)		31 (22.63%)		
Current psychiatry disorder	845		140			
Present		769 (91.01%)		132 (94.29%)	$1.66_{(1)}$	0.198
Absent		76 (8.99%)		8 (5.71%)		
BZD used						
Lormetazepam	846		140			
Yes		519 (61.35%)		61 (43.57%)	$15.67_{(1)}$	**<0.001**
No		327 (38.65%)		79 (56.43%)		
Lorazepam	846		140			
Yes		90 (10.64%)		52 (37.14%)	$68.45_{(1)}$	**<0.001**
No		756 (89.36%)		88 (62.86%)		
Alprazolam	846		140			
yes		76 (8.98%)		42 (30.00%)	$50.36_{(1)}$	**<0.001**
No		770 (91.02%)		98 (70.00%)		

Table 2 (Continued).

	Mono-therapy users		Poly-therapy users			
	n	*n* (%)	*n*	*n* (%)	Chi-square$_{(df)}$	*p*
Clonazepam	846		140			
Yes		17 (2.01%)		25 (17.86%)	$73.97_{(1)}$	**<0.001**
No		829 (97.99%)		115 (82.14%)		
Bromazepam	846		140			
Yes		24 (2.84%)		15 (10.71%)	$19.62_{(1)}$	**<0.001**
No		822 (97.16%)		125 (89.28%)		
Triazolam	846		140			
Yes		16 (1.89%)		23 (16.43%)	$66.82_{(1)}$	**<0.001**
No		830 (98.11%)		117 (83.57%)		
Diazepam	846		140			
Yes		13 (1.54%)		21 (15.00%)	$65.40_{(1)}$	**<0.001**
No		833 (98.46%)		119 (85.00%)		
Delorazepam	846		140			
Yes		8 (0.95%)		13 (9.29%)	$40.08_{(1)}$	**<0.001**
No		838 (99.05%)		127 (90.71%)		
Flurazepam	846		140			
Yes		0 (0.00%)		12 (8.57%)	$73.41_{(1)}$	**<0.001**[a]
No		846 (100.00%)		128 (91.43%)		
Etizolam	846		140			
Yes		7 (0.83%)		2 (1.43%)	$0.48_{(1)}$	0.516[a]
No		839 (99.17%)		138 (98.57%)		
Flunitrazepam	846		140			
Yes		0 (0.00%)		4 (2.86%)	$24.27_{(1)}$	**<0.001**[a]
No		846 (100.00%)		136 (97.14%)		
Oxazepam	846		140			
Yes		0 (0.00%)		3 (2.14%)	$19.18_{(1)}$	**0.003**[a]
No		846 (100.00%)		137 (97.86%)		
Temazepam	846		140			
Yes		1 (0.12%)		1 (0.71%)	$2.11_{(1)}$	0.264[a]
No		845 (99.88%)		139 (99.29%)		
Brotizolam	846		140			
Yes		1 (0.12%)		1 (0.71%)	$2.11_{(1)}$	0.264[a]
No		845 (99.88%)		139 (99.29%)		
Prazepam	846		140			
Yes		1 (0.12%)		1 (0.71%)	$2.11_{(1)}$	0.264[a]
No		845 (99.88%)		139 (99.29%)		
Z-drugs used						
Zolpidem	846		140			
Yes		70 (8.27%)		37 (26.43%)	$40.92_{(1)}$	**<0.001**
No		776 (91.73%)		103 (73.57%)		

Table 2 (Continued).

		Mono-therapy users		Poly-therapy users		
	n	*n* (%)	*n*	*n* (%)	Chi-square$_{(df)}$	*p*
Zoplicone	846		140			
Yes		2 (0.24%)		1 (0.71%)	$0.90_{(1)}$	0.342
No		844 (99.76%)		139 (99.29%)		
Formulation of BZD/Z-drugs used	846		140			
Tablets		221 (26.12%)		77 (55.00%)	$47.50_{(1)}$	**<0.001**
Drops		625 (73.88%)		63 (45.00%)		

Note: BZD: benzodiazepine; Z-drugs: non-benzodiazepine receptor agonists; a = Fisher test.

BZDs/Z-drugs were more frequently consumed in drops than in tablets, with a mean daily dose of 100.39 ± 197.19 mg, a mean DDD of 52.20 ± 64.15, and a mean diazepam equivalent dose of 357.31 ± 483.80 mg. The use of BZDs/Z-drugs lasted 86.30 ± 86.07 months. The mean age of first use was 30.44 ± 10.52 years. In the whole sample, 846 (85.80%) subjects were mono-therapy users while 140 (14.20%) were poly-therapy users.

When mono-therapy users were compared with poly-therapy users, no statistically significant differences were found for sex (males: 448, 52.96% vs 67, 47.86%, $x^2_{(df)} = 1.25_{(1)}$, $p = 0.263$) and age (44.96 ± 10.85 vs 44.85 ± 10.77 years, $p = 0.944$). Table 2 shows the comparisons on demographic and clinical variables. Being employed was more represented among mono- than poly-therapy users. Lormetazepam was more frequently used by mono-therapy users; vice versa zolpidem. BZD/Z-drug drops were more likely used by mono- than poly-therapy users. Mono-therapy users showed lower daily dose (99.62 ± 194.89 vs 105.02 ± 211.31 mg, $p = 0.005$), higher DDD (54.33 ± 65.64 vs 38.73 ± 52.03, $p < 0.001$), older age of first use (mean ± SD: 30.97 ± 10.45 vs 27.19 ± 10.45 years, $p < 0.001$) than poly-therapy users. The two groups did not differ for diazepam equivalent dose (354.67 ± 500.46 vs 375.26 ± 350.82, $p = 0.350$) or duration of use (82.67 ± 81.15 vs 109.57 ± 110.16 months, $p = 0.058$).

Among subjects with current SUDs ($n = 112$), 95 (84.82%) were mono- and 17 (15.18%) poly-therapy users. No statistically significant differences were found for sex (males: 47, 49.47% vs 7, 41.18%, $x^2_{(df)} = 0.39_{(1)}$, $p = 0.528$) and age (mean ± SD: 45.67 ± 11.09 vs 45.94 ± 10.36 years, $p = 0.761$). Table 3 shows the comparisons on demographic and clinical variables. Concerning BZDs use, lormetazepam was more likely used by mono-therapy users than poly-therapy users while, among Z-drugs, zolpidem was less frequently used by mono- than poly-therapy users. BZD/Z-drug drops were more likely used by mono-therapy users. Mono-therapy users showed statistically significant lower diazepam equivalent dose (mean ± SD: 295.55 ± 357.77 vs 383.84 ± 251.11, $p = 0.014$) and older age of first use (mean ± SD: 31.88 ± 11.28 vs 23.62 ± 11.03 years, $p = 0.019$) than poly-therapy users. No differences were found for daily dose (mean ± SD: 56.98 ± 72.88 vs 121.09 ± 222.92 mg, $p = 0.852$), DDD (mean ± SD: 47.52 ± 64.86 vs 38.43 ± 49.66, $p = 0.476$), duration of use (mean ± SD: 85.56 ± 76.12 vs 73.79 ± 101.52 months, $p = 0.147$).

Among subjects with lifetime SUDs ($n = 231$), 192 (83.12%) were mono-therapy users and 39 poly-therapy users (16.88%). No statistically significant differences were found for sex (males: 124, 64.58% vs 21, 53.85%, $x^2_{(df)} = 1.60_{(1)}$, $p = 0.206$) and age (mean ± SD: 45.14 ± 10.76 vs 45.69 ± 10.72 years, $p = 0.674$). Table 4 shows the comparisons concerning demographic and clinical variables. The lifetime rate of alcohol use was significantly lower among mono- than poly-therapy users. Lorazepam, alprazolam,

Table 3
Comparison between mono-therapy users (n = 95) and poly-therapy users (n = 17) among subjects with current substance use disorder. Chi-square and Fisher test

	Mono-therapy users		Poly-therapy users			
	n	n (%)	n	n (%)	Chi-square$_{(df)}$	p
DEMOGRAPHIC VARIABLES						
Marital status	83		14			
Married		25 (30.12%)		7 (50.00%)	$2.25_{(1)}$	0.521
Unmarried		50 (60.24%)		6 (42.86%)		
Cohabitant		7 (8.43%)		1 (7.14%)		
Widower		1 (1.20%)		0 (0.00%)		
Education	87		16			
Primary school		0 (0.00%)		1 (6.25%)	$8.97_{(3)}$	**0.030**
Secondary school		22 (25.29%)		3 (18.75%)		
High school		40 (45.97%)		4 (25.00%)		
Graduation		25 (28.74%)		8 (50.00%)		
Working status	91		17			
Employed		51 (56.04%)		9 (52.94%)	$0.950_{(2)}$	0.622
Unemployed		23 (25.27%)		6 (35.29%)		
Housewife or retired or invalid		17 (18.68%)		2 (11.76%)		
CLINICAL VARIABLES						
Substance used currently	93		17			
Heroin						
Yes		4 (4.30%)		2 (11.76%)	$1.55_{(1)}$	0.232[a]
No		89 (95.70%)		15 (88.23%)		
Cocaine	93		17			
Yes		18 (19.57%)		7 (41.18%)	$3.79_{(1)}$	0.064[a]
No		74 (80.43%)		10 (58.82%)		
THC	93		17			
Yes		12 (12.90%)		4 (23.53%)	$1.31_{(1)}$	0.268[a]
No		81 (87.10%)		13 (76.47%)		
Alcohol	93		17			
Yes		66 (69.47%)		9 (52.94%)	$1.78_{(1)}$	0.182
No		29 (30.53%)		8 (47.06%)		
Barbiturates	93		17			
Yes		4 (4.21%)		0 (0.00%)	$0.74_{(1)}$	1.000[a]
No		91 (95.79%)		17 (100.00%)		
Smoking status	93		17			
Current smokers		66 (70.97%)		12 (70.59%)	$0.85_{(2)}$	0.652
Past smokers		4 (4.30%)		0 (0.00%)		
Non smokers		23 (24.73%)		5 (29.41%)		
Current psychiatry disorder	94		17			
Present		89 (94.68%)		15 (88.24%)	$1.01_{(1)}$	0.291[a]
Absent		5 (5.32%)		2 (11.76%)		

Table 3 (Continued).

	Mono-therapy users		Poly-therapy users			
	n	*n* (%)	*n*	*n* (%)	Chi-square$_{(df)}$	*p*
BZD used						
Lormetazepam	95		17			
Yes		61 (64.21%)		5 (29.41%)	$7.21_{(1)}$	**0.014**[a]
No		34 (35.79%)		12 (70.59%)		
Lorazepam	95		17			
Yes		9 (9.47%)		6 (35.29%)	$8.29_{(1)}$	**0.011**[a]
No		86 (90.53%)		11 (64.71%)		
Alprazolam	95		17			
Yes		12 (12.63%)		5 (29.41%)	$3.15_{(1)}$	0.133[a]
No		83 (87.37%)		12 (70.59%)		
Clonazepam	95		17			
Yes		1 (1.05%)		4 (23.53%)	$17.08_{(1)}$	**0.002**[a]
No		94 (98.95%)		13 (76.47%)		
Bromazepam	95		17			
Yes		1 (1.05%)		1 (5.88%)	$1.918_{(1)}$	0.282[a]
No		94 (98.95%)		16 (94.12%)		
Triazolam	95		17			
Yes		1 (1.05%)		4 (23.53%)	$17.08_{(1)}$	**0.002**[a]
No		94 (98.95%)		13 (76.47%)		
Diazepam	95		17			
Yes		2 (2.11%)		2 (11.76%)	$3.91_{(1)}$	0.109[a]
No		93 (97.89%)		15 (88.24%)		
Delorazepam	95		17			
Yes		2 (2.11%)		2 (11.76%)	$3.91_{(1)}$	0.109[a]
No		93 (97.89%)		15 (88.24%)		
Flurazepam	95		17			
Yes		0 (0.00%)		0 (0.00%)	–	–
No		95 (100.00%)		17 (100.00%)		
Etizolam	95		17			
Yes		0 (0.00%)		2 (11.76%)	$11.38_{(1)}$	**0.022**[a]
No		95 (100.00%)		15 (88.24%)		
Flunitrazepam	95		17			
Yes		0 (0.00%)		1 (5.88%)	$5.64_{(1)}$	0.152[a]
No		95 (100.00%)		16 (94.12%)		
Oxazepam	95		17			
Yes		0 (0.00%)		1 (5.88%)	$5.64_{(1)}$	0.152[a]
No		95 (100.00%)		16 (94.12%)		
Temazepam	95		17			
Yes		0 (0.00%)		0 (0.00%)	–	–
No		95 (100.00%)		17 (100.00%)		

Table 3 (Continued).

	Mono-therapy users		Poly-therapy users			
	n	*n* (%)	*n*	*n* (%)	Chi-square$_{(df)}$	*p*
Brotizolam	95		17			
Yes		0 (0.00%)		0 (0.00%)	–	–
No		95 (100.00%)		17 (100.00%)		
Prazepam	95		17			
Yes		0 (0.00%)		0 (0.00%)	–	–
No		95 (100.00%)		17 (100.00%)		
Z-drug used						
Zolpidem	95		17			
Yes		6 (6.32%)		7 (41.18%)	$17.08_{(1)}$	**0.001**[a]
No		89 (93.68%)		10 (58.82%)		
Zoplicone	95		17			
Yes		95 (100.00%)		17 (100.00%)	–	–
No		0 (0.00%)		0 (0.00%)		
Formulation of BZD/Z-drugs	95		17			
Tablets		25 (26.32%)		10 (58.82%)	$7.09_{(1)}$	**0.008**
Drops		70 (73.68%)		7 (41.18%)		

Note: BZD: benzodiazepine; Z-drugs: non-benzodiazepine receptor agonists; a = Fisher test.

clonazepam, triazolam, diazepam, delorazepam, flurazepam, and oxazepam were used less frequently by mono- than poly-therapy users, vice versa zolpidem. BZD/Z-drug drops were more likely used by mono-therapy users. Mono-therapy users showed statistically significant higher DDD (mean ± SD: 55.11 ± 62.17 vs 40.83 ± 54.38, $p = 0.045$) and older age of first use (mean ± SD: 31.13 ± 11.1 vs 26.97 ± 9.03 years, $p = 0.029$) than poly-therapy users. No differences were found for daily dose (mean ± SD: 107.58 ± 207.98 vs 122.76 ± 183.01 mg, $p = 0.805$), diazepam equivalent dose (mean ± SD: 383.71 ± 384.98 vs 407.87 ± 402.38, $p = 0.930$), duration of use (mean ± SD: 85.07 ± 82.57 vs 100.62 ± 100.86 months, $p = 0.739$).

Among subjects with current and lifetime SUDs ($n = 183$), 155 (84.70%) were mono-therapy users and 28 (15.30%) poly-therapy users. Mono-therapy users were more frequently males (124 vs 17, $x^2_{(df)} = 4.98_{(1)}$, $p = 0.026$) while age was not statistically significantly different (40.39 ± 8.92 vs 40.68 ± 8.60 years, $p = 0.927$). Table 5 shows the comparisons concerning demographic and clinical variables. The rate of barbiturates use was lower among mono- than poly-therapy users. Concerning BZDs, lorazepam, alprazolam, clonazepam, triazolam, diazepam, delorazepam, and flurazepam were used less frequently by mono-therapy users, vice versa zolpidem.

BZD/Z-drug drops were used more likely by mono- than poly-therapy users. No statistically significant differences were observed between mono-therapy and poly-therapy users for daily dose (mean ± SD: 102.58 ± 211.87 vs 68.42 ± 90.25 mg, $p = 0.100$), DDD (mean ± SD: 52.29 ± 67.51 vs 46.81 ± 70.64, $p = 0.123$), diazepam equivalent dose (mean ± SD: 355.37 ± 454.01 vs 456.80 ± 442.75, $p = 0.320$), age of first use (mean ± SD: 28.24 ± 9.07 vs 25.85 ± 9.36 years, $p = 0.210$), duration of use (mean ± SD: 62.56 ± 65.76 vs 74.48 ± 71.44 months, $p = 0.549$).

Among subjects without SUDs ($n = 460$), 404 (87.83%) were mono-therapy users and 56 (12.17%) poly-therapy users. No statistically significant differences were found for sex (males: 153, 37.87% vs

Table 4
Comparison between mono-therapy users (n = 192) and poly-therapy users (n = 39) among subjects with lifetime substance use disorder. Chi-square and fisher test

	Mono-therapy users		Poly-therapy users			
	n	*n* (%)	*n*	*n* (%)	Chi-square$_{(df)}$	*p*
DEMOGRAPHIC VARIABLES						
Marital status	184		37			
Married		44 (23.91%)		9 (24.32%)	$0.959_{(3)}$	0.811
Unmarried		111 (60.33%)		24 (64.86%)		
Cohabitant		26 (14.13%)		4 (10.81%)		
Widower		3 (1.63%)		0 (0.00%)		
Education	188		37			
Primary school		16 (8.51%)		0 (0.00%)	$8.67_{(3)}$	**0.034**
Secondary school		70 (37.23%)		8 (21.62%)		
High school		73 (38.83%)		22 (59.46%)		
Graduation		29 (15.42%)		7 (18.92%)		
Working status	192		39			
Employed		92 (47.92%)		17 (43.59%)	$4.54_{(2)}$	0.103
Unemployed		60 (31.25%)		8 (20.51%)		
Housewife or retired or invalid		40 (20.83%)		14 (35.90%)		
CLINICAL VARIABLES						
Substance used lifetime						
Heroin	192		39			
Yes		63 (32.81%)		11 (28.21%)		
No		129 (67.19%)		28 (71.79%)	$0.316_{(1)}$	0.574
Cocaine	192		39			
Yes		97 (50.52%)		16 (41.03%)	$1.17_{(1)}$	0.279
No		95 (49.48%)		23(58.97%)		
THC	189		39			
Yes		73 (38.62%%)		16 (41.03%)	$0.078_{(1)}$	0.780
No		116 (61.38%%)		23 (58.97%%)		
Alcohol	191		39			
Yes		109 (57.07%)		29 (74.36%)	$4.03_{(1)}$	**0.045**
No		82 (42.93%)		10 (25.64%)		
Barbiturates	191		39			
Yes		0 (0.00%)		0 (0.00%)	–	–
No		191 (100.00%)		39 (100.00%)		
Smoking status	192		39			
Current smokers		162 (84.38%)		28 (71.79%)	$3.74_{(2)}$	0.154
Past smokers		17 (8.85%)		7 (17.95%)		
Non smokers		13 (6.77%)		4 (10.26%)		
Current psychiatry disorder	192		39			
Present		171 (89.06%)		37 (94.87%)	$1.22_{(1)}$	0.384[a]
Absent		21 (10.94%)		2 (5.13%)		

Table 4 (Continued).

	Mono-therapy users		Poly-therapy users			
	n	*n* (%)	*n*	*n* (%)	**Chi-square**$_{(df)}$	*p*
BZD used						
Lormetazepam	192		39			
Yes		108 (56.25%)		17 (43.19%)	$2.09_{(1)}$	0.148
No		84 (43.75%)		22 (56.41%)		
Lorazepam	192		39			
Yes		22 (11.46%)		15 (38.46%)	$17.57_{(1)}$	**<0.001**
No		170 (88.54%)		24 (61.54%)		
Alprazolam						
Yes		21 (10.94%)		13 (33.33%)	$12.95_{(1)}$	**<0.001**
No		171 (89.06%)		26 (66.67%)		
Clonazepam	192		39			
Yes		7 (3.65%)		7 (17.95%)	$11.64_{(1)}$	**0.003**[a]
No		185 (96.35%)		32 (82.05%)		
Bromazepam	192		39			
Yes		3 (1.56%)		3 (7.69%)	$4.81_{(1)}$	0.062[a]
No		189 (98.44%)		36 (92.31%)		
Triazolam	192		39			
Yes		7 (3.65%)		5 (12.82%)	$5.54_{(1)}$	**0.034**[a]
No		185 (96.35%)		34 (87.18%)		
Diazepam	192		39			
Yes		3 (1.56%)		7 (17.95%)	$21.02_{(1)}$	**<0.001**[a]
No		189 (98.44%)		32 (82.05%)		
Delorazepam	192		39			
Yes		2 (1.04%)		2 (5.13%)	$3.18_{(1)}$	**0.133**[a]
No		190 (99.96%)		37 (94.87%)		
Flurazepam	192		39			
Yes		0 (0.00%)		4 (10.26%)	$20.04_{(1)}$	**0.001**[a]
No		192 (100.00%)		35 (89.74%)		
Etizolam	192		39			
Yes		3 (1.56%)		0 (0.00%)	$0.617_{(1)}$	0.432
No		189 (98.44%)		39 (100.00%)		
Flunitrazepam	192		39			
Yes		0 (0.00%)		1 (2.56%)	$4.94_{(1)}$	0.169[a]
No		192 (100.00%)		38 (97.44%)		
Oxazepam	192		39			
Yes		0 (0.00%)		1 (2.56%)	$4.94_{(1)}$	**0.169**[a]
No		192 (100.00%)		38 (97.46%)		

Table 4 (Continued).

	Mono-therapy users		Poly-therapy users			
	n	*n* (%)	*n*	*n* (%)	**Chi-square**$_{(df)}$	*p*
Temazepam	192		39			
Yes		0 (0.00%)		0 (0.00%)	–	–
No		192 (100.00%)		39 (100.00%)		
Brotizolam	192		39			
Yes		0 (0.00%)		1 (2.56%)	$4.94_{(1)}$	0.169[a]
No		192 (100.00%)		38 (97.44%)		
Prazepam	192		39			
yes		0 (0.00%)		1 (2.56%)	$4.94_{(1)}$	0.169[a]
No		192 (100.00%)		38 (97.44%)		
Z-drugs used						
Zolpidem	192		39			
Yes		16 (8.33%)		11 (28.20%)	$12.40_{(1)}$	**0.001[a]**
No		176 (91.67%)		28 (71.79%)		
Zoplicone	192		39			
Yes		0 (0.00%)		0 (0.00%)	–	–
No		192 (100.00%)		39 (100.00%)		
Formulation of BZD/Z-drugs used	192		39			
Tablets		57 (29.69%)		23 (58.97%)	$12.28_{(1)}$	**0.001[a]**
Drops		135 (70.31%)		16 (41.03%)		

Note: BZD: benzodiazepine; Z-drugs: non-benzodiazepine receptor agonists; a = Fisher test.

22, 30.28%, $x^2_{(df)} = 0.04_{(1)}$, $p = 0.838$) and age (mean ± SD: 46.47 ± 11.07 vs 46.02 ± 11.62 years, $p = 0.849$). Table 6 shows comparisons concerning demographic and clinical variables. Lormetazepam was more likely used by mono- than poly-therapy users, vice versa zolpidem. BZD/Z-drug drops were more likely used by mono- than poly-therapy users. Mono-therapy users showed statistically significant lower daily dose (mean ± SD: 104.63 ± 200.46 vs 105.42 ± 263.86 mg, $p < 0.001$), higher DDD (mean ± SD: 56.32 ± 66.79 vs 33.26 ± 39.61, $p < 0.001$), older age of first use (mean ± SD: 31.67 ± 10.26 vs 28.75 ± 11.59 years, $p = 0.027$), lower duration of use (mean ± SD: 88.34 ± 85.76 vs 139.38 ± 124.93 months, $p = 0.002$) than poly-therapy users. The two groups did not differ for diazepam equivalent dose (354.65 ± 585.06 vs 305.13 ± 266.90, $p = 0.487$).

Table 7 shows the hierarchical multiple regression analyses testing the risk of being mono-therapy users versus poly-therapy users on the whole sample and on groups of patients with current SUDs, lifetime SUDs, current and lifetime SUDs, or without SUDs.

In the whole sample, the predicting variables explained 14.1% of the overall variance ($\chi^2_{(df)} = 57.65_{(11)}$, $p < 0.001$). Step 1 variables (i.e., sex, working activity, education, lifetime alcohol use, current or lifetime barbiturates use) explained 3.3% of the overall variance ($R^2 = 0.033$, $\chi^2_{(df)} = 13.26_{(5)}$ $p = 0.021$). Step 2 variable (duration of drug use, in months) predicted an additional 1.8% of unique variance ($R^2 = 0.051$, $\chi^2_{(df)} = 7.18_{(1)}$, $p = 0.007$). Long-term drug use was less likely among mono- than poly-therapy users. Step 3 variable (diazepam equivalent dose) ($\chi^2_{(df)} = 2.47_{(1)}$, $p = 0.116$) and Step 4 variable (daily dose)

Table 5
Comparison between mono-therapy users (n = 155) and poly-therapy users (n = 28) among subjects with current and lifetime substance use disorder. Chi-square and Fisher test

	Mono-therapy users		Poly-therapy users			
	n	n (%)	n	n (%)	Chi-square$_{(df)}$	p
DEMOGRAPHIC VARIABLES						
Marital status	145		25			
Married		27 (18.62%)		5 (20.00%)	$0.217_{(3)}$	0.975
Unmarried		104 (71.72%)		18 (72.00%)		
Cohabitant		13 (8.97%)		2 (8.00%)		
Widower		1 (0.69%)		0 (0.00%)		
Education	150		25			
Primary school		11 (7.33%)		1 (4.00%)	$3.59_{(3)}$	0.309
Secondary school		64 (42.67%)		11 (44.00%)		
High school		60 (40.00%)		13 (52.00%)		
Graduation		15 (100.00%)		0 (0.00%)		
Working status						
Employed		76 (49.67%)		7 (25.00%)	$6.05_{(2)}$	**0.049**
Unemployed		62 (50.52%)		16 (57.14%)		
Housewife or retired or invalid		15 (9.80%)		5 (17.86%)		
CLINICAL VARIABLES						
Heroin use	155		27			
Current		26 (16.77%)		5 (18.52%)		
lifetime		62 (40.00%)		14 (51.85%)	$1.85_{(2)}$	0.397
Absent		67 (43.23%)		8 (29.63%)		
Cocaine use	154		27			
Current		34 (22.08%)		7 (25.932)		
Lifetime		86 (55.84%)		15 (55.56%)	$0.286_{(2)}$	0.867
Absent		34 (22.08%)		5 (18.52%)		
THC use	154		27			
Absent		55 (35.71%)		7 (25.93%)	$1.87_{(2)}$	0.393
Current		24 (15.58%)		3 (11.11%)		
Past		75 (48.70%)		17 (62.96%)		
Alcohol use	153		28			
Current		60 (39.22%)		11 (39.29%)		
Lifetime		44 (28.76%)		9 (32.14%)	$0.182_{(2)}$	0.913
Absent		49 (32.02%)		8 (28.57%)		
Barbiturates use	155		27			
Current		1 (0.65%)		1 (3.70%)	$8.56_{(2)}$	**0.014**
Lifetime		1 (0.65%)		2 (7.41%)		
Absent		153 (98.70%)		24 (88.89%)		
Smoking status	154		27			
Current smokers		137 (88.96%)		24 (88.89%)	$0.13_{(2)}$	0.936
Past smokers		4 (2.60%)		1 (3.70%)		
Non smokers		13 (8.44%)		2 (7.41%)		

Table 5 (Continued).

	Mono-therapy users		Poly-therapy users			
	n	*n* (%)	*n*	*n* (%)	Chi-square$_{(df)}$	*p*
Current psychiatry disorder	155		28			
Present		141 (90.97%)		27 (96.43%)	$0.940_{(1)}$	0.474[a]
Absent		14 (9.03%)		1 (3.57%)		
BZD used						
Lormetazepam	155		28			
Yes		87 (56.13%)		15 (53.57%)	$0.63_{(1)}$	0.838
No		68 (43.87%)		13 (46.43%)		
Lorazepam	155		28			
Yes		21 (13.55%)		13 (46.43%)	$16.95_{(1)}$	**<0.001**
No		134 (86.45%)		15 (53.57%)		
Alprazolam	155		28			
Yes		10 (6.45%)		6 (21.43%)	$6.67_{(1)}$	**0.020[a]**
No		145 (93.55%)		22 (78.57%)		
Clonazepam	155		28			
Yes		6 (3.87%)		5 (17.86%)	$8.21_{(1)}$	**0.014[a]**
No		149 (96.13%)		23 (82.14%)		
Bromazepam	155		28			
Yes		7 (4.52%)		4 (14.29%)	$4.01_{(1)}$	0.068
No		148 (95.48%)		24 (85.71%)		
Triazolam	155		28			
Yes		5 (3.23%)		4 (14.29%)	$6.20_{(1)}$	**0.032[a]**
No		150 (96.77%)		24 (85.71%)		
Diazepam	155		28			
Yes		2 (1.29%)		3 (10.71%)	$7.92_{(1)}$	**0.026$_{(1)}$**
No		153 (98.71%)		25 (89.29%)		
Delorazepam	155		28			
Yes		1 (0.65%)		3 (10.71%)	$11.25_{(1)}$	**0.012[a]**
No		154 (99.35%)		25 (89.29%)		
Flurazepam	155		28			
Yes		0 (0.00%)		3 (10.71%)	$16.88_{(1)}$	**0.003[a]**
No		155 (100.00%)		25 (89.29%)		
Etizolam	155		28			
Yes		1 (0.65%)		0 (0.00%)	$0.18_{(1)}$	1.000[a]
No		154 (99.35%)		28 (100.00%)		
Flunitrazepam	155		28			
Yes		0 (0.00%)		0 (0.00%)	–	–
No		155 (100.00%)		28 (100.00%)		

Table 5 (Continued).

	Mono-therapy users		Poly-therapy users			
	n	*n* (%)	*n*	*n* (%)	Chi-square$_{(df)}$	*p*
Oxazepam	155		28			
Yes		0 (0.00%)		0 (0.00%)	–	–
No		155 (100.00%)		28 (100.00%)		
Temazepam	155		28			
Yes		0 (0.00%)		0 (0.00%)	–	–
No		155 (100.00%)		28 (100.00%)		
Brotizolam	155		28			
Yes		1 (0.65%)		0 (0.00%)	$0.18_{(1)}$	1.00[a]
No		154 (99.35%)		28 (100.00%)		
Prazepam	155		28			
Yes		1 (0.65%)		0 (0.00%)	$0.18_{(1)}$	1.000[a]
No		154 (99.35%)		28 (100.00%)		
Z-drugs used						
Zolpidem	155		28			
Yes		12 (7.74%)		6 (21.43%)	$5.01_{(1)}$	**0.037[a]**
No		143 (92.26%)		22 (78.57%)		
Zoplicone	155		28			
Yes		1 (0.65%)		1 (3.57%)	$1.87_{(1)}$	0.283[a]
No		154 (99.35%)		27 (96.43%)		
Formulation of BZD/Z-drugs used	155		28			
Tablets		46 (29.68%)		15 (53.57%)	$6.09_{(1)}$	**0.014**
Drops		109 (70.32%)		13 (46.43%)		

Note: BZD: benzodiazepine; Z-drugs: non-benzodiazepine receptor agonists; a = Fisher test.

($\chi^2_{(df)} = 0.77_{(1)}$, $p = 0.380$) did not significantly increase the predictive ability of the model beyond Steps 2 and 3. Step 5 variable (DDD) predicted an additional 2.8% of unique variance ($R^2 = 0.083$, $\chi^2_{(df)} = 9.59_{(1)}$, $p = 0.002$). Higher DDD was more likely among mono-therapy than poly-therapy users. Step 6 variable (age of first use) predicted an additional 1.5% of unique variance ($R^2 = 0.098$, $\chi^2_{(df)} = 6.30_{(1)}$, $p = 0.012$). First use of BDZs/Z-drugs at later age was more likely among mono- than poly-therapy users. Step 7 variable (formulation) predicted an additional 4.3% of unique variance ($R^2 = 0.141$, $\chi^2_{(df)} = 18.06_{(1)}$, $p < 0.001$). BZD/Z-drug drops were more likely used by mono- than poly-therapy users.

Among subjects with current SUDs, the variables analysed did not significantly influence the risk of being mono-therapy or poly-therapy users ($\chi^2_{(df)} = 11.33_{(10)}$, $p = 0.332$) (Table 7).

Among subjects with lifetime SUDs, the predicting variables explained 27.5% of the overall variance ($\chi^2_{(df)} = 32.73_{(10)}$, $p < 0.001$). Step 1 variables (i.e., sex, working activity, education, lifetime alcohol use) explained 10.3% of the overall variance ($R^2 = 0.103$, $\chi^2_{(df)} = 11.63_{(4)}$, $p = 0.020$). Step 2 variable (duration of drug use) ($\chi^2_{(df)} = 0.49_{(1)}$, $p = 0.484$), Step 3 variable (diazepam equivalent dose) ($\chi^2_{(df)} = 0.95_{(1)}$, $p = 0.329$), Step 4 variable (daily dose) ($\chi^2_{(df)} = 0.50_{(1)}$, $p = 0.445$), Step 5 variable (DDD) ($\chi^2_{(df)} = 1.91_{(1)}$, $p = 0.167$) did not significantly increase the predictive ability of the model previous steps. Step 6 variable (age

Table 6
Comparison between mono-therapy users (n = 404) and poly-therapy users (n = 56) among subjects without substance use disorder. Chi-square and Fisher test

	Mono-therapy users		Poly-therapy users			
	n	*n* (%)	*n*	*n* (%)	Chi-square$_{(df)}$	*p*
DEMOGRAPHIC VARIABLES						
Marital status	362		46			
Married		151 (41.72%)		16 (34.78%%)	$1.79_{(3)}$	0.616
Unmarried		172 (47.51%%)		23 (50.00%)		
Cohabitant		32 (8.34%%)		5 (10.87%)		
Widower		7 (1.93%)		2 (4.35%)		
Education	376		50			
Primary school		21 (5.58%)		5 (10.00%)	$6.64_{(1)}$	0.084
Secondary school		96 (25.53%)		16 (32.00%)		
High school		167 (44.41%)		13 (26.00%)		
Graduation		92 (24.47%)		16 (32.00%)		
Working status	388		53			
Employed		212 (54.64%)		24 (45.28%)	$1.88_{(2)}$	0.390
Unemployed		87 (22.42%)		13 (24.53%)		
Housewife or retired or invalid		89 (22.94%)		16 (30.19%)		
CLINICAL VARIABLES						
Smoking status	391		54			
Current smokers		182 (46.55%)		26 (48.15%)	$2.55_{(2)}$	0.279
Past smokers		34 (8.69%)		8 (14.81%)		
Non smokers		175 (44.76%)		20 (37.04%)		
Current psychiatry disorder	404		56			
Present		368 (91.09%)		53 (94.64%)	$0.80_{(1)}$	0.371
Absent		36 (8.91%)		3 (5.36%)		
BZD used						
Lormetazepam	404		56			
Yes		263 (65.10%)		24 (42.86%)	$10.37_{(1)}$	**0.001**
No		141 (34.90%)		32 (57.14%)		
Lorazepam	404		56			
Yes		38 (9.41%)		18 (32.14%)	$23.78_{(1)}$	**<0.001**
No		366 (90.59%)		38 (67.86%)		
Alprazolam	404		56			
Yes		33 (8.17%)		18 (32.14%)	$28.68_{(1)}$	**<0.001**
No		371 (91.83%)		38 (67.86%)		
Clonazepam	404		56			
Yes		3 (0.74%)		9 (16.07%)	$45.49_{(1)}$	**<0.001**[a]
No		401 (99.26%)		47 (83.93%)		
Bromazepam	404		56			
Yes		13 (3.22%)		7 (12.50%)	$10.18_{(1)}$	**0.001**
No		391 (96.78%)		49 (87.50%)		

Table 6 (Continued).

	Mono-therapy users		Poly-therapy users			
	n	*n* (%)	*n*	*n* (%)	Chi-square$_{(df)}$	*p*
Triazolam	404		56			
Yes		3 (0.74%)		10 (17.86%)	$52.46_{(1)}$	**<0.001[a]**
No		401 (99.26%)		46 (82.14%)		
Diazepam	404		56			
Yes		6 (1.49%)		9 (16.07%)	$33.17_{(1)}$	**<0.001**
No		398 (98.51%)		47 (83.93%)		
Delorazepam	404		56			
Yes		3 (0.74%)		6 (10.71%)	$25.49_{(1)}$	**<0.001[a]**
No		401 (99.26%)		50 (89.29%)		
Flurazepam	404		56			
yes		0 (0.00%)		5 (8.93%)	$36.47^{(1)}$	**<0.001[a]**
No		404 (100.00%)		51 (91.07%)		
Etizolam	404		56			
Yes		3 (0.74%)		0 (0.00%)	$0.42_{(1)}$	1.000[a]
No		401 (99.26%)		56 (100.00%)		
Flunitrazepam	404		56			
Yes		0 (0.00%)		2 (3.57%)	$14.49_{(1)}$	**0.015[a]**
No		404 (100.00%)		54 (96.43%)		
Oxazepam	404		56			
Yes		0 (0.00%)		1 (1.79%)	$7.23_{(1)}$	0.122[a]
No		404 (100.00%)		55 (98.21%)		
Temazepam	404		56			
Yes		1 (0.25%)		1 (1.79%)	$2.68_{(1)}$	0.229[a]
No		403 (99.75%)		55 (98.21%)		
Brotizolam	404		56			
Yes		0 (0.00%)		0 (0.00%)	–	–
No		404 (100.00%)		56 (100.00%)		
Prazepam	404		56			
Yes		0 (0.00%)		0 (0.00%)	–	–
No		404 (100.00%)		56 (100.00%)		
Z-drugs used						
Zolpidem	404		56			
Yes		36 (8.91%)		13 (23.21%)	$10.57_{(1)}$	**0.001**
No		368 (91.09%)		43 (76.79%)		
Zoplicone	404		56			
Yes		1 (0.25%)		0 (0.00%)	$0.14_{(2)}$	1.000[a]
No		403 (99.75%)		56 (100.00%)		

Table 6 (Continued).

	n	Mono-therapy users n (%)	n	Poly-therapy users n (%)	Chi-square$_{(df)}$	p
Formulation of BZD/Z-drugs used	404		56			
Tablets		93 (23.02%)		29 (51.79%)	$20.88_{(1)}$	**<0.001**
Drops		311 (77.98%)		27 (48.21%)		

Note: BZD: benzodiazepine; Z-drugs: non-benzodiazepine receptor agonists; a = Fisher test.

of first use) predicted an additional 4.2% of unique variance ($R^2 = 0.178$, $\chi^2_{(df)} = 5.05_{(1)}$, $p = 0.025$). First use of BDZs/Z-drugs at later age was more likely among mono- than poly-therapy users. Step 7 variable (formulation) predicted an additional 9.7% of unique variance ($R^2 = 0.275$, $\chi^2_{(df)} = 12.26_{(1)}$, $p < 0.001$). BZD/Z-drug drops were more likely used by mono- than poly-therapy users (Table 7).

Among subjects with current and lifetime SUDs, the variables analysed did not significantly influence the risk of being mono- or poly-therapy users ($\chi^2_{(df)} = 11.29_{(11)}$, $p = 0.419$) (Table 7).

Among subjects without SUDs, the predicting variables explained 16.2% of the overall variance ($\chi^2_{(df)} = 29.37_{(9)}$, $p = 0.001$). Step 1 variables (i.e., sex, working activity, education) did not significantly increase the predictive ability of the model ($\chi^2_{(df)} = 4.41_{(3)}$, $p = 0.22$). Step 2 variable (duration of drug use) predicted an additional 5.5% of unique variance ($R^2 = 0.080$, $\chi^2_{(df)} = 9.73_{(1)}$, $p = 0.002$). Long-term drug use was less likely among mono- than poly-therapy users. Step 3 variable (diazepam equivalent dose) ($\chi^2_{(df)} = 0.01_{(1)}$, $p = 0.927$) and Step 4 variable (daily dose) ($\chi^2_{(df)} = 0.25_{(1)}$, $p = 0.618$) did not significantly increase the predictive ability of the model beyond Steps 2 and 3, respectively. Step 5 variable (DDD) predicted an additional 5.7% of unique variance ($R^2 = 0.138$, $\chi^2_{(df)} = 10.39_{(1)}$, $p = 0.001$). Higher DDD was more likely among mono- than poly-therapy users. Step 6 variable (age of first use) ($\chi^2_{(df)} = 0.94_{(1)}$, $p = 0.332$) and Step 7 variable (formulation) ($\chi^2_{(df)} = 3.64_{(1)}$, $p = 0.057$) did not significantly increase the predictive ability of the model beyond previous steps (Table 7).

4. Discussion

The present study suggests that mono- and poly-therapy users have different patterns of BZD/Z-drug use. In the whole sample, mono-therapy users used less frequently zolpidem [4] (which was observed among current SUDs subjects, lifetime SUDs subjects, current and lifetime SUDs subjects, subjects without SUDs, thus it seems strictly related to the poly-therapy condition), had lower daily dose and older age of first BDZ/Z-drug use [4,6,30]. In addition, lormetazepam was more frequently used in mono-therapy, this result was maintained among subjects without SUDs and might be explained by a relatively low dependence liability and low risk to produce hang-over effects of lormetazepam [31–34]. Drops were more likely used by mono-therapy users, which is explained by the high prevalence of lormetazepam use in drops [35]. Similar findings were observed among current SUDs subjects, lifetime SUDs subjects, current and lifetime SUDs subjects, and subjects without SUDs. Mono-therapy users had higher DDD, which might be related to the fact that patients may try to manage the symptoms of their original disease as well as withdrawal manifestations increasing the dose of the drug that they are using rather than adding other drugs. Similar results were found among lifetime SUDs subjects as well as non-SUDs subjects. Among current SUDs subjects, mono-therapy users had lower diazepam equivalent dose and older age of

Table 7
Predicting variables of being mono-therapy users vs poly-therapy users in the whole sample and in different groups. Hierarchical multiple regression analyses

	Whole sample (n = 986)			Subjects with current SUD (n = 112)			Subjects with lifetime SUD (n = 231)			Subjects with current and lifetime SUD (n = 183)			Subjects without SUD (n = 460)		
Model	ΔR^2 (p-value)	B (p-value)	SE	ΔR^2 (p-value)	B (p-value)	SE	ΔR^2 (p-value)	B (p-value)	SE	ΔR^2 (p-value)	B (p-value)	SE	ΔR^2 (p-value)	B (p-value)	SE
Step 1	**0.033** (***p* = 0.021**)			0.068 (p = 0.619)			**0.103** (***p* = 0.020**)			0.016 (p = 0.951)			0.025 (p = 0.220)		
Sex		0.30 (p = 0.196)	0.23		0.37 (p = 0.627)	0.78		0.26 (p = 0.538)	0.43		0.39 (p = 0.534)	0.63		0.40 (p = 0.314)	0.39
Working		0.23 (p = 0.107)	0.14		−0.94 (p = 0.188)	0.71		0.37 (p = 1.452)	0.15		0.15 (p = 0.705)	0.41		0.29 (p = 0.172)	0.21
Education		0.11 (p = 0.453)	0.14		0.13 (p = 0.812)	0.55		0.55 (p = 0.036)	0.26		0.02 (p = 0.964)	0.37		−0.14 (p = 0.870)	0.21
Lifetime alcohol use		0.73 (p = 0.004)	0.25		–			0.92 (p = 0.067)	0.50		0.20 (p = 0.73)	0.58		–	–
Barbiturates use		−19.41	22888.09		−19.23 (p = 1.00)	40192.97		–			−19.44 (p = 0.990)	28391.56		–	–
Step 2	**0.018** (***p* = 0.007**)			0.001 (p = 0.915)			0.005 (p = 0.484)			0.001 (p = 0.791)			**0.055** (***p* = 0.002**)		
Duration of drug use (months)		0.003 (p = 0.005)	0.001		−0.001 (p = 0.91)	0.01		0.002 (p = 0.476)	0.002		0.001 (p = 0.789)	0.004		0.005 (p = 0.001)	0.002

Table 7 (Continued).

Model	Whole sample (*n* = 986)			Subjects with current SUD (*n* = 112)			Subjects with lifetime SUD (*n* = 231)			Subjects with current and lifetime SUD (*n* = 183)			Subjects without SUD (*n* = 460)		
	ΔR^2 (*p*-value)	B (*p*-value)	SE	ΔR^2 (*p*-value)	B (*p*-value)	SE	ΔR^2 (*p*-value)	B (*p*-value)	SE	ΔR^2 (*p*-value)	B (*p*-value)	SE	ΔR^2 (*p*-value)	B (*p*-value)	SE
Step 3	0.006 (*p* = 0.116)			0.022 (*p* = 0.352)			0.008 (*p* = 0.329)			0.028 (*p* = 0.154)			0.000 (*p* = 0.927)		
Diazepam equivalent dose (mg)		0.0004 (*p* = 0.098)	0.0002		0.001 (*p* = 0.319)	0.001		0.0004 (*p* = 0.310)	0.0005		0.001 (*p* = 0.131)	0.0004		0.0001 (*p* = 0.927)	0.001
Step 4	0.002 (*p* = 0.380)			0.063 (*p* = 0.110)			0.004 (*p* = 0.505)			0.014 (*p* = 0.324)			0.01 (*p* = 0.618)		
Daily dose (mg)		−0.001 (*p* = 0.419)	0.001		0.005 (*p* = 0.132)	0.003		−0.001 (*p* = 0.539)	0.001		−0.002 (*p* = 0.471)	0.003		−0.001 (*p* = 0.646)	0.001
Step 5	**0.024** (***p* = 0.002**)			0.070 (*p* = 0.088)			0.016 (*p* = 0.167)			0.000 (*p* = 0.926)			**0.057** (***p* = 0.001**)		
DDD		−0.01 (*p* = 0.005)	0.003		−0.021 (*p* = 0.158)	0.015		−0.007 (*p* = 0.193)	0.005		0.0004 (*p* = 0.926)	0.005		−0.02 (*p* = 0.005)	0.007
Step 6	**0.015** (***p* = 0.012**)			0.052 (*p* = 0.133)			**0.042** (***p* = 0.025**)			0.031 (*p* = 0.770)			0.005 (*p* = 0.332)		
Age of first use		−0.030 (*p* = 0.014)	0.012		−0.06 (*p* = 0.155)	0.043		−0.51 (*p* = 0.033)	0.024		−0.051 (*p* = 0.145)	0.03		−0.020 (*p* = 0.334)	0.02

Table 7 (Continued).

Model	Whole sample (n = 986)			Subjects with current SUD (n = 112)			Subjects with lifetime SUD (n = 231)			Subjects with current and lifetime SUD (n = 183)			Subjects without SUD (n = 460)		
	ΔR^2 (p-value)	B (p-value)	SE	ΔR^2 (p-value)	B (p-value)	SE	ΔR^2 (p-value)	B (p-value)	SE	ΔR^2 (p-value)	B (p-value)	SE	ΔR^2 (p-value)	B (p-value)	SE
Step 7	**0.043** (***p* < 0.001**)			0.002 (p = 0.774)			**0.097** (p < 0.001)			0.064 (p = 0.029)			0.019 (p = 0.057)		
Formulation		−1.17 (p < 0.001)	0.274		−0.325 (0.776)	1.141		−1.90 (p = 0.001)	0.565		−1.43 (p = 0.029)	0.65		−0.870 (p = 0.056)	0.46
Total R^2	**0.141** (***p* < 0.001**)			0.278 (p = 0.332)			**0.275** (***p* < 0.001**)			0.154 (p = 0.419)			**0.162** (***p* < 0.001**)		

Note: formulation was coded as 0 = tablets, 1 = drops. SUD = substance use disorder; DDD = defined daily dose.

first use [4,6,30]. Among subjects without SUDs, mono-therapy users had lower daily dose, older age of first use, and lower duration of use [4,6,30].

The variance of being mono- vs poly-therapy users was explained by several variables: BZD/Z-drugs formulation, followed by DDD, duration of drug use, age of first use. The results on drug formulation are new in the literature and suggest that tablets should be used with caution since subjects assuming zolpidem by tablets had around 2-fold increase risk of problem use than those using liquid formulation [36].

The result on DDD seems consistent to the rationale that using lower doses of two or more drugs could achieve efficacy with less severe side effects than would be expected from higher dosage of a single drug [37–39]. However, there is no evidence that poly-therapy had lower side effects than mono-therapy [10–12], thus limiting BZD/Z-drugs dose is crucial [25]. Findings on duration of BZD/Z-drug use and on age of first use support current recommendations to limit their prescription, the duration of use, and to delay the beginning of these treatments as much as possible.

Among subjects with current SUDs as well as among subjects with current and lifetime SUDs, the variables analysed did not explain the variance of being mono-or poly-therapy users. Among subjects with lifetime SUDs, the variance of being mono- vs poly-therapy users was explained by BZD/Z-drugs formulation followed by age of first use. Thus, the use of tablets and a prescription at early age should be carefully evaluated in this population. Finally, among non-SUDs subjects, the variance of being mono- versus poly-therapy users was explained by DDD and duration of use. Once again, limiting the dose [25] and the duration of treatment [40] seem crucial.

The present research has some limitations. First, subjects were enrolled at a tertiary care clinic limiting generalizability of results. Second, some variables were assessed retrospectively, thus a recall bias could not be excluded. Third, this is an observational study and was not possible to establish a causal relationship between the variables under study and the status of mono-/poly-therapy user. Finally, variables other than those here considered (e.g., medical illness, compliance, illness behaviour, personality) [11,13] may have influenced the risk of being mono- vs poly-therapy users. For these reasons, future research involving several single tertiary care clinics, applying a longitudinal design, and assessing other potential confounding variables are warranted.

5. Conclusions

Lormetazepam appears less likely associated to poly-therapy than other benzodiazepines while zolpidem seems more likely associated. Tablets, high drug doses, long duration of treatment, and early age of first use were more likely associated to poly- than mono-therapy. Interestingly, such variables differently explained the variance of being mono- versus poly-therapy users when the hierarchical multivariate regression analyses were run stratifying for groups of subjects. In particular, among subjects with current SUDs and among subjects with current and lifetime SUDs, the variables analysed did not explain the variance of being mono-or poly-therapy users. Among subjects with lifetime SUDs, the variance was explained by BZD/Z-drugs formulation followed by age of first use while, among non-SUDs subjects, the variance was explained by DDD and duration of use. This suggests that patients have different clinical features and a pharmacological prescription should be tailored to them also based on the variables here analysed. Once again, it is important not to refer to the “average patients” [41], for whom differences in terms of severity of symptoms, comorbidity and other clinical nuances are neglected, but to consider any variable which may demarcate prognostic and therapeutic differences [41] among patients who otherwise may be deceptively considered similar only because they share the same diagnostic label or clinical problem.

Conflict of interest

The authors report no conflict of interest.

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