

## Long Term Users of Benzodiazepine Attending the Department of Medicine in a Tertiary Care Hospital

\*Islam MR<sup>1</sup>, Sultana UKT<sup>2</sup>, Khan TR<sup>3</sup>, Sultan-E-Monzur M<sup>4</sup>, Rahman MM<sup>5</sup>, Juwel MFI<sup>6</sup>

Although comprehensive epidemiological data related to long term use and abuse of benzodiazepine (BZD) in our country is scarce, undocumented clinical observation suggests that the prevalence is quite high and constitutes a significant public health problem. This cross-sectional study was carried out in the Department of Medicine, Shaheed Ziaur Rahman Medical College hospital, Bogra, from 1<sup>st</sup> October 2015 to 31<sup>st</sup> March 2016. The objectives of the study were to evaluate the indication, dosage, duration and untoward effects of use of benzodiazepine for one month or longer among the patients attending the inpatient and outpatient departments of medicine. A total of 100 cases of long term benzodiazepine users aged between 18 to 72 years with mean age of 44.0±15.02 years were taken for the study. Male to female ratio of the cases was 1.08:1.00, 97.0% were Muslims, 96.0% were married; 77.0% were rural dwellers. Fifty four (54.0%) cases were from middle class society and 39.0% were housewives by occupation. The benzodiazepine dosage ranged from <5mg to 10mg equivalent to diazepam, with mean dose of 7.5±1.71 and the duration ranged from 1-60 months. Benzodiazepine tolerance was found in 21.0% and dependence in 18.0%. The common reason for taking was benzodiazepine for long duration was the different anxiety disorders in 63.0% followed sleep disturbance in 33.0%. Common cause of long term continuation reported by the respondents was rapid relief of symptoms (51.0%) and lack of awareness (21.0%). In 56.0% cases, the drugs were prescribed by providers other than registered physicians. Only 23.0% of patients were counseled beforehand regarding the probable hazards of long term use of the drugs and the counseling were provided only by registered physicians. In conclusion, it can be said that, large scale epidemiologic studies are warranted to evaluate the weight of burden of benzodiazepines abuse in our community and the needs for changes in clinical approach.

[Mymensingh Med J 2024 Oct; 33 (4): 1121-1130]

**Key words:** Benzodiazepine, Long term users, Dependence, Tolerance

### Introduction

**B**enzodiazepines (BZDs) are commonly prescribed as a treatment for anxiety and insomnia. Both prescription and nonprescription use of BZD is very common in our community. Inappropriate BZD use is accompanied by adverse health consequences including cognitive impairment, risk of falling, and dependence. Further, there is little evidence for the effectiveness of BZDs during chronic use. Recent reviews advice to restrain the use of BZDs in general practice for anxiety disorders and sleep disturbance. BZDs act on GABA receptor which is an inhibitory neurotransmitter and the potency of individual generic BZD is proportional to its receptor affinity. In some countries BZDs are used during alcohol withdrawal with an idea of possible shifts of dependence from alcohol to BZD. But such practice is not evidence based. Also the prescription of BZD for muscle spasms, back pain or neck pain is no longer advisable.

1. \*Professor Md Rafiqul Islam, Professor and Head, Department of Medicine, North Bengal Medical College, Sirajganj, Bangladesh; E-mail: mrafiqpr@gmail.com
2. Dr UKM Tahmina Sultana, Assistant Registrar, Medicine, Shaheed Ziaur Rahman Medical College Hospital, Bogura, Bangladesh
3. Professor Tapashi Rahman Khan, Professor (CC) of Radiology and Imaging, Ad-Din Women's Medical College, Moghbazar, Dhaka, Bangladesh
4. Dr Md Sultan-E-Monzur, Assistant Professor of Psychiatry, North Bengal Medical College, Sirajganj, Bangladesh
5. Dr Mohammad Mustafizur Rahman, Junior Consultant (Surgery), Mymensingh Medical College Hospital, Mymensingh, Bangladesh
6. Dr Md Fakhrul Islam Juwel, Junior Consultant (Medicine), Shaheed Ziaur Rahman Medical College, Bogura, Bangladesh

*\*for correspondence*

BZD can cause physical dependence evidenced by withdrawal syndrome that is often encountered after sudden cessation in the long term users. To our best of knowledge, the exact prevalence of using total spectrum of long term BZD in our country has not been well studied. Undocumented clinical observation suggests that the prevalence is quite high and constitutes a significant public health problem. In absence of elaborate ethical or legal guideline on indications of long term use of BZDs in our country, this study was not focused on justifiability of their use in the cases studied.

**Methods**

This cross-sectional study was carried out in the Department of Medicine, Shaheed Ziaur Rahman Medical College Hospital, Bogura, Bangladesh

from 1<sup>st</sup> October 2015 to 31<sup>st</sup> March 2016. Among the patients attending inpatient and outpatient departments of Internal Medicine, those using Benzodiazepine (BZD) regularly for 1 month or longer, were taken as study population. Total number of 100 consecutive cases was included by purposive sampling. The demographic details including age, sex, self-reported socioeconomic status, inhabitation, marital status, religion and occupation were recorded. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) of The American Psychiatric Association criteria were adopted in relevant cases. The relative details of long term BZD use including dose, duration and type of BZD with indications, prescription status and detectable side effects were all noted.

**Results**

A total of 100 cases of long term users of Benzodiazepine (BZD) in the present study were aged between 18 to 72 years with mean age of 44±15.02 (mean±SD) years. Number of males (52) was just higher than females (48) in the ratio of 1.08:1 (Figure 1). Of the respondents, 97.0% were from Muslim community and 96.0% were married (Table I). Rural dwellers were 77.0%. Socioeconomic background of the cases reveals 32.0% from poor, 54.0% from middle class and 14.0% from rich families (Table II). Occupational categories of the cases shows housewife 39.0% followed by farmers 24.0% (Figure 2). The Diazepam equivalent dosage of BZDs use ranged from ≤5 to 10 mg with mean dose of 7.5±1.71 mg. (Table III). Duration ranged from 1-60 months with a mean of 30.36 months. Features of tolerance were found in 21.0% and dependence in 18.0% (Table IV). Clonazepam was the most common generic used by 66.0% (Figure 3). Common indications were different anxiety disorders (63.0%) followed by sleep disturbance (33.0%) (Table V). Self-reported causes of long term continuation was rapid relief of symptoms (51.0%) followed by lack of awareness (21.0%) (Table VI). BZDs were prescribed for long term use by registered doctors only in 2.0% of the cases, while 56.0% were prescribed by providers other than registered doctors and 42.0% used to take by self-continuation from registered doctors' prescriptions. Prior counseling about the risks of long term BZD therapy was done only in 23.0% of cases and all by the registered doctors (Table VII).

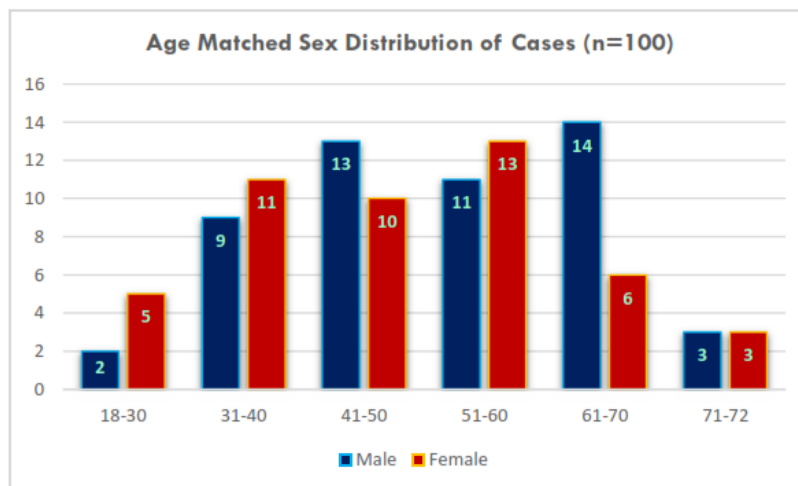


Figure 1: Bar chart for age matched sex distribution of the long term users of BZD showing most of the patients (87.0%) were within the age range of 31-70 years. Males were 52.0% and females were 48.0%

Table I: Distribution of respondents according to religion and marital status

<i>Religion (n=100)</i>			
Married	Unmarried	Others	Total
n (%)	n (%)	n (%)	n (%)
97(97.0)	03(03.0)	00(0.0)	100(100.0)
<i>Marital status (n=100)</i>			
Muslim	Hindu	Others	Total
n (%)	n (%)	n (%)	n (%)
96(96.0)	04(4.0)	00(0.0)	100(100.0)

Table I shows that 97% cases were Muslim and 96% were married.

Table II: Distribution according to habitation and socioeconomic class

<i>Background of habitation (n=100)</i>			
Rural	Urban	Others	Total
n (%)	n (%)	n (%)	n (%)
77 (77.0)	23 (23.0)	0 (0.0)	100 (100.0)
<i>Socioeconomic status (n=100)</i>			
Poor	Middle class	Rich	Total
n (%)	n (%)	n (%)	n (%)
32 (32.0)	54 (54.0)	14 (14.0)	100 (100.0)

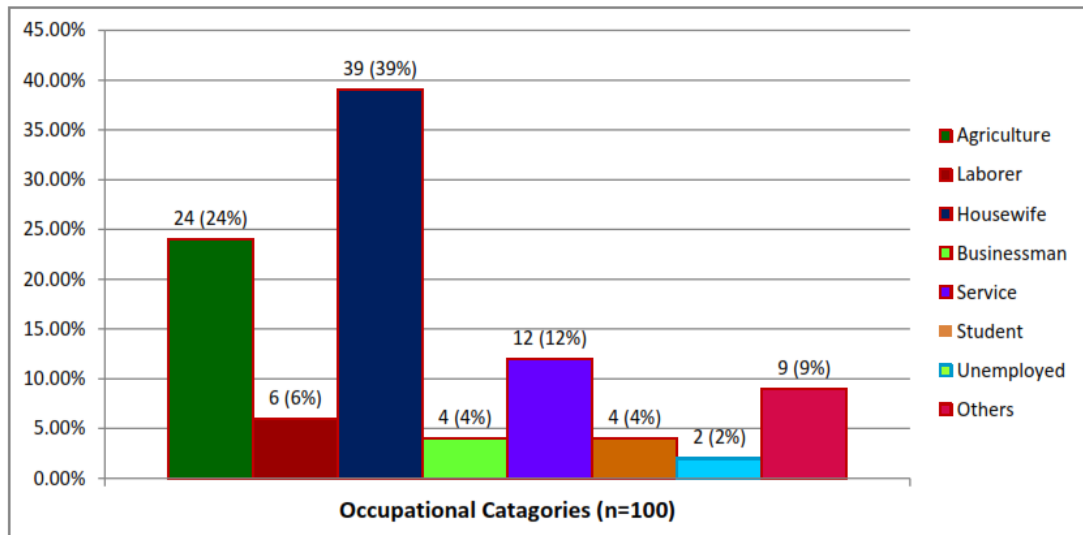


Figure 2: The Bar chart for the occupational categories of the 100 patients under study showing the most common were housewife (39%), followed by agriculturist i.e. farmer (24%)

Table III: Diazepam equivalent dosage of BZD (n=100)

Dose (Diazepam equivalent) in mg	n (%)	Mean±SD (mg)
≤5-5	56 (56.0)	7.5±1.71
>5-10	44 (44.0)	
Total	100 (100.0)	

Table IV: Duration of BZD use correlated with side effects (n=100)

Side effects	Duration of BZD use (months)			Total (%)
	1-6	6-12	12-60	
Tolerance	07	06	08	21 (21.0)
Dependence	05	04	09	18 (28.0)
None	41	13	07	61 (61.0)
Total	53	23	24	100 (100.0)

Table IV shows the duration of BZD use in this study ranged from 1 to 60 months. Developed tolerance 21.0% and 18.0% developed dependence.

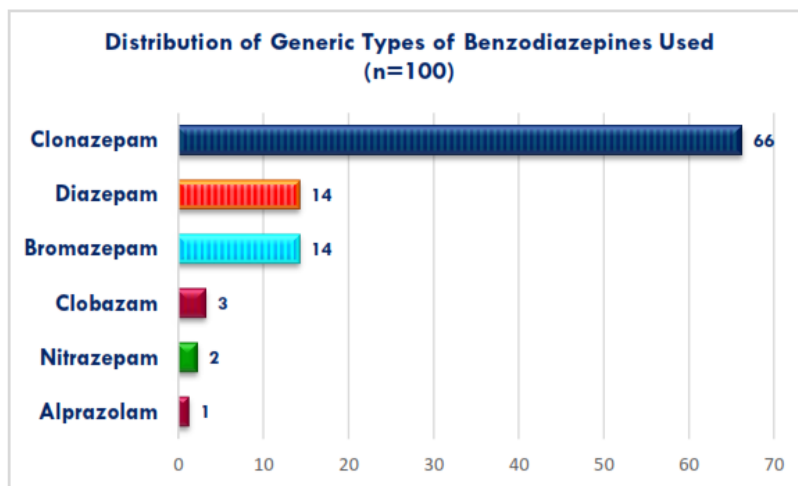


Figure 3: Bar chart shows that clonazepam (66.0%) as the most commonly used BZD

Table V: Indication of BZD use (n=100)

Indication	Male (n=52)	Female (n=48)	Total
	n (%)	n (%)	n (%)
<i>Anxiety disorders</i>	39 (39.0)	25 (25.0)	63 (63.0)
Generalized anxiety disorder	05 (05.0)	11 (11)	15 (15.0)
Panic anxiety disorder	03 (03.0)	01 (01.0)	04 (04.0)
Anxiety disorder with other medical condition	29 (29.0)	10 (10.0)	39 (39.0)
Unspecified anxiety disorder	02 (02.0)	03 (03.0)	05 (05.0)
Sleep disturbance	12 (12.0)	21 (21.0)	33 (33.0)
Others	01 (01.0)	02 (02.0)	04 (04.0)
Total	52 (52.0)	48 (48.0)	100 (100.0)

Table V shows that, long term BZDs were prescribed for different anxiety disorders in 63.0% including 39.0% males and 25.0% females. For sleep disturbance in 33.0% were prescribed that included 12.0% males and 21.0% females.

Table VI: Reason for long term continuation of BZD use (n=100)

Reasons for use	n (%)
Rapid relief of symptoms	51 (51.0)
Lack of awareness of untoward effects	21 (21.0)
Easy availability	11 (11.0)
Low cost	09 (09.0)
Others	08 (08.0)
Total	100 (100.0)

Table VI showing self-reported causes of long term continuation of BZD use.

Table VII: Category of health care provider and prior counseling status (N=100)

Healthcare provider (n=100)	n (%)	Prior counseling (n=100)	
		Yes	Yes
		n (%)	n (%)
Registered physician	02 (02.0)	01 (01.0)	01 (01.0)
Registered physician followed by self-continuation	42 (42.0)	22 (22.0)	20 (20.0)
<i>Other than registered physician</i>	<i>56 (56.0)</i>	<i>00 (00.0)</i>	<i>56 (56.0)</i>
Medical assistant	14 (14.0)		
Health assistant	06 (06.0)		
Family welfare visitor	01 (10.0)		
Pharmacist	00 (00.0)		
Drug seller	27 (27.0)		
Others	08 (08.0)		
Total	100 (100.0)	23 (23.0)	77 (77.0)

Table VII shows that, 56.0% of BZD users' providers other than registered physician. Prior counseling was not done in 77.0% cases.

### Discussion

Benzodiazepine (BZD), the most frequently prescribed psychotropic medications and are used by 5.0-10.0% in communities of the developed world<sup>1,2,3</sup>. In the United States, BZD are prescribed around 5.0% of the adults<sup>4,5</sup>. Electronic health care data based study of 5 Western European countries showed prevalence of 570 to 1700 per 10 000 person-years during 2001 to 2009 and revealed decreasing trends in The Netherlands, Germany and Denmark but increasing trends in Spain and United Kingdom<sup>6</sup>. Definition of long term use of BZD varies in duration from 1 month to couple of years<sup>7,8</sup>. Different studies have defined long term use, for example, continuous use for  $\geq 12$  months<sup>9</sup>,  $\geq 120$  days<sup>5</sup>, more than 3 months<sup>10</sup>, monthly prescription 3 or more in a year<sup>11</sup>, continuous use for 180 days<sup>12,13,14</sup>, medication possession ratio  $>30.0\%$  in one year after prescription<sup>15</sup> and longer than 12

weeks<sup>1</sup>. Guidelines cautioned limiting prescribing BZD for patients unacceptably distressed from severe anxiety just for 2-4 weeks and for extreme insomnia<sup>16,17,18,19</sup>. Dutch and Belgian guidelines recommend use in insomnia only for 1-2 weeks<sup>20,21</sup>. In insomniacs, the effect of BZD wears off within a few weeks and on cessation, insomnia often rebounds<sup>22</sup>. After regular use of BZD just for one month, withdrawal symptoms can develop<sup>23</sup>. In Japan, hypnotics can be filled in one prescription for not more than one month<sup>8</sup>. In this small scale study, we defined regular use of BZD for 1 month or longer as long term use. In a Brazilian study, common mental disorders were more among lower income groups but the use of psychotropic drugs including antidepressant and BZD were more among higher income groups<sup>23</sup>. WHO World Mental Health Survey Initiative estimated 12-month prevalence of major depressive episodes is 5.5% in developed

countries and 5.9% in developing countries<sup>24</sup>. Whereas in a systematic review mostly using US data shows that, lower educational level, unemployment, low income, and unmarried status are associated with higher BZD misuse<sup>25</sup>. In spite of the potential for abuse, dependence, withdrawal symptoms, motor vehicle accidents and other side effects like higher risk of falls, fractures, fatal events and cognitive disturbances in particular among elderly<sup>12,26,27</sup>, prevalence of BZD use among adults at some time in a year remaining high and vary between 7.5% and 21.3% across countries<sup>9,14,18,25,26,27,28,29,30</sup>. Survey on BZDs use by US adults during 2015 and 2016 reported 10.4% use as-prescribed and 2.2% with misuse totaling a prevalence of 12.6%<sup>4</sup>. Misuse was highest in 18-25 age group and more among males. The common association of misuse was alcohol and other substance use, anxiety, insomnia and poor access to better care like cognitive behavioural measures. In this study the age of the long term BZD users were ranged from 18-70 year with mean age 44.0±15.02 (Mean±SD) years. Most of the patients (87.0%) were within the age range of 31-70 years. Cross-sectional study on BZD prescriptions in a tertiary care hospital, Mumbai, India shown the age range 16-78 years with mean 36.33±14.3 years<sup>32</sup>. In a similar study conducted in the department of Internal Medicine, Aga Khan University, Pakistan, on subjects aged ≥18 years, Patel MJ et al.<sup>33</sup> reported the mean age 45.0±17.0 years and interquartile range 32-60 years which are very close to ours. In the present study, there is slight male preponderance with male (52.0%), which is comparable similar to Raouf M et al.<sup>34</sup> study showing 58.5% male and exactly same as that of Patel MJ et al.<sup>33</sup>. A French population-based cohort study among age group 18-69 years reported long term BZD user in 2.8% men and 3.8% in women<sup>2</sup>. Prevalence study on 5 Western European countries showed BZD use two fold higher among females<sup>6</sup>, while in another study, such prevalence was much higher in U.S. males than in female but equal among Ontarian and Australian males and females<sup>35</sup>. Women are more likely to have insomnia and anxiety disorders but the variations may also reflect study designs used and socio-cultural differences of the respondents. In this study, 97.0% of the respondents were Muslims which may nearly reflect the religious distribution of this study population. In this study, majority of long term BZD users were married

(96.0%) which can be correlated with 2 other studies reporting 78.0%<sup>33</sup> and 73.5%<sup>34</sup>. Rural dwellers comprised 77.0% of this study cases which is somewhat more than the proportion of our rural population and may reflect their choice for lower cost public hospital care. Socioeconomic background of the 100 subject under study revealed 32.0% were from poor, 54.0% from middle class and 14.0% from rich families which are concordant with another study in the subcontinent reporting 19.6%, 49.0% and 24.0% respectively<sup>34</sup>. Occupational distribution of this study cases shows housewife 39.0% followed by farmers 24.0%. Occupational categorization differ among studies but housewife also constituted the most common category in two other studies<sup>33,34</sup>. Diazepam equivalent dosage of BZDs used in our cases ranged from >5 to 10 mg with the mean dose of 7.5±1.71 which very close to 7.04±4.0 reported in another study<sup>33</sup>. In this study, Clonazepam, Diazepam and Bromazepam were commonly used. Similar generics including Clonazepam, Lorazepam, Alprazolam, Midazolam, Diazepam and Bromazepam, Oxazepam are reported in other studies<sup>2,32,33,34</sup>. A Finnish cohort study found Clonazepam to have greater risk of long-term use compared with other BZDs<sup>12</sup>. The duration of BZD use in our cases ranged from 1 month to 60 months a mean of 30.36 months. Features of tolerance were found in 21.0% and dependence in 18.0%. Common initial indications for starting BZD were various anxiety disorders (63.0%) and sleep disturbance (33.0%). Self-reported causes of long term continuation include rapid relief of symptoms (51.0%) lack of awareness of untoward effects (21.0%), easy availability (11.0%) and low cost (9.0%). BZDs are commonly prescribed for anxiety, insomnia, painful physical conditions and with medications for depressive illness<sup>1,2,5</sup>. The causes of continuation explained by the respondents are also logical but the pharmacological reason lies in the development of tolerance, abuse or dependence<sup>3</sup>. Development of tolerance to BZD in respect to hypnotic, anxiolytic and anticonvulsant effect can develop within a few days or weeks of daily use<sup>3,22</sup>. The mechanism of tolerance is thought to result from neuroadaptation that involve hyposensitization and down regulation of GABA receptors as well as sensitization of excitatory glutaminergic receptors<sup>3</sup>. BZD abuse or dependence is diagnosed on the basis of criteria<sup>36</sup>.

Clinical clues to BZD dependence are history of long term use, withdrawal symptoms, rebound anxiety or insomnia, dosage escalation or unsuccessful previous attempts for stopping<sup>3</sup>. However, American Psychiatric Association revised and abolished hierarchical diagnoses of abuse and dependence in favour of single term "Substance Use Disorder"<sup>37,38</sup>. In this series, only 2.0% patients had been using BZD for long term as prescribed by registered physician and another 42.0% were continuing by self after initial prescription from registered physician. Prior counseling was done only by registered physician in 23.0% cases. To limit long term use of BZD and its consequences, value of evidence based prescribing by competent physician with proper counselling cannot be overemphasized<sup>17,20,21</sup>. An US survey<sup>4</sup> reported prevalence of BZD misuse, defined as not prescribed or more than or other than as prescribed, among 2.2% adults and of those 4.6% and 6.8% met criteria for abuse and dependence, respectively. Sources of misused drugs were commonly friends or relatives. Clinicians' awareness in recognizing associations of misuse and possible permissive role of their prescribed BZD for misuse by others were emphasized. A systematic review of European Union data<sup>31</sup> revealed high potential BZDs for misuse, abuse and dependence potential. Study on web based cryptomarket<sup>39</sup> shown that with the advent of online pharmacies using banners of 'no prescription required', 'free online consultation', etc and various online healthcare services, the sale and nonmedical use of BZDs have risen globally with resultant increases in drug overdose related accidents, hospital visits and deaths. Monitoring and legitimacy assessment of the online vendors is difficult as some of these websites are short lived and obscure actual vendor location by using proxy servers. The situation in our community is beset with multifaceted problems. United Nations Office on Drugs and Crime (UNODC), report on South Asia emphasized that narcotic and psychotropic drugs including BZDs are largely available through pharmacies, primarily due to lack of affordable health care systems for the common people in the region<sup>40</sup>. The report also warned that, illicit use of pharmaceutical products surpasses the use of illicit drugs because of users' perception of relative legality, safety, free of stigma and lower cost. Nattala P et al. reported nonmedical use of BZDs in South India which

were obtained from pharmacies<sup>41</sup>. Raof M et al.<sup>34</sup> also mentioned nonprescription availability and self-poisoning of BZD are common in Pakistan. Pertinent studies in Bangladesh shown that other than Registered Doctors, many other categories of providers are prescribers<sup>42,43,44</sup>. There are drug shops without a license and in majority of pharmacies, drugs are dispensed by persons without a required professional qualification<sup>43</sup>. BZDs are very often purchased from pharmacies without a creditable prescription<sup>43,44</sup>. These practices in our community are linked to long term use of BZD without counseling.

### **Conclusion**

Although the study could not reflect the incidence or prevalence of long term benzodiazepine (BZD) user in the community, it emphasizes the need for enthusiasm of the physicians during clinical practice as well as enhanced awareness of the users to minimize long term use of this group of drugs and the undesirable consequences thereof. Increased access of the cases of anxiety and insomnia, in particular, to evidence based care especially involving counseling and non-pharmacological measures at an affordable cost appear to be a prerequisite. Epidemiologic studies are needed to evaluate the weight of burden related to long term use of BZD in our community and to formulate strategies for improvement at the level of healthcare provider and of regulatory agencies.

### **References**

1. Demyttenaere K, Bonnewyn A, Bruffaerts R, De Girolamo G, Gasquet I, Kovess V, Haro JM et al. Clinical factors influencing the prescription of antidepressants and benzodiazepines: results from the European study of the epidemiology of mental disorders (ESEMeD). *J Affect Disord.* 2008;110:84-93.
2. Airagnes G, Lemogne C, Renuy A, Goldberg M, Hoertel N, Roquelaure Y et al. Prevalence of prescribed benzodiazepine long-term use in the French general population according to socio-demographic and clinical factors: findings from the Constances cohort. *BMC Public Health.* 2019;19(566).
3. Ashton H. The diagnosis and management of benzodiazepine dependence. *Curr Opin Psychiatry.* 2005;18(3):249-55.

4. Maust DT, Lin LA, Blow FC. Benzodiazepine Use and Misuse among Adults in the United States. *Psychiatr Serv*. 2019;70(2):97-106.
5. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiatry*. 2015;72(2):136-42.
6. Huerta C, Abbing-Karahagopian V, Requena G, Oliva B, Alvarez Y, Gardarsdottir H et al. Exposure to benzodiazepines (anxiolytics, hypnotics and related drugs) in seven European electronic healthcare databases: a cross-national descriptive study from the PROTECT-EU Project. *Pharmaco-epidemiol Drug Saf*. 2016;25 Suppl 1:56-65.
7. Kurko TA, Saastamoinen LK, Tähkäpää S, Tuulio-Henriksson A, Taiminen T, Tiihonen J et al. Long-term use of benzodiazepines: Definitions, prevalence and usage patterns - a systematic review of register-based studies. *Eur Psychiatry*. 2015;30(8):1037-47.
8. Enomoto M, Kitamura S, Tachimori H, Takeshima M, Mishima K. Long-term use of hypnotics: Analysis of trends and risk factors. *General Hospital Psychiatry*. 2020;62:49-55.
9. Barbui C, Gregis M, Zappa M. A cross-sectional audit of benzodiazepine use among general practice patients. *Acta Psychiatr Scand*. 1998;97:153-6.
10. Guaiana G, Barbui C. Discontinuing benzodiazepines: best practices. *Epidemiol Psychiatr Sci*. 2016;25(3):214-6.
11. Moore TJ, Mattison DR. Adult Utilization of Psychiatric Drugs and Differences by Sex, Age, and Race. *JAMA Intern Med*. 2017;177(2):274-5.
12. Taipale H, Särkilä H, Tanskanen A, Kurko T, Taiminen T, Jari Tiihonen J et al. Incidence of and Characteristics Associated With Long-term Benzodiazepine Use in Finland. *JAMA Netw Open*. 2020;3(10):e2019029.
13. Godfrey C, Heather N, Bowie A, Brodie J, Parrott S, Ashton H et al. Randomized controlled trial of two brief interventions against long-term benzodiazepine use: Cost-effectiveness. *Addiction Research and Theory*. 2008;16(4):309-17.
14. Magrini N, Vaccheri A, Parma E, D'Alessandro R, Bottoni A, Occhionero M et al. Use of benzodiazepines in the Italian general population: prevalence, pattern of use and risk factors for use. *Eur J Clin Pharmacol*. 1996;50(1-2):19-25.
15. Gerlach LB, Maust DT, Leong SH, Mavandadi S, Oslin DW. Factors Associated With Long-term Benzodiazepine Use Among Older Adults. *JAMA Intern Med*. 2018;178(11):1560-2.
16. Donaldson L. Benzodiazepines warning. London (UK), CMO's Update 37: Department of Health. 2004. Available from: [www.benzo.org.uk/cmo.htm](http://www.benzo.org.uk/cmo.htm).
17. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2012;60(4):616-31.
18. Alessi-Severini S, Bolton JM, Enns MW, Dahl M, Collins DM, Chateau D et al. Use of benzodiazepines and related drugs in Manitoba: a population-based study. *CMAJ Open*. 2014;2(4):E208-16.
19. A Case for Appropriate Prescribing of Benzodiazepines. NCPA Annual Meeting. Asheville, NC. September 9, 2016. Stephen A. Wyatt, D.O. Aug 15, 2016. Available from: [www.ncpsychiatry.org/assets/2016AnnualMeeting/Handouts/4a\\_a\\_case\\_for\\_appropriate\\_prescribing\\_of\\_benzodiazepines-stephen\\_wyatt.pdf](http://www.ncpsychiatry.org/assets/2016AnnualMeeting/Handouts/4a_a_case_for_appropriate_prescribing_of_benzodiazepines-stephen_wyatt.pdf).
20. Damen-van Beek Z, Lucassen PL, Gorgels W, Smelt AF, Knuistingh Neven A, Bouma M. De NHG-standaard 'Slaapproblemen en slaappmiddelen'. *Ned Tijdschr Geneesk*. 2015;159:A8679.
21. Aanpak van slaapklachten en insomnie bij volwassenen in de eerste lijn herziening (versie 28/06/2018) Hanne Cloetens, Tom Declercq, Hilde Habraken, Jan Callens, Ann Van Gastel In opdracht van de Werkgroep Ontwikkeling Richtlijnen Eerste Lijn van EB Practice Net Gevalideerde versie: 30/6/2018. Available from: [www.domusmedica.be/sites/default/files/WOREL%20RL%20Aanpak%20insomnie%20NL%2010102018.pdf](http://www.domusmedica.be/sites/default/files/WOREL%20RL%20Aanpak%20insomnie%20NL%2010102018.pdf).
22. Johnson B, Streltzer J. Risks associated with long-term benzodiazepine use. *Am Fam Physician*. 2013;88(4):224-6.
23. Lima MC, Menezes PR, Carandina L, Cesar CL, Barros MB, Goldbaum M. Common mental disorders and the use of psychoactive drugs: the impact of socioeconomic conditions. *Rev Saude Publica*. 2008;42(4):717-23.



24. Kessler RC, Birnbaum HG, Shahly V, Bromet E, Hwang I, McLaughlin KA et al. Age differences in the prevalence and co-morbidity of DSM-IV major depressive episodes: results from the WHO World Mental Health Survey Initiative. *Depress Anxiety*. 2010;27:351-64.
25. Votaw VR, Geyer R, Rieselbach MM, McHugh RK. The epidemiology of benzodiazepine misuse: A systematic review. *Drug Alcohol Depend*. 2019;200:95-114.
26. Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996-2013. *Am J Public Health*. 2016;106(4):686-8.
27. Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert ASB. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ*. 2015;350:h2698.
28. Madruga CS, Paim TL, Palhares HN, Miguel AC, Massaro LTS, Caetano R, Laranjeira RR. Prevalence of and pathways to benzodiazepine use in Brazil: the role of depression, sleep and sedentary lifestyle. *Braz J Psychiatry*. 2019;41(1):44-50.
29. Ribeiro CS, Azevedo RCS, da Silva VF, Botega NJ. Chronic use of diazepam in primary healthcare centers: user profile and usage pattern. *Sao Paulo Med J*. 2007;125:270-4.
30. Ten Wolde GB, Dijkstra A, Van Empelen P, Neven AK, Zitman FG. Social-cognitive predictors of intended and actual benzodiazepine cessation among chronic benzodiazepine users. *Addict Behav*. 2008;33:1091-1103.
31. Casati A, Sedefov R, Pfeiffer-Gerschel T. Misuse of medicines in the European Union: a systematic review of the literature. *Eur Addict Res*. 2012;18(5):228-45.
32. Nerlekar S, Roy N, Karia S et al. A study of benzodiazepine prescription patterns in a tertiary general hospital. *Natl J Physiol Pharm Pharmacol*. 2019;9(5):379-82.
33. Patel MJ, Ahmer S, Khan F, Qureshi AW, Shehzad MF, Muzaffar S. Benzodiazepine use in medical out-patient clinics: a study from a developing country. *J Pak Med Assoc*. 2013;63(6):717-20.
34. Raouf M, Nawaz H, Nusrat R, Pabaney AH, Randhawa AR, Rehman R et al. Awareness and use of Benzodiazepines in healthy volunteers and ambulatory patients visiting a tertiary care hospital: a cross sectional survey. *PLoS One*. 2008;3(3):e1804.
35. Brett J, Maust DT, Bouck Z, Ignacio RV, Mecredy G, Kerr EA, Bhatia S, Elshaug AG, Pearson SA. Benzodiazepine Use in Older Adults in the United States, Ontario and Australia from 2010 to 2016. *J Am Geriatr Soc*. 2018;66(6):1180-5.
36. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV. 4<sup>th</sup> ed. Washington (DC): American Psychiatric Association; 1994. p.866. Available form: [www.psychiatryonline.com/DSMPDF/dsm-iv.pdf](http://www.psychiatryonline.com/DSMPDF/dsm-iv.pdf).
37. Substance Abuse and Mental Health Services Administration. Impact of the DSM-IV to DSM-5 Changes on the National Survey on Drug Use and Health. Rockville (MD): Substance Abuse and Mental Health Services Administration (US). 2016 Jun. 2, Substance Use Disorders. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK519702/>.
38. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5<sup>th</sup> ed. American Psychiatric Association. 2013. DSM-V.
39. Cunliffe J, Décary-Hêtu D, Pollak TA. Non-medical prescription psychiatric drug use and the darknet: A cryptomarket analysis. *Int J Drug Policy*. 2019;73:263-72.
40. United Nations Office on Drugs and Crime (UNODC) New Delhi: UNODC; 2002. Available from: [www.unodc.org/documents/southasia/reports/Misuse\\_of\\_Prescription\\_Drugs\\_-\\_A\\_South\\_Asia\\_Perspective\\_UNODC\\_2011.pdf](http://www.unodc.org/documents/southasia/reports/Misuse_of_Prescription_Drugs_-_A_South_Asia_Perspective_UNODC_2011.pdf).
41. Nattala P, Murthy P, Thennarasu K, Cottler LB. Non-medical use of sedatives in urban Bengaluru. *Indian J Psychiatry*. 2014;56(3):246-52.
42. Mahmood SS, Iqbal M, Hanifi SMA et al. Are 'Village Doctors' in Bangladesh a curse or a blessing? *BMC Int Health Hum Rights*. 2010.
43. Ahmed SM, Naher N, Hossain T, Rawal LB. Exploring the status of retail private drug shops in Bangladesh and action points for developing an accredited drug shop model: a facility based cross-sectional study. *J of Pharm Policy and Pract*. 2017;10(21).

44. Jakaria M, Rahman A, Rahat MRU, Islam M, Clinton CD, Talukder MB et al. The irrational offering of benzodiazepines by medicine shops in Bangladesh: Recommends implementation of retail pharmacy as soon as possible. Bangladesh J Medical Sci. 2018; 17(1):175-7.