

## ORIGINAL PAPER

# Benzodiazepines use and dependence in female patients with overactive bladder symptoms – prevalence and clinical correlations

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**Introduction** GABAergic sedative-hypnotics, including benzodiazepines (BDZs) and Z-drugs, are some of the most used and misused psychotropic medications in developed countries. Growing evidence points to the role of psychiatric comorbidities in overactive bladder (OAB) and in urge urinary incontinence. The aim of the present study was to evaluate: 1) the prevalence of BDZs and/or Z-drugs use in female OAB patients, 2) the risk of dependence on BDZs and/or Z-drugs in female OAB patients, 3) the relationship between the use of BDZs and/or Z-drugs and the severity of OAB symptoms.

**Material and methods** The prevalence of BDZs and/or Z-drugs use, the risk of dependence on BDZs and/or Z-drugs, and the relationship between the use of BDZs and/or Z-drugs and the severity of OAB symptoms was assessed in OAB patients recruited in the urogynecological outpatient clinic.

**Results** A higher percentage of OAB patients confirmed the use of GABAergic sedative-hypnotics in the last 12 months as compared to the non-OAB outpatients presenting for routine gynecological prophylaxis. A larger number of OAB patients (5.6%) met the diagnosis of lifetime BDZ (and/or Z-drug) dependence as compared to the controls (0.9%). The use of sedative-hypnotics did not correlate with OAB symptoms.

**Conclusions** Our results suggest that the use of and dependence on GABAergic sedative-hypnotics may be associated with the OAB diagnosis in female urogynecological patients.

**Key Words:** overactive bladder ↔ urinary incontinence ↔ benzodiazepines ↔ Z-drugs  
↔ use ↔ dependence ↔ urogynecology

## INTRODUCTION

Benzodiazepines (BDZs) and drugs with mode of action similar to BDZs (Z-drugs) are some of the most used psychotropic medications in developed countries [1, 2], including in Poland [3]. All BDZs (e.g. diazepam, lorazepam, temazepam,

clonazepam) and Z-drugs (e.g. zolpidem, zopiclone, zaleplon) share a pharmacological mechanism which involves potentiation of the GABAA receptor in the brain and peripheral tissues. GABAergic effects in the brain may produce subjective states of relaxation, anxiolysis, and sleepiness which are desirable in the acute phase of various psychiatric disorders

(e.g. exacerbation of anxiety disorders or depression with insomnia) [1, 3, 4]. GABAergic medications may also be administered as a self-medication by patients without a formal psychiatric diagnosis, including by older gynecological patients [5, 6]. Thus, it is not uncommon for BDZs and Z-drugs to be used and misused by various groups of patients outside the context of psychiatry. Although the risk of dependence on BDZs and Z-drugs in non-psychiatric settings is not high, the consequences of prolonged dependence may be serious and involve falls, respiratory depression, cognitive decline, and dementia-like symptoms [6–8]. The widespread use of BDZs and Z-drugs reflects their popularity among psychiatric and non-psychiatric patients and affects up to 50% of hospitalized patients in Germany [9] and up to 44% of older nursing home residents in Israel [10]. In Poland, the prevalence of BDZ and/or Z-drug use increases with age and has reached around 7.5% for women over 65 years of age selected from the general population [11].

Lower urinary tract symptoms (LUTS), including overactive bladder (OAB), are an increasing medical, social, and economic problem for ageing societies [12–14]. Several factors have been implicated in OAB pathophysiology, including urothelium, detrusor, and urethra disorders as well as local and central nervous system lesions [15, 16]. Growing evidence points to the role of psychiatric comorbidities in OAB and in urge urinary incontinence [17–20]. A link between OAB and psychiatric disorders may reflect psychological consequences of OAB (shame, anxiety, social withdrawal) and/or common neurotransmitter mechanisms involved in LUTS and brain disorders [for review see: 21, 22]. Recently, our group has shown that OAB symptomatology is positively correlated with psychiatric history and that psychotropic medications used by urogynecological patients may alter the severity of OAB and urge urinary incontinence (UUI) [23]. More specifically, we have shown that treatment with at least two psychotropic medications may be associated with the severity of OAB in ambulatory urogynecological patients [23].

Given the high prevalence of BDZ use in older patients [6, 11] and the serious clinical consequences of BDZ abuse and dependence [6, 24], it is surprising that the use of BDZs has rarely been assessed in urogynecological patients. The aim of the present study was to evaluate: 1) the prevalence of BDZs and/or Z-drugs use in female OAB patients, 2) the risk of dependence on BDZs and/or Z-drugs in female OAB patients, 3) the relationship between the use of BDZs and/or Z-drugs and the severity of OAB symptoms.

## MATERIAL AND METHODS

### Overactive bladder group

Female patients (n = 170) aged  $\geq 18$  years, referred by their family physicians or gynecologists to a urogynecological ambulatory center for diagnosis and treatment of presumed OAB symptoms from June 2018 to December 2019, were considered potential participants. Exclusion criteria were: active urinary tract infection, cancer diagnosis, current radio- or chemotherapy, pelvic organ prolapse [25], serious somatic states (e.g. uncontrolled diabetes, long-term-steroid treatment), transplant history, pregnancy, and lactation, serious neuropsychiatric disorders which could alter OAB symptoms (e.g. multiple sclerosis, recent stroke) and/or make communication with the patient difficult (Alzheimer's disease, schizophrenia and other psychotic disorders). One hundred and sixty women diagnosed with OAB, as described below [26, 27], were included in the study.

### Control group

The control group included 107 gynecological patients without symptoms of OAB, did not meeting the exclusion criteria (see above), presenting for routine gynecological visit (oncological prophylaxis, cytological examination, pelvic ultrasound examination).

### Study procedures

#### *Urogynecological examination*

A large part of the procedures used in the present study were described in detail by Rogowski et al. [23]. Considering OAB and urinary incontinence, all conditions, methods, definitions, and units conformed to the standards recommended by the International Urogynecological Association and the ICS [28]. The patient's evaluation followed institutional protocol, including detailed medical history, vaginal examination with a cough stress test (CST). OAB was diagnosed according to the ICS definition in its Standardization of Terminology of Lower Urinary Tract Function [26, 28]. It was assumed that when symptoms of both urinary urgency and frequency, with or without urinary incontinence, were present and self-reported as bothersome, the patient could be diagnosed with OAB [26, 27]. The presence of OAB symptoms (urgency, frequency, and UUI) was confirmed using questions selected from the Pelvic Floor Distress Inventory as formulated by Foster et al. [29] and Rogowski et al. [30]. The self-reported

severity of OAB symptoms was assessed with the aid of the Indevus Urgency Severity Scale (IUSS) [31, 32]. Urinary incontinence and OAB were further quantified with the Urinary Distress Inventory-6 (UDI-6) [33–35]. The severity and impact of urinary incontinence on the quality of life were evaluated using the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI-SF) [35, 36]. The patients were also interviewed about possible symptoms of stress urinary incontinence (SUI) symptoms using the Stamey Incontinence Score (grade 0: continent; grade 1: loss of urine with a sudden increase in abdominal pressure, such as coughing, sneezing, laughing; grade 2: leaks with lesser degrees of physical stress, i.e., walking, sitting up in bed; grade 3: urine loss without any relation to physical activity or body position) [37]. A vaginal examination was performed with the patient in a semi-lithotomy position. The CST was carried out with the patient in the supine lithotomy position with the bladder comfortably filled with 200–400 mL of urine. Leakage of urine from the urethral meatus simultaneous with a cough was considered a positive test result [38].

#### **Assessment of use of and dependence on benzodiazepines and Z-drugs**

Use of and dependence on GABAergic sedative-hypnotics (BDZs, e.g. diazepam, lorazepam, alprazolam, and Z-drugs, e.g. zolpidem, zopiclone, zaleplon) were assessed with the aid of the Mini-International Neuropsychiatric Interview (M.I.N.I.) [39]. The M.I.N.I. is a short, structured clinical tool designed to make diagnoses of various psychiatric disorders according to the ICD-10 criteria. The M.I.N.I. is divided into modules corresponding to diagnostic criteria for specific psychiatric disorders. Only the module assessing drug dependence was used in the present study. Drug use in the last 12 months and drug dependence (in the last 12 months or in one's lifetime) were analyzed and reported [39, 40]

#### **Assessment of depression, insomnia, and alcohol consumption**

Depression, insomnia, and alcohol consumption are thought to be related to the risk of use and dependence on benzodiazepines and Z-drugs [4, 41, 42]. Therefore, the Patient's Health Questionnaire-2 (PHQ-2) was used to evaluate symptoms of depression. The PHQ-2 is a shortened version of the PHQ-9 with two items referring to anhedonia and lowered mood [43]. In order to quantify the severity of insomnia symptoms, the Athens Insomnia Scale (AIS)

was used [44]. Alcohol consumption was assessed with the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) [45].

#### **Statistical analysis**

Sociodemographic and clinical parameters were expressed as means ( $\pm$ SD) or percentages (%). The Student's *t*-test and chi<sup>2</sup>-test were used for between-group comparisons of means and proportions, respectively. A probability level (*p*) of less than 0.05 was considered significant. The study was exploratory in nature and no correction for multiple comparisons was applied. All statistical analyses were performed using the Statistica 10.0 software package (StatSoft, Tulsa, OK, USA).

#### **Bioethical standards**

The study was carried out in accordance with the Declaration of Helsinki of the World Medical Association. The study protocol was approved by the Ethics Committee for Human Studies of the Mother and Child Institute, Warsaw, Poland (protocol no. 29/2018). All participants signed an informed consent form after study procedures had been fully explained.

## **RESULTS**

#### **Sociodemographic and basic clinical characteristics of overactive bladder and control patients**

All the patients in the OAB group met the criteria for OAB and none of the patients in the control group met these criteria (see Material and methods for details).

Table 1 shows the basic sociodemographic and clinical characteristics of the study groups. The age difference between the study groups was not statistically significant. Body mass index (BMI) of the control group was significantly lower than BMI of the OAB group. The OAB group reported more chronic medical states and medications taken than the control group. The two groups did not differ in gravity, parity or postmenopausal status. Likewise, the study groups did not differ in their smoking status or university education.

#### **Use of and dependence on benzodiazepines and Z-drugs in overactive bladder and control patients**

The OAB group used BDZs and/or Z-drugs in the last 12 months more frequently than the control

subjects (Table 2). The cases of BDZ and/or Z-drug dependence in the last 12 months were rare in both groups but there was a significant between-group difference in the frequency of lifetime BDZ and/or Z-drug dependence (Table 2).

Specific GABAergic sedative-hypnotics taken by the study subjects are listed in Table 3.

### Depressive and insomnia symptoms and alcohol consumption in overactive bladder and control patients

The OAB patients reported more depressive and insomnia symptoms than the control subjects. In contrast, self-reported alcohol consumption was significantly lower in the OAB group as compared to the controls (Table 4).

### Severity of overactive bladder symptoms in overactive bladder patients using and not using benzodiazepines and/or Z-drugs

As shown in Table 2, 26 out of 160 OAB patients reported using BDZs and/or Z-drugs in the last year [OAB/BDZ(+)], while one hundred and thirty-four OAB patients reported not using these medications in the last year [OAB/BDZ(-)]. The two subgroups of OAB patients did not differ in terms of LUTS symptomatology, including IUSS, UDI-6, and Stamey test scores (Table 5).

## DISCUSSION

To the best of our knowledge this is the first study on the use of and dependence on BDZs and Z-drugs in female OAB patients. A higher percentage of OAB patients recruited in the urogynecological outpatient clinic confirmed the use of GABAergic sedative-hypnotics in the last 12 months as compared to the non-OAB outpatients presenting for routine gynecological prophylaxis. In line with the above, a larger number of OAB patients (5.6%) met the diagnosis of lifetime BDZ dependence as compared to the controls (0.9%). Given the well-known association between the use of BDZs and mental and somatic health problems [4, 6, 24], it was not surprising that the OAB group presented more depressive and insomnia symptoms as well as more somatic complaints than the controls. The prevalence of BDZs and/or Z-drugs use in our control group (7.4%) fits well with epidemiological data from a recent study on mental health in the Polish population. The use of GABAergic sedative-hypnotics varied between 6% and 8% in a representative group of women older than 65 years of age [11]. Thus, it seems that the prevalence of use of BDZs and/or

Z-drugs among our OAB patients (16.3%) is higher than expected based on recent epidemiological data. Our results suggest that the use of and dependence on GABAergic sedative-hypnotics may be associated with the OAB diagnosis. This higher risk of use of and dependence on GABAergic sedative-hypnotics in OAB subjects may result from several non-exclusive factors. Both the chronic use of BDZs (or Z-drugs) and the diagnosis of OAB may be related to a higher risk of psychiatric disorders, including depression, anxiety, and insomnia [24, 46, 47]. Hence, OAB patients may more frequently use BDZs/Z-drugs because they more frequently experience psychiatric symptoms effectively attenuated, at least temporarily, by self-medication with sedative-hypnotics. One may assume that with time, as in other patient populations [47, 48], the chronic use of BDZs (and/or Z-drugs) in OAB patients may lead to tolerance and secondary dose escalation as well as withdrawal symptoms on attempts to reduce the dose. Furthermore, the above

**Table 1.** Sociodemographic and clinical characteristics of study subjects

Parameter	OAB group (n = 160)	Control group (n = 107)	p
Age (years)*	62.3 ± 10.6	60.1 ± 8.3	>0.05**
BMI (kg/m <sup>2</sup> )	29.0 ± 4.9	27.0 ± 4.5	<0.001
Number of medical states	1.9 ± 1.5***	0.9 ± 1.1	<0.0001
Number of medications taken	2.5 ± 2.3****	1.2 ± 1.7	<0.0001
Gravidity, mean ± SD	2.1 ± 1.4	2.3 ± 1.5	>0.05
Parity, mean ± SD	1.8 ± 1.1	2.1 ± 1.4	>0.05
University education, n (%)	45 (28.1)	35 (32.7)	>0.05
Current smokers, n (%)	29 (18.1)	25 (23.4)	>0.05
Postmenopausal status, n (%)	136 (85.0)	85 (79.4)	>0.05

\* Means ± standard deviations (SD) or percentages (%)

\*\* Student's t-test

\*\*\* Medical states (other than OAB)

\*\*\*\* Medications taken (other than BDZs)

BMI – body mass index; OAB – overactive bladder; SD – standard deviation

**Table 2.** Use of and dependence on BDZs and/or Z-drugs in OAB and control patients

	OAB group (n = 160)	Control group (n = 107)	p
Use of BDZs and/or Z-drugs in the last 12 months, n (%)	26 (16.3)	8 (7.4)	<0.05*
Dependence on BDZs and/or Z-drugs in the last 12 months, n (%)	3 (1.9)	0 (0)	>0.05
Lifetime BDZ and/or Z-drug dependence, n (%)	9 (5.)	1 (0.9)	<0.05

\*  $\chi^2$  test

BDZs – benzodiazepines; OAB – overactive bladder



processes may lead to drug dependence [1, 2] which is also reflected in the results of the present study.

One may also hypothesize that OAB symptoms may directly lead to BDZ/Z-drug use without psychiatric disorders as moderating factors. It is possible that some OAB patients try to self-medicate with sedative-hypnotic his/her insomnia resulting from

**Table 3.** BDZs and Z-drugs taken by OAB and control patients in the last 12 months

GABAergic sedative-hypnotics	Number of patients*
Alprazolam	3
Diazepam	8
Estazolam	2
Clorazepate	2
Lorazepam	2
Nitrazepam	1
Temazepam	4
Zaleplon	1
Zolpidem	18

\* The sum of drugs taken is greater than the number of patients using BDZs and/or Z-drugs as some patients reported taking more than one medication in the last 12 months

**Table 4.** Depressive and insomnia symptoms and alcohol consumption in OAB and control patients

	OAB group (n = 160)	Control group (n = 107)	p
PHQ-2*	1.1 ±1.3	0.4 ±0.8	<0.0001**
AIS	7.8 ±4.4	4.1 ±3.7	<0.0001
AUDIT-C	2.8 ±2.0	3.8 ±1.8	<0.0001

\* Means ±standard deviations (SD)

\*\* Student's t-test

AIS – Athens Insomnia Scale; AUDIT-C – Alcohol Use Disorder Identification Scale-Consumption; PHQ-2 – Patients Health Questionnaire-2

**Table 5.** Severity of LUTS in OAB patients using [OAB/BDZ(+)] and not using BDZs and/or Z-drugs [OAB/BDZ(-)]

Parameter	OAB/BDZ(+) (n = 26)	OAB/BDZ(-) (n = 134)	p
Age (years)*	65.4 ±11.0	61.6 ±10.4	>0.05**
IUSS	2.4 ±0.7	2.1 ±0.8	>0.05
UDI-6	48.6 ±18.8	47.9 ±20.1	>0.05
ICIQ-SF	11.3 ±5.6	11.9 ±5.1	>0.05
Stamey test	1.3 ±0.8	1.3 ±0.9	>0.05

\* Means ±standard deviations (SD)

\*\* Student's t-test

IUSS – Indevus Urgency Severity Scale; ICIQ-SF – International Consultation on Incontinence Questionnaire Short Form; OAB/BDZ(+) – patients with OAB reporting the use of BDZs and/or Z-drugs in the last 12 months; OAB/BDZ(-) – patients with OAB not using BDZs and/or Z-drugs in the last 12 months

nocturia [49–51], secondary fear of urinary incontinence in public places and/or subjective feelings of stigmatization [50, 51]. Finally, one cannot exclude the possibility that OAB patients use BDZ and/or Z-drugs because these medications directly interfere with OAB symptoms through GABAergic receptors located in the lower urinary tract [49].

In the present study, the use of BDZs (or Z-drugs) was not associated with severity of OAB symptoms. Although negative, our findings does not rule out the possibility that OAB patients could feel temporary relief from their symptoms after initiation of BDZ (or Z-drug) treatment. The protocol used in the present study with the retrospective analysis of drug use does not allow us to fully elucidate this issue. More studies are needed to assess the full spectrum of possible clinical consequences of chronic BDZ use in OAB female patients (e.g. LUTS, falls, cognitive impairment, withdrawal seizures).

Given the data reported by Rogowski et al. [23] (see Introduction), it is not surprising that the OAB patients reported more depressive and insomnia symptoms as compared to the controls. However, it is surprising that the same patients reported consuming less alcohol in comparison with the control group. The relationship between OAB and alcohol consumption has not been studied in much detail. Alcohol has a complex mechanism of action within the human body, including central GABAergic effects which may be responsible for its sedative-hypnotic properties. A cross-tolerance and cross-dependence between alcohol and other sedative-hypnotic agents, like BDZs and Z-drugs, has been repeatedly reported for various patient populations [52, 53]. Thus, one may speculate that our OAB patients consumed less alcohol as a consequence of a higher intake of BDZs and Z-drugs. It is possible that older urogynecological patients prefer prescription medications to alcohol products because of cultural factors and tabooization of alcohol drinking among older females. These hypotheses should be validated in further studies.

The present study has several potential limitations, including a relatively small sample size and the fact that all the subjects were recruited in a single urban tertiary-care center. The BMI in the controls was significantly lower than the one in the OAB group. The severity of LUTS and the use of sedative-hypnotics were based on self-reports which are prone to personal bias. Further studies with larger groups of patients could address the above issues in a more controlled manner.

In conclusion, our data suggest that:

- 1) the diagnosis of OAB in urogynecological patients may be associated with a heightened risk of BDZ (and/or Z-drug) use and dependence;

2) the use of GABAergic sedative-hypnotics in OAB female patients does not correlate with the severity of OAB symptoms.

## CONCLUSIONS

Our results suggest that the use of and dependence on GABAergic sedative-hypnotics may be associated with the OAB diagnosis in female urogynecological patients.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## ETHICS APPROVAL STATEMENT

The study protocol was approved by the Ethics Committee for Human Studies of the Mother and Child Institute, Warsaw, Poland (protocol no. 29/2018).

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