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Brief Report

Further evidence on the interplay between benzodiazepine and Z-drug abuse and emotion dysregulation

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A B S T R A C T

Background: Long-term benzodiazepine (BDZ)/Z-drug use, which is a risk factor for dependence, is frequent in neuropsychiatric conditions, especially emotional disorders. Also, BDZ/Z-drug misuse is associated with increased emotion dysregulation symptoms. This study aimed to investigate neuropsychiatric distress in patients with BZD/Z-drug use disorder, with particular attention to emotional symptoms.

Methods: Forty-two patients hospitalized for BZD/Z-drug use disorder (males/females= 20/22) were enrolled and dichotomized into a high-dose and a low-dose BZD/Z-drug user group. Neuropsychiatric distress was measured using standardized measures. The relationship between symptom profiles and BZD/Z-drug use disorder severity was explored using t-tests and negative binomial regression analyses.

Results: Twenty-seven patients (61.9%) presented with one or more psychiatric disorders, mostly an emotional disorder. Ten patients had a lifetime history of suicide attempt(s) (23.8%), while 11 presented recent suicidal ideation (26.2%), which resulted in suicidal behavior in 2 cases. High rates of depression, anxiety, and emotion dysregulation were reported. The high-dose BZD/Z-drug user group presented with higher depressive symptoms ($p = 0.016$) and emotion dysregulation ($p = 0.044$) than the low-dose BZD/Z-drug user group. Further, the higher the depressive symptomatology, the more severe was the BZD/Z-drug abuse ($p = 0.028$).

Limitations: Long-term patterns of BDZ/Z-drug use disorder among patients with emotional disorders and the role of other potential risk factors, such as gender, other substance use disorder, and personality disorders, need further investigation in larger samples.

Conclusions: This study showed high emotional symptoms among patients with BZD/Z-drug use disorder, with severe depression being associated with a more severe BZD/Z-drug dependence.

1. Introduction

Known since 1960, benzodiazepines (BZDs) have made a huge contribution to clinical practice, resulting in an exceptional diffusion of medical prescriptions worldwide (Soyka, 2017). Along with Z-drugs which emerged in the 1980s, such drugs act as positive allosteric modulators at the ɣ-aminobutyric acid A (GABA-A) binding site, potentiating GABA's inhibitory effect (Stahl, 2013). Such effect may help controlling anxiety, psychomotor agitation, alcohol and opioid withdrawal symptoms, sleep difficulties, catatonia, muscle spasms, psychosis-related violent and agitated behaviors, neuroleptic-induced side effects such as tardive dyskinesia or akathisia, epilepsy, restless legs syndrome, and dysphoric mood (Ashok and Sheehan, 2006; Ashworth and Gerada, 1997; Bandelow et al., 2012; Bartolommei et al., 2012; Davidson and Connor, 2006; Kennedy et al., 2009; Ramakrishnan and Scheid, 2007; ScHARR, 2004; Shorvon, 2009). Short-term treatments with BZDs and Z-drugs, generally within 4 weeks, are highly tolerated and induce relatively limited side effects, while clinical benefits of longer-term use are less clear (Ashton, 1994; Dell'osso and Lader, 2013). Nevertheless, it frequently happens that patients may exceed the recommended duration or dose, or that medical practitioners prescribe BZDs or Z-drugs beyond the recommended 4 weeks (EMCDDA Perspectives on Drugs, 2018).

Among BZD users, an estimated 6–76% may become long-term users (Kurko et al., 2015), 15–30% may develop moderate-to-severe withdrawal symptoms and rebound symptoms, especially if abrupt cessation of use occurs after 4 weeks of regular intake (Lader and Morton, 1991), and 3–4% may develop misuse or dependence (Faccini et al., 2019; Lader, 2011). Many risk factors for BZD or Z-drug dependence have been suggested, including comorbid neuropsychiatric disorders, ineffective treatments, other substance use, and social factors (Dell'osso and Lader, 2013; Guerlais et al., 2015; Kurko et al., 2015; Manthey et al., 2012). As long-term treatment is *per se* a risk factor for dependence and misuse (Brett and Murnion, 2015; Lader, 2011) and is frequent in neuropsychiatric conditions, especially emotional disorders (Dell'osso and Lader,

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2013), individuals suffering from emotional disorders may be particularly at risk for the detrimental effects of BDZs and Z-drugs. Also, BDZ or Z-drug misuse are associated with increased depressive symptoms, sleep difficulties, disinhibited behavior, anxiety, aggression, impulsivity, and suicidal risk (Ben-Hamou et al., 2011; Cato et al., 2019; Manconi et al., 2017; Panes et al., 2018; Tiihonen et al., 2012).

This study investigated neuropsychiatric distress in high-dose BZD and Z-drug users, with particular attention to emotional symptoms and suicidal risk, examining whether the severity of the BZD or Z-drug use was associated with more pronounced emotional symptoms.

2. Materials and methods

2.1. Study design and sample

This study was conducted at the Addiction Medicine Unit, Department of Medicine, of the Integrated University Hospital of Verona, a nationwide tertiary referral inpatient facility specifically devoted to the detoxification from high-dose BZD and Z-drugs dependence by slow flumazenil infusion (Faccini et al., 2016, 2019) in people aged > 18 years. All consecutive admissions to the inpatient service over the period November 2019 to March 2020 (recruitment was interrupted due to global Covid-19 pandemic) were included into the study. All patients had a history of BZD/Z-drug use disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, with a daily use of at least 5 times the recommended maximum dose (i.e., > 50 mg of daily diazepam dose equivalent, DDDE) (APA, 2013). BZD and Z-drug dose was standardized as DDDE (mg) according to conversion tables (Galanter and Kleber, 2008; Tamburin et al., 2017).

2.2. Socio-demographic and clinical information collected at admission

Socio-demographic information including gender and age at the time of admission was collected. Drug use was assessed by collecting data on (i) BZD/Z-drug active ingredient of use, (ii) number of BZD/Z-drug active ingredient(s) of use, and (iii) concomitant use of other substances (alcohol, opioids, cocaine or cannabinoids as secondary drug). Any presence and type of psychiatric disorders was also assessed by using diagnosis interviews according to DSM-5 criteria and psychometric tests within an extensive clinical evaluation as well as based on analysis of any previous medical documentation and anamnestic interviews.

2.3. Neuropsychiatric distress evaluation

2.3.1. Symptom checklist 90–revised (SCL-90-R)

SCL-90-R is a 90-item self-report instrument assessing psychopathological symptoms over a 5-point Likert scale from 0 (Not at all) to 4 (Extremely) across nine domains: somatization, obsessive-compulsive symptoms, interpersonal sensitivity, anxiety, depression, hostility, phobic anxiety, paranoid ideation, and psychoticism. Each domain is scored by summing the items and dividing such score by the number of non-missing responses. A global severity index (GSI) is also computed by summing all 90 items and dividing such score by the number of non-missing responses (Derogatis, 1994).

2.3.2. Beck depression inventory ii (BDI-II)

BDI-II is a 21-question self-report inventory, assessing the somatic, affective and cognitive symptoms of depression in the preceding 2 weeks over a 4-point scale ranging from 0 to 3. Total scores can range from 0 to 63. BDI-II total scores ranging from 0 to 13 indicate "Minimal" depression, total scores from 14 to 19 indicate "Mild" depression; total scores from 20 to 28 indicate "Moderate" depression, and total scores from 29 to 63 indicate "Severe" depression (Beck et al., 1996).

2.3.3. Difficulties in emotion regulation scale (DERS)

DERS is a 36-item self-report questionnaire, referring to six clinically relevant domains of emotion dysregulation: nonacceptance of emotion responses ("nonacceptance"), lack of emotional awareness ("awareness"), limited access to emotion regulation strategies ("strategies"), difficulties engaging in goal-directed behavior when emotionally aroused ("goals"), impulse control difficulties ("impulse"), and lack of emotional clarity ("clarity"). Responses are rated over a 5-point Likert scale from 1 (almost never) to 5 (almost always) (Giromini et al., 2012; Gratz and Roemer, 2004).

2.3.4. Clinical global impression scale (CGI)

CGI provides the clinician's global impression of disease severity in a patient. This study adopted the Clinical Global Impression – Severity scale (CGI-S), a 7-point scale rating the severity of the patient's illness at the time of assessment, based on the clinician's past experience with patients with the same diagnosis (0: not at all ill; 7: among the most extremely ill). The rating takes into account medical history, psychosocial circumstances, symptoms, behavior, and symptom impact (Busner and Targum, 2007).

2.3.5. Columbia-suicide severity rating scale (C-SSRS)

Besides anamnestic data collection on past suicidal behavior, current risk was investigated by using the C-SSRS. This scale performs an overall suicide risk assessment through a series of healthcare professional-administered questions. The scale ranks the degree of suicidal ideation and behaviors which could be indicative of an individual's intention to commit suicide (Posner et al., 2011).

2.4. Data analysis

Descriptive statistics were used to provide baseline information concerning patients' socio-demographic and clinical characteristics. To gain interpretability and simplicity, the sample's BDZ and Z-drug use was restructured into a dichotomous variable by using the median score (high users, top 50% of the sample; low users, bottom 50% of the sample). Then, independent t-tests were used to compare the two groups across the study variables. Finally, an exploratory negative binomial regression was used to test for an effect of the neuropsychiatric distress severity on the extent of BDZ and Z-drug use. Statistical analysis was carried out by statistical package SPSS.

2.5. Ethics

Protocols and procedures were approved by the research ethics committee at the Integrated University Hospital of Verona (CESC 683). After complete description of the study, all patients provided written informed consent for participation into the study and for the publication of anonymized data originating from the study. The authors assert that the work described here has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans as well as the Uniform Requirements for manuscripts submitted to biomedical journals.

3. Results

3.1. Socio-demographic and clinical characteristics

Data were obtained on 42 patients (20 males), with an average age of 48.2 ± 10.8 years (M±SD). In terms of BZD and Z-drug use, 32 patients used a single BZD or Z-drug (zolpidem was the only Z-drug used; 76.2%), while 10 patients used two or more drugs (23.8%), with lormetazepam being the most commonly used drug (N = 25, 59.5%), followed by alprazolam (N = 6, 14.3%), lorazepam (N = 4, 9.5%), zolpidem (N = 4, 9.5%), and other BZDs (delorazepam, N = 1; diazepam, N = 1; triazolam, N = 1). According to DSM-5 criteria, 7 patients suffered from

another substance use disorder (SUD; 16.6%), with 3 suffering from alcohol use disorder (7.1%) and 4 from opioid use disorder (9.5%). Out of the total sample, 27 patients (61.9%) presented with one or more psychiatric disorders, for which they were receiving psychopharmacological therapy. Most diagnosed conditions were mood disorder (N = 17), followed by anxiety disorder (N = 16), personality disorder (N = 12), and post-traumatic stress disorder (N = 4). Ten patients had a lifetime history of suicide attempt(s) (23.8%), while 11 patients had presented suicidal ideation in the past 30 days (26.2%). Of the latter, 8 patients had presented a fleeting suicidal ideation whereas 3 had reported a persistent suicidal ideation, resulting in suicidal behavior in 2 cases (one failed suicide attempt and one aborted suicide attempt).

3.2. Neuropsychiatric distress evaluation

SCL-90-R scale administration confirmed that a relevant proportion of patients were presenting with clinically relevant difficulties in the depression (scores > 1, N = 30, 71.4%), obsession-compulsion (scores > 1, N = 30, 71.4%), anxiety (scores > 1, N = 26, 61.9%), somatization (scores > 1, N = 25, 59.5%), and paranoid ideation (scores > 1, N = 19, 45.2%) domains as well as in the global severity index (GSI) of general psychopathology (scores > 1, N = 26, 61.9%). BDI-II scores revealed that most patients were currently suffering from depressive symptoms, with 28 patients reporting at least mild symptoms (scores > 13 points, 66.7%), of whom 16 with severe depression (scores > 28, 38.1%). DERS total score (95.7) was markedly higher than that reported among Italian normative (61.4) (Sighinolfi et al., 2010) and nonclinical samples (73.6) (Giromini et al., 2012) and CGI administration revealed medium to high severity scores for all subjects. Descriptive statistics of all data collected are reported in Table 1.

3.3. Differences in neuropsychiatric distress between high-dose and low-dose BDZ and Z-drug users

Independent t-tests indicated significant differences between the two groups, with the high-dose BZD and Z-drug user group (daily diazepam dose equivalent, DDDE, ≥ 250 mg) presenting with higher depressive symptoms (BDI-II total score, p = 0.016) as well as greater emotion dysregulation (DERS total score, p = 0.044) and lack of emotional awareness (DERS "awareness" domain, p = 0.002) than the low-dose BZD and Z-drug user group (DDDE < 250 mg). Weak differences emerged also in terms on anxiety symptoms which tended to be more severe among the high-dose BZD and Z-drug user group as compared to the low-dose BZD and Z-drug user group (SCL-90-R anxiety, p = 0.093). All comparisons are reported in Table 1.

3.4. Exploratory analyses of the association between emotional symptoms and BDZ and Z-drug use

A negative binomial regression tested for an effect of depressive symptomatology (BDI-II total score) on the severity of BDZ and Z-drug use (DDDE), indicating a satisfying goodness-of-fit (p = 0.355). The severity of depression was significantly associated with the severity of BDZ and Z-drug use (B = 0.021, SE = 0.010, Chi square = 4.824, p = 0.028; Fig. 1). A further negative binomial regression failed to show a significant effect of emotion dysregulation (DERS total score) on the severity of BDZ and Z-drug use (DDDE).

4. Discussion

This study clarified several issues regarding the co-occurrence of emotional symptoms among patients with BZD/Z-drug use disorder. First, one every six patients with BZD/Z-drug use disorder present with a co-occurring SUD, up to one in four presents with suicidal ideation, and almost two-thirds suffer from a psychiatric condition, mostly an emotional disorder. Second, patients with BZD/Z-drug use disorder suffer from elevated levels of depression, anxiety, and emotion dysregulation and such symptoms are higher among those with a more severe BZD/Z-drug use disorder. Third, the higher the depressive symptomatology, the more severe is the BZD/Z-drug abuse.

The finding of high SUD and emotional disorder comorbidity among patients with BZD/Z-drug use disorder is in line with previous studies

Table 1
Neuropsychiatric distress in a group of patients suffering from BDZ/Z-drug use disorder.

	Entire sample (N = 42)			Low-dose user group (N = 19)			High-dose user group (N = 23)			Statistics	
	M	SD	N (%)	M	SD	N (%)	M	SD	N (%)	t	p value
SCL-90-R			> 1			> 1			> 1		
somatization	1.29	0.82	25 (59.5)	1.33	0.61	15 (78.9)	1.26	0.97	10 (43.5)	0.27	0.786
obsessive-compulsive	1.62	0.81	30 (71.4)	1.45	0.85	12 (63.2)	1.75	0.75	18 (78.3)	−1.21	0.235
interpersonal sensitivity	0.93	0.88	19 (45.2)	0.79	0.89	7 (36.8)	1.04	0.87	12 (52.2)	−0.93	0.359
depression	1.67	0.96	30 (71.4)	1.39	0.80	12 (63.2)	1.89	1.04	18 (78.3)	−1.70	0.096
anxiety	1.50	0.87	26 (61.9)	1.25	0.73	9 (47.4)	1.70	0.94	17 (73.9)	−1.72	0.093
hostility	0.78	0.84	11 (26.2)	0.79	0.97	4 (21.1)	0.77	0.74	7 (30.4)	0.08	0.940
phobic anxiety	0.58	0.64	10 (23.8)	0.48	0.46	3 (15.8)	0.66	0.75	7 (30.4)	−0.92	0.362
paranoid ideation	1.16	0.87	19 (45.2)	1.11	1.03	8 (42.1)	1.21	0.72	11 (47.8)	−0.40	0.693
psychoticism	0.91	0.76	16 (38.1)	0.85	0.67	7 (36.8)	0.97	0.83	9 (39.1)	−0.52	0.608
global severity index	1.21	0.65	26 (61.9)	1.10	0.62	10 (52.6)	1.30	0.67	16 (69.6)	−1.01	0.317
BDI-II			> 13; > 28				> 13; > 28				
total score	23.71	15.45	28 (66.7); 16 (38.1)	17.53	13.42	10 (52.6); 4 (21.1)	28.83	15.39	18 (78.3); 12 (52.2)	−2.51	0.016
DERS											
total score	95.67	24.61		87.32	22.65		102.57	24.47		−2.08	0.044
nonacceptance	14.88	5.73		14.21	6.16		15.43	5.43		−0.69	0.498
goals	16.19	4.30		15.58	4.53		16.70	4.13		−0.84	0.408
impulse	16.21	4.73		14.68	4.63		17.48	4.52		−1.97	0.056
awareness	14.69	5.22		12.05	4.50		16.87	4.82		−3.32	0.002
strategies	21.83	7.44		20.11	7.04		23.26	7.61		−1.38	0.174
clarity	12.02	5.20		10.68	4.24		13.13	5.73		−1.54	0.131
CGI	4.93	0.75		4.84	0.76		5.00	0.74		−0.68	0.501
DDDE	306.79	221.16		146.84	46.40		438.91	221.46		−5.64	< 0.001

SCL-90-R, Symptom Checklist 90–Revised; BDI-II, Beck Depression Inventory II; DERS, Difficulties in Emotion Regulation Scale; CGI, Clinical Global Impression Scale; DDDE, daily diazepam dose equivalent.

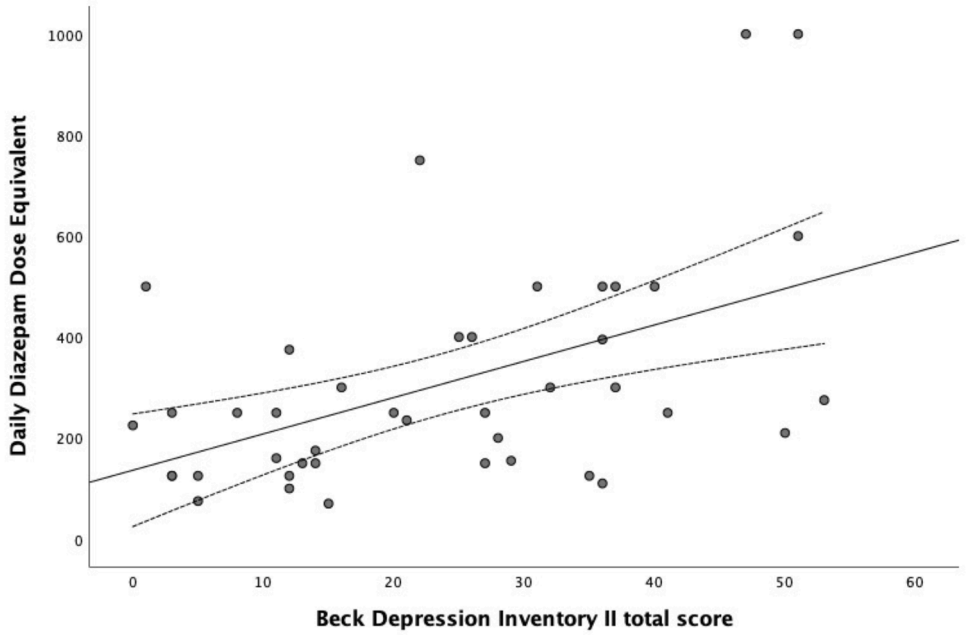

Fig. 1. Association between depression symptom severity and extent of benzodiazepine (BDZ) and Z-drug use in a group of patients suffering from BDZ/Z-drug use disorder.

reporting high use of BDZs and its fast-acting/high-potency formulations in people with complex and severe psychiatric conditions, especially emotional disorders (Manthey et al., 2011), and if also suffering from other SUDs (Clark et al., 2004). Also, additional SUDs and psychiatric disorders have been suggested to confer vulnerability to BDZ abuse development (Brunette et al., 2003) and to differentiate patients with BDZ dependence from therapeutic-dose BDZ users (Busto et al., 1996). Further, the finding of greater emotional difficulties in those with a more severe BZD/Z-drug use disorder confirms previous evidence that patients with psychiatric disorders and SUDs who take BDZs experience worse emotional symptoms than patients not taking BDZs (Brunette et al., 2003). Finally, we replicated and extended previous studies suggesting that emotion dysregulation is a solid predictor of regular BDZ use and abuse development (Brunette et al., 2003; Manthey et al., 2011; Rizvi et al., 2015), indicating a gradient of BZD/Z-drug use disorder severity as a function of the severity of depressive symptoms.

Findings from this study have at least two not mutually exclusive explanations. First, prolonged exposure to BDZs increases the risk of BDZ abuse among already emotionally vulnerable individuals. Second, the development of a BDZ use disorder exacerbates emotion dysregulation. In fact, the relationship between emotional disorders and BZD/Z-drug use disorders has been suggested to be bidirectional. On one hand, inadequate treatment of emotional disorders may predispose patients to problematic use of BDZs and Z-drugs. On the other, independent evidence suggests that long-term use of or withdrawal from BDZs and Z-drugs could lead to the development of an emotional disorder (Ashton, 2005). The latter is corroborated by clinical trials indicating that participants randomized to commonly prescribed Z-drugs present with a 2.1 times higher risk of depression than participants randomized to placebo (Kripke, 2007). Also, similar neurobiological effects to those exerted by other central nervous system depressants, such as alcohol, have been hypothesized for sedative-hypnotic drugs (Brady and Sinha, 2005).

Dual diagnosis of emotional disorders and BZD/Z-drug use disorders deserves more research as both emotional disorders and BZD/Z-drug use disorders are common and their comorbidity has been associated with greater treatment difficulties (Chen et al., 2013; Mojtabai et al., 2014) and poorer outcome (Mojtabai et al., 2014). BDZs and Z-drugs are routinely used in the treatment of emotional disorders, making particularly challenging to obtain relief from commonly reported symptoms such as anxiety and sleep difficulties without using these medications. However, due to the increased incidence of depression in the context of sedative-hypnotic drug use as well as potential misuse or BDZ and Z-drug use disorders in individuals with depression, their use may be contraindicated when a risk of depression has been identified (Ashton, 2005; Kripke, 2007). Thus, a more integrated treatment consisting of both behavioral (e.g., cognitive-behavioral therapy; bright light) and pharmacological (e.g., antidepressants) approaches is needed to manage emotional difficulties in individuals with BDZ/s-drug use disorder, to achieve the most favorable possible outcome.

The current study used standardized measures and assessed emotional difficulties from multiple perspectives, including both the categorical/hetero-evaluation (physician-reported qualitative data) and the dimensional/self-evaluation (patient-reported quantitative data) diagnostic approach. However, further studies will have to clarify its limitations, including documenting the long-term pattern of BDZ/Z-drug use disorder among patients with co-occurring emotional disorders as well as controlling for other potential risk factors, such as gender, other substance use disorder, and personality disorders, in larger samples. More specifically, to disentangle the association between emotional dysregulation and BDZ and Z-drug abuse, and be able to infer shared vulnerability or causality, and in the latter case its directionality, future research will integrate longitudinal information to track the long-term changes in emotional symptomatology and related psychobiological markers induced by sustained BDZ and Z-drug use and vice versa.

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None.

CRediT authorship contribution statement

Marco Colizzi: Conceptualization, Visualization, Data curation, Formal analysis, Writing – review & editing. **Nicolò Meneghin:** Conceptualization, Visualization, Data curation, Formal analysis, Writing – review & editing. **Anna Bertoldi:** Conceptualization, Visualization, Data curation, Formal analysis, Writing – review & editing. **Fabio Lugoboni:** Conceptualization, Visualization, Data curation, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

M.C. has been a consultant/advisor to GW Pharma Limited, outside of this work. All the other authors declare no conflict of interest.

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